Manejo integrado en un centro de atención y seguimiento para el cribado y tratamiento de la infección por el virus de la hepatitis C en pacientes con trastorno por uso de sustanci

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Tesis doctoral

Universitat Autònoma de Barcelona

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ABREVIATURAS

AAD – Antivirales de acción directa

ADN – Ácido desoxirribonucleico

ALT – Alanina aminotransferasa

Anti-HBc – Anticuerpos contra el core de la hepatitis B

Anti-VHC – Anticuerpos contra el virus de la hepatitis C

Anti-VIH – Anticuerpos contra el virus de la inmunodeficiencia humana

ARN – Ácido ribonucleico

AST – Aspartato aminotransferasa

BDI – Inventario de depresión de Beck

BID – Dos veces al día

CAS – Centro de atención y seguimiento

DSM-5 – Manual Diagnóstico y Estadístico de los Trastornos Mentales, 5ª Edición

F – Fibrosis

FAE – Fármaco antiepiléptico/psicotrópico

FIB-4 – Fibrosis-4

GT – Genotipos

GLE – Glecaprevir

HBsAg – Antígeno de superficie de la hepatitis B

HSH – Hombres que tienen sexo con hombres

LPV – Ledipasvir

NA – no administrado

OMS – Organización Mundial de la Salud

OR – Odds ratio

PCR – Reacción en cadena de la polimerasa

PIB – Pibrentasvir

RVS – Respuesta viral sostenida

SARS-CoV2 – Coronavirus de tipo 2 causante del síndrome respiratorio agudo severo

SF-36 – Cuestionario de salud Short-Form-36 Health Survey

SOF – Sofosbuvir

TID – Tres veces al día

TUS – Trastornos por uso de sustancias

VEL – Velpatasvir

VHB – Virus de la hepatitis B

VHC – Virus de la hepatitis C

VIH – Virus de la inmunodeficiencia humana

ÍNDICE

RESUMEN

El manejo del virus de la hepatitis C (VHC) ha experimentado grandes cambios en los últimos años, permitiendo un fácil diagnóstico y tratamiento de la infección. A pesar de ello, la atención del VHC sigue siendo un desafío en pacientes con trastorno por uso de sustancias (TUS) y en pacientes con interacciones farmacológicas.

Esta tesis tiene como objetivo evaluar la utilidad de implementar un programa para el cribado, diagnóstico y tratamiento de la infección por VHC para facilitar el acceso al sistema sanitario de todos los pacientes con TUS que asistieron a un Centro de Atención y Seguimiento (CAS). Además, se quiso analizar las características de los pacientes con TUS en relación con el VHC y abordar una de las pocas contraindicaciones para el tratamiento del VHC que aún existen: las interacciones farmacológicas.

El trabajo principal de esta tesis doctoral fue un estudio prospectivo de cohortes clínicas que utilizó un modelo colaborativo y multidisciplinar para ofrecer atención de la infección por VHC a personas con TUS que asistían a un CAS. Se compararon las características de los participantes, la prevalencia de VHC, el porcentaje de sujetos que inició tratamiento y la adherencia al mismo según las características de consumo y la presencia de patología dual. Entre noviembre 2018 y junio 2019 asistieron 528 sujetos al CAS y 401 (76%) aceptaron cribado. En total, 112 (28 %) eran anti-VHC positivos y 42 (10 %) tenían ARN VHC detectable, pero solo 20 de éstos últimos iniciaron tratamiento contra el VHC. El desempleo, el bajo nivel educativo y el consumo de cocaína impactaron negativamente en el inicio del tratamiento. Se encontraron 253 (63%) pacientes con patología dual y no hubo diferencias en la prevalencia ni tratamiento de la infección por VHC entre éstos y los pacientes con sólo TUS. A los 18 meses, solo 242 (60%) de los 401 pacientes previamente testeados seguían

vinculados al centro y 176 (72%) aceptaron ser cribados de nuevos. Se detectaron únicamente 2 (1.1%) infecciones nuevas.

El segundo trabajo de esta tesis, estudio retrospectivo y colaborativo entre el hospital Vall d'Hebrón y el hospital Marqués de Valdecilla, tuvo como objetivo evaluar las interacciones farmacológicas entre los antivirales de acción directa (AAD) y los fármacos antiepilépticos que son ampliamente usados en población psiquiátrica pero, a su vez, los que hasta la fecha más contraindicaciones presentan para el tratamiento con AAD. Se encontraron y describieron cinco pacientes con infección crónica por VHC que recibían medicación antiepiléptica y fueron tratados con AAD. Todos los pacientes alcanzaron respuesta a final de tratamiento así como a las 12 semanas. No se reportaron efectos adversos ni necesidad de modificación de dosis.

En conclusión, a pesar de un modelo de atención descentralizado, un alto número de personas con TUS no aceptan el cribado del VHC. La prevalencia del VHC y la incidencia de nuevas infecciones son altas en esta población y la asistencia a los centros de adicciones es baja, con una tasa de abandono del 40%. La dificultad de cribado y acceso al sistema sanitario y al tratamiento del VHC así como las interacciones medicamentosas son los principales obstáculos para la eliminación del VHC en la población con TUS. Abordar estas barreras es crucial para lograr los objetivos de la OMS para la eliminación del VHC.

ABSTRACT

Hepatitis C virus (HCV) management has undergone great changes in recent years, allowing easy diagnosis and treatment of the infection. Despite this, HCV care remains a challenge in patients with substance use disorder (SUD) and in patients with drug-drug interactions.

This thesis aimed to evaluate the usefulness of implementing a program for the screening, diagnosis and treatment of HCV infection to facilitate linkage to care in all patients with SUD attending a dedicated addiction and dual diagnosis centre (ADDC). It also aimed to analyze the characteristics of SUD patients in relation to HCV, and to address one of the few contraindications to HCV treatment that still exist: drug-drug interactions.

The main work of this doctoral thesis was a prospective clinical cohort study using a collaborative, multidisciplinary model to offer HCV care to individuals with SUD attending a dedicated hospital clinic. The characteristics of the participants, prevalence of HCV infection, percentage who started therapy and adherence to treatment were compared according to the patients' consumption characteristics and presence of dual diagnosis. 528 individuals attended the center (November 2018-June2019) and 401 (76%) accepted screening. In total, 112 (28%) were anti-HCV-positive and 42 (10%) had detectable HCV RNA, but only 20 of the latter started HCV therapy. Unemployment, low educational level and cocaine consumption negatively impacted the start of treatment. Among the 253 (63%) patients with a dual diagnosis, there were no differences in HCV infection prevalence or treatment versus patients with SUD alone. After 18 months, only 242 (60%) of the 401 previously tested were still linked to the center and 176 (72%) agreed to be screened diagnosing only 2 (1.1%) new infections.

The second work in this thesis, a retrospective and collaborative study between Vall d'Hebrón hospital and Marqués de Valdecilla hospital, aimed to evaluate the drug-drug

interactions between the direct-acting antivirals (DDAs) and antiseizure medication which are widely used in the psychiatric population, but in turn, to date, those that most contraindicate DDA treatment. Five patients with chronic HCV infection receiving antiseizure medication and treated with DDAs were found and described. All patients achieved an end-of-treatment response and at week 12. No adverse events or required dose modifications were reported.

In conclusion, despite a decentralized model of care, a high number of individuals with SUD do not accept HCV screening. The HCV prevalence and incidence of new infection is high in this population and the attendance to addiction centers low, with a 40% dropout rate. The difficulty of screening and access to the health system and treatment for HCV as well as drug interactions are the main obstacles to the elimination of HCV in the population with SUD. Addressing these barriers is crucial to achieve the WHO targets for HCV elimination.

INTRODUCCIÓN

1. INTRODUCCIÓN

1.1 Virus de la hepatitis C

El virus de la hepatitis C (VHC) es un virus ARN perteneciente a la familia Flaviviridae y al género Hepacivirus (1). Fue descubierto en los años 70 (2) denominándose por aquel entonces como hepatitis no A no B. No fue hasta 1988 que se aisló un ADN complementario de la sangre de una persona infectada hecho que permitió el aislamiento del ARN viral, el desarrollo de pruebas serológicas diagnósticas, su secuenciación y la identificación final del VHC (3).

Los viriones del VHC están envueltos por una bicapa lipídica en la que están ancladas dos glicoproteínas de la envoltura (E1 y E2) formando unas partículas con un diámetro de 56-65nm (4,5). La envoltura rodea la nucleocápside de unos 45nm de diámetro que contiene el genoma de ARN de cadena simple positiva (6). Los análisis filogenéticos de cepas de VHC aisladas en distintas regiones del mundo han evidenciado que se trata de un virus muy heterogéneo. En total se han identificado hasta la fecha siete genotipos principales numerados del 1 al 7, y un gran número de subtipos identificados por letras minúsculas (1a, 1b, etc.) (7). El genotipo del VHC influye en el curso de la enfermedad y la respuesta a la terapia antiviral basada en interferón.

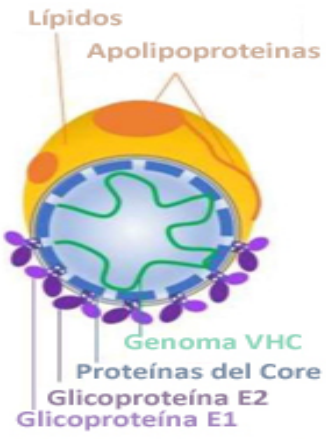

Figura 1. Viriones de VHC. Los viriones de VHC contienen el genoma de ARN de cadena positiva asociado a proteínas del Core, todo ello envuelto por una membrana lípidica en la que se encuentran las glicoproteínas E1 y E2. Adaptado de Alazard-Dany N, et al (5).

El VHC se transmite fundamentalmente por vía parenteral. Las formas más frecuentes de transmisión a nivel mundial son la inadecuada esterilización de material médico, la transfusión de hemoderivados no cribados y el uso de drogas por vía intravenosa con material compartido. La transmisión sexual es posible pero rara, a excepción de los casos de hombres que tienen sexo con hombres (HSH), sobre todo si están coinfectados por el virus del inmunodeficiencia humana (VIH) (8). La transmisión vertical es muy poco frecuente (inferior al 5%) aunque también es más probable en aquellos casos de madres coinfectadas por el VIH (9).

La biología del VHC es relativamente sencilla. Su ciclo replicativo se inicia con la entrada del virión a la célula mediante la interacción de las glicoproteínas E1 y E2 con la membrana de la célula huésped (10). Aunque los hepatocitos son la principal diana del VHC, éste también puede infectar otras células, como los linfocitos B y las células dendríticas, entre otras (11). Tras la unión a la membrana, el virión entra a la célula por endocitosis fusionándose posteriormente con la membrana del endosoma y liberando el genoma viral al citoplasma

celular. Una vez en el citoplasma, el ARN viral funciona como ARN mensajero, sirviendo tanto para la replicación como para su traducción en una poliproteína única. Esta poliproteína es dividida por proteasas virales y del huésped en tres proteínas estructurales (core, E1 y E2) y siete proteínas no estructurales (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) de la maquinaria de replicación viral (12). La proteasa NS3/4, la polimerasa NS5B y la proteína NS5A son las principales enzimas encargadas de la replicación viral. La proteína NS5A participa también en el ensamblaje de las partículas virales (13). Posteriormente comienza el ensamblaje de las nuevas partículas virales en el retículo endoplasmático, y finalmente son transportadas y liberadas fuera de la célula por exocitosis.

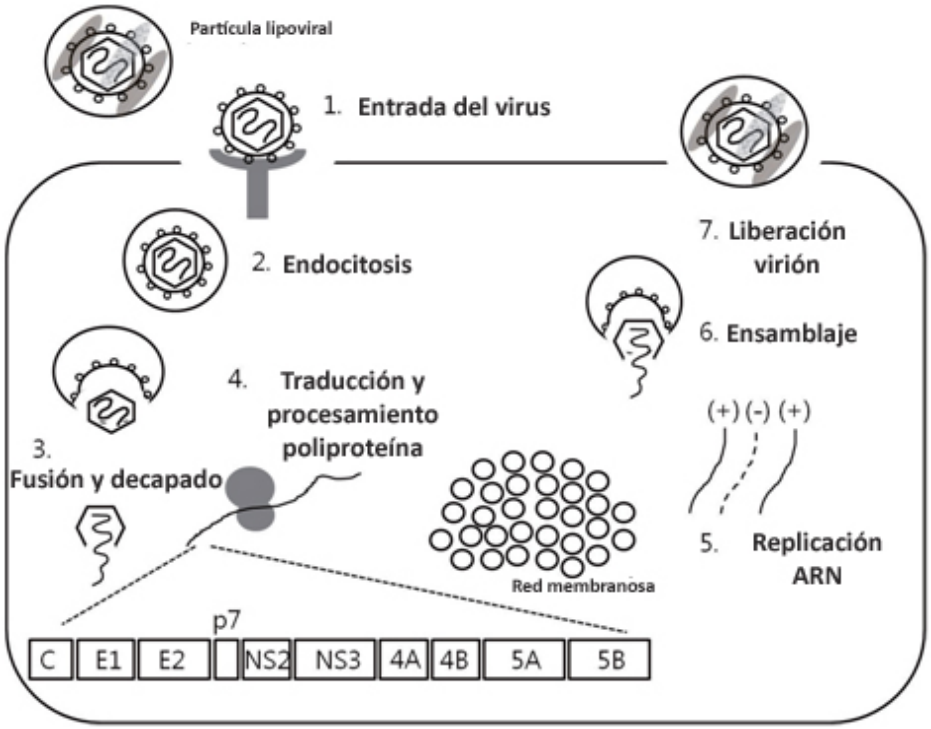

Figura 2. Ciclo replicativo del VHC. Representación esquemática del ciclo replicativo del VHC que incluye la unión y entrada del VHC a la célula, liberación del genoma viral, traducción y procesamiento de la poliproteína, replicación del ARN viral, ensamblaje y liberación del virión. Adaptado de Kim CW, et al (14).

1.2 Infección por virus de la hepatitis C

La infección por el VHC causa una hepatitis aguda, que en la mayoría de los pacientes es asintomática (70-80% de los casos) (15). En aquellos que manifiestan síntomas, estos empiezan de 3 a 12 semanas después de la exposición e incluyen astenia, anorexia e ictericia como los más frecuentes (16). La hepatitis aguda por VHC puede ser grave, pero es muy infrecuente el desarrollo de hepatitis fulminante (17).

Tras la infección aguda, un 50-80% de los casos evoluciona a hepatitis crónica (18). La hepatitis aguda por VHC tiene una mayor tasa de cronificación en caso de cursar de forma asintomática. Otros factores de riesgo asociados a una tasa mayor de cronificación son: edad en el momento de la infección > 25 años, sexo masculino, raza afroamericana, coinfección por el VIH y tratamiento inmunosupresor concomitante (19–21).

La infección crónica por VHC induce fibrosis hepática. Se estima que aproximadamente a los 20-30 años de la infección por VHC, el 10-15% de los sujetos infectados desarrollarán cirrosis hepática. La ratio anual de carcinoma hepatocelular en pacientes con fibrosis avanzada por VHC es del 1-4% (22–24). A diferencia de la infección por virus de la hepatitis B (VHB) que es un virus oncogénico que puede causar carcinoma hepatocelular incluso en personas sin cirrosis hepática (25), en el contexto de infección por VHC raramente se evidencia carcinoma hepatocelular en ausencia de fibrosis hepática avanzada o cirrosis (26).

La infección por VHC se asocia además a numerosas manifestaciones extrahepáticas, que pueden estar presentes en hasta el 2% de los sujetos infectados (27). Las personas con infección crónica por VHC tienen más probabilidades de desarrollar crioglobulinemia y linfoma no Hodgkin (27). También se ha evidenciado un aumento de riesgo en el desarrollo de resistencia a la insulina y diabetes mellitus, ambos factores asociados con un mayor riesgo cardiovascular (28). Se han descrito manifestaciones neurológicas como la fatiga, la

depresión y el deterioro cognitivo, y de hecho, los pacientes infectados crónicamente por el VHC tienen una peor calidad de vida (29). Los mecanismos que causan estas manifestaciones extrahepáticas no son completamente conocidos, si bien se cree que la replicación del VHC en células extrahepáticas y reacciones inmunitarias podrían jugar un papel patogénico (27).

1.3 Diagnóstico de la infección por virus de la hepatitis C

El diagnóstico de la infección por el VHC se suele efectuar en dos pasos. El primero es la detección de anticuerpos anti-VHC en suero o plasma mediante inmunoensayo enzimático. Esta técnica es sensible y específica e indica contacto con el VHC. Su principal limitación es que tras la exposición al virus, los anticuerpos anti-VHC no se detectan hasta pasadas 2-8 semanas por lo que pueden infradiagnosticar infecciones agudas durante el denominado "período ventana" de una hepatitis aguda C, cuando el individuo será anti-VHC negativo pero con viremia detectable. Estos anticuerpos persisten tanto en aquellas personas en que la infección progresa a la cronicidad como en aquellos que eliminan la infección, pudiendo desaparecer décadas más tarde en estos últimos (30,31).

El segundo paso es la detección y cuantificación del ARN del VHC. Esta técnica es útil para diagnosticar infección activa e identificar a aquellos pacientes candidatos a tratamiento, así como monitorizar la respuesta al mismo (32). Su determinación se basa en técnicas de PCR a tiempo real o amplificación mediada por transcripción siendo ambas sensibles y específicas. El ARN del VHC puede detectarse en suero tras 1 o 2 semanas después de la exposición al VHC. La persistencia de ARN VHC en sangre seis meses después de la infección define la presencia de hepatitis crónica (32). Además, la detección del antígeno del *core* del VHC mediante inmunoensayo enzimático también permite el diagnóstico de infección activa y

evaluar la respuesta al tratamiento, aunque es menos usado en la práctica clínica habitual. El nivel de replicación viral no predice el curso natural de la enfermedad pero ha sido un buen predictor de la respuesta al tratamiento particularmente en la era del interferón, siendo ahora de menor importancia con el uso de los antivirales de acción directa (AAD).

En resumen, el cribado de la infección por VHC se basa en la determinación de anticuerpos anti-VHC y si estos son positivos se realiza el diagnóstico de infección activa mediante la detección de ARN VHC. Actualmente la mayoría de laboratorios usan un cribado basado en dos pasos que incluye realización de analítica y determinación de anticuerpos anti-VHC en el paso uno y de ser éstos positivos, nueva analítica y determinación de ARN VHC en el paso dos. Como resultado de este proceso, a un elevado número de pacientes anti-VHC positivos nunca se les realiza una determinación de ARN VHC. De cara a incrementar el diagnóstico de infección activa, disminuir el tiempo de acceso al tratamiento, la pérdida de pacientes y facilitar el cribado de poblaciones con acceso limitado al sistema sanitario se han desarrollado nuevos circuitos y test diagnósticos (33,34). Por un lado, la implementación en los últimos años del "diagnóstico de un solo paso" que consiste en la determinación refleja del ARN del VHC en la misma muestra de sangre en la que se ha obtenido un resultado positivo de anticuerpos anti-VHC. Por otro lado, se han desarrollado e implementado los test de diagnóstico rápido y los test en sangre seca que permiten el diagnóstico de la infección por VHC sin requerir la disponibilidad de un laboratorio ni de personal entrenado y además la muestra para análisis se puede obtener con sangre (venopunción o punción dactilar) o fluido oral (35). Estos test han demostrado una sensibilidad y especificidad superior al 97% tanto para la determinación de anticuerpos anti-VHC como para el ARN VHC (36,37).

La determinación del genotipo de VHC y en algunos casos del subtipo ha sido de gran importancia para guiar el tratamiento (régimen, duración y necesidad de ribavirina) aunque desde la aparición de los AAD pangenotípicos su determinación se ha visto restringida a determinados grupos con alto riesgo de reinfección por el VHC. Su determinación puede ayudar a diferenciar reinfecciones de recidivas y a conocer la epidemiología de la infección en escenarios concretos. El método de referencia es el análisis filogenético de la secuencia de nucleótidos de una porción del genoma viral. En la práctica clínica se usan los métodos estandarizados basados en análisis de secuenciación directa o hibridación reversa (30).

La reinfección por VHC puede ocurrir después de la curación espontánea o tras la respuesta al tratamiento. La reinfección se define como la reaparición de ARN VHC (o antígeno del *core* del VHC) después de una respuesta viral sostenida (RVS) y de demostrar que la infección está causada por una cepa distinta de VHC (32).

Otro dato importante a conocer en los pacientes con infección crónica por VHC es el grado de fibrosis hepática que presentan como consecuencia de la infección (32). Hace años su determinación solo era posible mediante la realización de una biopsia hepática, pero a lo largo de los años han aparecido test que permiten su valoración de forma no invasiva. Los test no invasivos incluyen test serológicos (Fibrotest, Fibrometer, Hepascore, FIB-4, APRI) (38) o test morfológicos mediante elastografía hepática (Fibroscan, Shear Wave) (39). Estas pruebas permiten evaluar la fibrosis (F) usando la clasificación Metavir en la que F0 y F1 corresponden a ausencia o mínima fibrosis en contraposición a F3 y F4 que indican fibrosis avanzada o cirrosis, requiriéndose en éstos últimos seguimiento ecográfico semestral dado el riesgo potencial de desarrollar hepatocarcinoma, incluso tras la curación de la infección por VHC (26,40).

Las estrategias de cribado de la infección por VHC deberían ser definidas conforme a la epidemiologia local, idealmente en el marco de los planes de acción establecidos por las políticas locales (40). En Cataluña se recomienda el cribado a todas aquellas personas con: antecedente de exposición o factores de riesgo, elevación de transaminasas sin causa conocida, infectados por VIH o VHB, inmigrantes de zonas geográficas con alta prevalencia, pacientes que acuden a las unidades de prevención y control de infecciones de transmisión sexual (41).

1.4 Tratamiento de la infección por virus de la hepatitis C

El objetivo del tratamiento del VHC es lograr la curación de la infección y evitar el desarrollo de cirrosis, cirrosis descompensada y cáncer hepático. La curación entendida como la RVS se define como un ARN del VHC (o antígeno del core del VHC) indetectable 12 semanas después del final del tratamiento. La eliminación del VHC se ha asociado a un mejor pronóstico desde el punto de vista hepático, con menor tasa de descompensaciones, menor necesidad de trasplante, desarrollo de hepatocarcinoma y disminución global de la mortalidad (42).

Así mismo, la curación del VHC se ha asociado a una mayor calidad de vida de los pacientes, además de ayudar a eliminar el estigma vinculado con la infección, y prevenir su transmisión.

La replicación viral y la organogénesis del VHC son exclusivamente citoplasmáticas, lo que facilita el uso de fármacos antivirales. A diferencia del VIH o del VHB, no hay reservorio, ADN proviral, microcromosomas ni integración genómica. Esto explica que con el tratamiento se pueda lograr una verdadera cura virológica.

El tratamiento del VHC ha experimentado importantes modificaciones con el tiempo. Inicialmente se basaba en la monoterapia con interferón-alfa, usado por sus propiedades antivirales y de estimulación inmune, logrando RVS en menos del 20% de los casos. Posteriormente se asoció ribavirina, un análogo de nucleósido, al tratamiento con interferón logrando aumentar la RVS a más de 40%. Finalmente, previo a la introducción de los nuevos AAD, se introdujo el interferón pegilado con ribavirina elevando la RVS por encima del 60%. Aún así, estos tratamientos ocasionaban numerosos efectos secundarios indeseables que impedían su administración a un número elevado de pacientes (9). En 2011 se aprobaron los dos primeros AAD, boceprevir y telaprevir, que actuaban como inhibidores de la proteasa pero tenían que ser combinados con interferón pegilado y ribavirina, no sólo no pudiendo eliminar los efectos secundarios sino en la mayoría de los pacientes empeorándolos (43). A partir de 2013 otros AAD fueron aprobados; la combinación de dos o tres AADs, sin necesidad de uso de interferón pegilado ni ribavirina, alcanzó tasas de curación de superiores al 90% (43). La limitada eficacia asociada a la mala tolerancia de los tratamientos basados en interferón explica que la aparición de los AAD, inhibidores específicos de proteínas virales, haya sido una verdadera revolución terapéutica.

La evolución en el conocimiento del ciclo replicativo del VHC ha permitido el desarrollo de los AAD que interfieren a distintos niveles del ciclo viral, progresos que fueron premiados con el premio Nobel de Medicina en el año 2020. Existen hasta la fecha tres grupos de AAD que se diferencian según la fase del ciclo sobre la que actúan: 1) inhibidores de la proteasa NS3/4A, 2) inhibidores de la polimerasa NS5B y 3) inhibidores del complejo de replicación NS5A (Tabla 1). Dada la alta tasa de mutaciones que presenta el VHC, un único AAD en monoterapia no puede emplearse como tratamiento por el alto riesgo de desarrollo de resistencias. Desde 2014, la combinación de 2-3 AADs ha sido usada para el tratamiento

permitiendo una alta tasa de RVS, con un perfil de seguridad muy favorable sin apenas efectos secundarios ni contraindicaciones para su uso. Durante los primeros años tras su introducción, varios regímenes han estado disponibles con diferentes tasa de eficacia según el genotipo del VHC (44,45). Sin embargo, desde el año 2017 existen los tratamientos pangenotípicos que permiten el tratamiento de todos los pacientes independientemente del genotipo del VHC. Estas combinaciones consisten en la toma de 1 a 3 cápsulas por día durante 8-12 semanas. Estos tratamientos presentan una tasa de RVS superior al 97% e incluyen la siguientes combinaciones: glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir (46–50).

Tabla 1. Tipos de AAD usados para el tratamiento del VHC.

Inhibidores de la proteasa NS3/4A	Inhibidores de la polimerasa NS5B	Inhibidores del complejo de replicación NS5A
Boceprevir	Sofosbuvir	Daclatasvir
Telaprevir	Dasabuvir	Elbasvir
Paritaprevir		Ledipasvir
Simeprevir		Ombitasvir
Asunaprevir		Velpatasvir
Grazoprevir		Pibrentasvir
Voxilaprevir		
Glecaprevir		

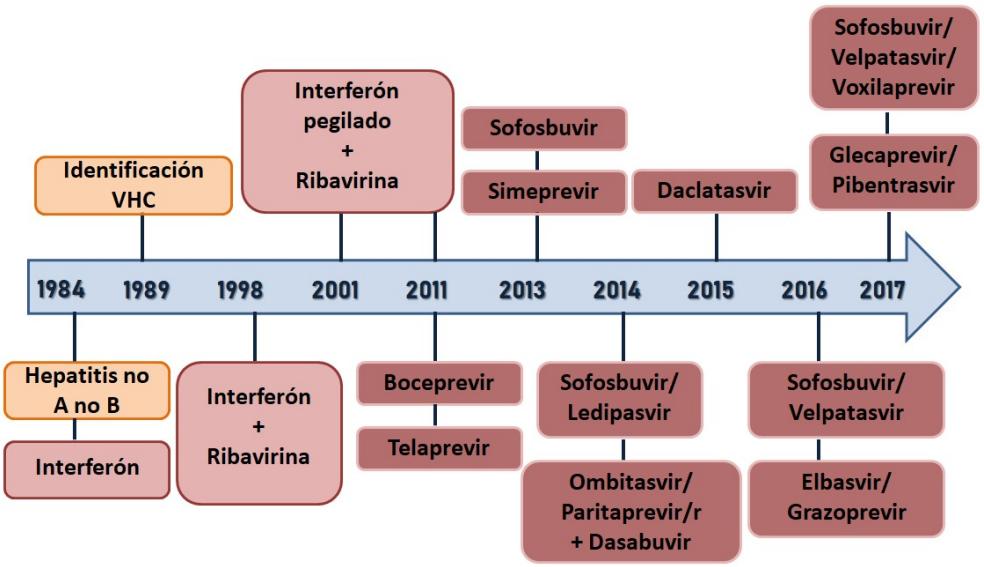

Figura 3. Línea temporal de la aparición de tratamientos para el VHC.

Desde la aparición de los AAD existen pocas contraindicaciones o limitaciones para el tratamiento del VHC. La principal contraindicación es debida a las interacciones farmacológicas (40). Las interacciones medicamentosas con los tratamientos antiepilépticos son especialmente importantes dado que la evidencia clínica ha demostrado que en algunos casos es imposible sustituir o discontinuar estos tratamientos. Los fármacos antiepilépticos (fenitoína, carbamazepina, oxcarbacepina, fenobarbital, eslicarbacepina, etc.) son potentes inductores del CYP/P-gp y pueden reducir significativamente las concentraciones plasmáticas de los AADs aumentando así el riesgo de fracaso terapéutico (40,51). Algunos de estos fármacos se usan para el tratamiento de la epilepsia pero también como tratamientos psicotrópicos.

Hasta la fecha existen muy pocos estudios de vida real que aborden este problema. Seyen et al. presentó una serie de casos que incluía 6 pacientes a los que se mantuvo el tratamiento antiepiléptico mientras recibían daclatasvir a dosis mayores de las habituales más sofosbuvir

(52). Los autores evidenciaron que las concentraciones plasmáticas tanto de daclatasvir como de sofosbuvir disminuían, siendo los niveles variables dependiendo de la dosis de AADs recibida y el fármaco antiepiléptico administrado. Todos los pacientes lograron alcanzar RVS. Otra serie de casos presentó cinco pacientes que alcanzaron RVS después de ser tratados con AADs a dosis estándares mientras recibían tratamiento antiepiléptico (53).

Otra contraindicación establecida de los AAD es el uso de aquellos que contienen inhibidores de la proteasa NS3-4A (grazoprevir, glecaprevir o voxilaprevir) en pacientes con cirrosis descompensada (Child-Pugh B o C) debido al aumento de la concentración del inhibidor de la proteasa y el riesgo potencial de toxicidad secundario (40).

Todos los pacientes con infección por VHC aguda o crónica independientemente de si han sido tratados con anterioridad deberían ser considerados como candidatos a tratamiento antiviral. Una limitación al tratamiento es la baja expectativa de vida al momento del diagnóstico de la infección por VHC de algunos pacientes (40). Desde la introducción de los AADs, el manejo de los pacientes con enfermedad hepática por VHC ha mejorado notablemente, permitiendo la cura de la infección por VHC en casi todos los casos independientemente del genotipo viral, el grado de fibrosis o la comorbilidad (43). Estas importantes mejoras en el tratamiento del VHC han propiciado que la Organización Mundial de la Salud (OMS) se haya marcado como objetivos el incrementar el diagnóstico, tratamiento y prevención de la enfermedad para lograr haber eliminado el VHC en el 2030 (54).

1.5 Epidemiología del virus de la hepatitis C

La prevalencia global de individuos con anticuerpos anti-VHC positivos se ha estimado del 1.6% (rango 1.3-2.1%) que corresponde a 115 millones de personas en todo el mundo (55).

La prevalencia global de personas con ARN VHC detectable se estima en un 1% (rango 0.8%-1.14%) lo que significa que hay 71 millones de personas infectadas por el VHC (56). La infección por VHC es la hepatitis viral más prevalente en los países occidentales y una causa importante de enfermedad crónica hepática (32). De hecho, es la primera causa de muerte por enfermedad hepática causando más de 670.000 muertes anuales a nivel mundial (57). Se calcula que solo en 2015 se produjeron más de 1.750.000 nuevas infecciones mayormente relacionadas con el uso de drogas por vía parenteral en los países desarrollados pero también a la falta de hemovigilancia en los países en vías de desarrollo (56). Existe una gran disparidad en la prevalencia entre las diferentes regiones. Las áreas más expuestas son Egipto y Mongolia con una prevalencia de anticuerpos anti-VHC del 15%. En estos países la contaminación se debe predominantemente a la causa nosocomial por la falta de hemovigilancia en Mongolia o al tratamiento sistemático de la esquistosomiasis sin material de un solo uso en Egipto (58). Estudios epidemiológicos recientes de la población adulta española han estimado que la prevalencia de la infección por VHC con ARN detectable es de 0.35%-0.41% (59,60), y el 29% de estos individuos desconocen estar infectados (61). Curiosamente, otro estudio realizado en Barcelona en 2020 que analizó la presencia de anticuerpos anti-VHC y ARN del VHC en todos los pacientes que acudían a urgencias y requerían una extracción sanguínea, determinó una prevalencia de anticuerpos anti-VHC del 4% y de ARN VHC del 0.7% (62). Estos datos traducen que la prevalencia real del VHC es difícil de cuantificar con exactitud y depende en gran medida de la población objeto de estudio.

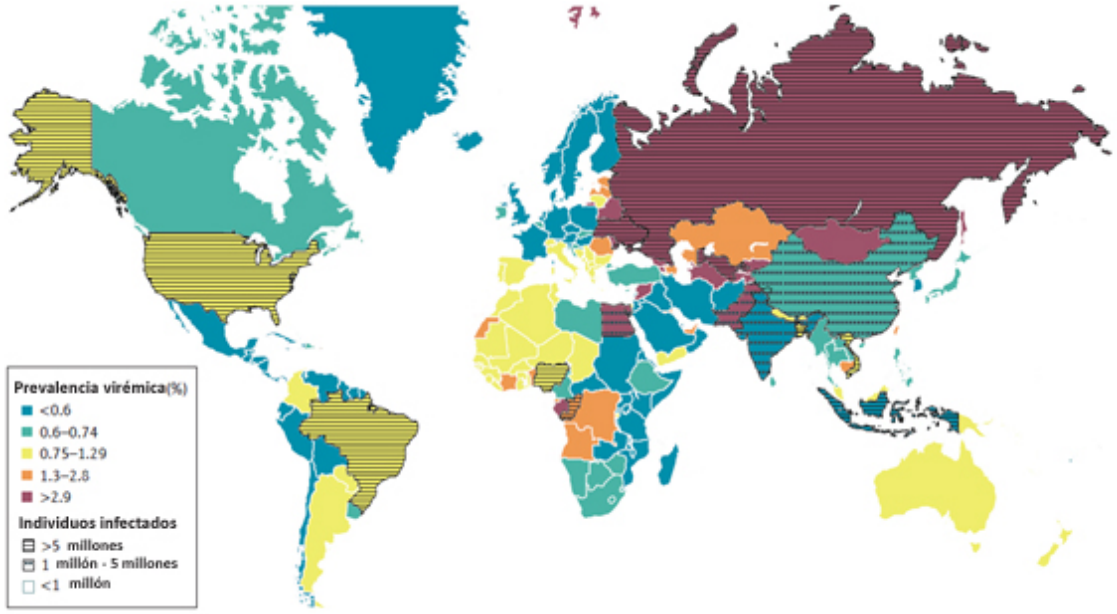

Figura 4. Prevalencia del VHC. Representación esquemática de la prevalencia de la infección por VHC con ARN detectable en 2015 y la extrapolación del número total de infectados por VHC por países. Adaptado de Manns MP, et al (43) y Polaris Observatory HCV collaborators (56).

La distribución por edad de la población con infección por VHC se correlaciona con la causa más habitual de contagio en cada país. En los países donde el uso de drogas por vía parenteral es un factor de riesgo importante, la mediana de edad de la población infectada se sitúa alrededor de los 35 años mientras que en los países donde el factor de riesgo predominante es la iatrogenia, la edad de las personas infectadas se sitúa entre los 50-60 años (63,64). Esta diferencia es debida a que los usuarios activos de drogas por vía parenteral son habitualmente jóvenes mientras que la mayoría de las infecciones iatrogénicas se produjeron antes de 1990, año en el que aparecieron los test diagnósticos contra el VHC. En algunos países en el que coinciden distintos factores de riesgo la distribución por edad es mixta.

1.6 Situación actual de la infección por hepatitis C en nuestro entorno

A pesar de que la eficacia y tolerancia al tratamiento antiviral ya no suponen una limitación, menos de un 1% de los pacientes infectados mundialmente han sido tratados (4.6% a nivel de la Unión Europea) y la mayoría ni siquiera saben que están infectados (65). Por lo tanto, en los últimos años, los esfuerzos en el ámbito del VHC se han centrado en mejorar el cribado, el acceso al tratamiento y disminuir el riesgo de nuevas infecciones. Teniendo en cuenta que no existe vacuna contra el VHC y, además, el hecho de que su único reservorio son las personas infectadas, resulta imprescindible la identificación de todos los sujetos infectados, como primer paso para luego tratarlos y lograr la curación del VHC, pasos que permitirían la reducción de la transmisión de la infección.

En nuestro contexto, los grupos más susceptibles de presentar altas prevalencias de infección por el VHC, y por tanto aquellas sobre las que se deberían focalizar las mejorías en el cribado, son (41):

- Personas nacidas entre 1950 y 1970, también conocidas como *baby boomers*, principalmente en caso de haber recibido transfusiones de sangre o hemoderivados antes de la década de los noventa (66).

- Personas que consuman drogas y compartan material para la inyección y, en menor grado, utensilios de consumo para fumar o esnifar. En la actualidad este grupo es el que tiene mayor riesgo de infección por el VHC (67).

- Personas internadas en prisión y con prácticas de riesgo (68).

- Personas que mantengan relaciones sexuales de riesgo, sin protección, especialmente los HSH, sobre todo si están coinfectadas por el VIH (69,70).

- Personas inmigrantes de países dónde la infección por VHC es endémica, como Egipto o Pakistán (71).

- Profesionales de la salud que hayan estado expuestos accidentalmente a sangre o hemoderivados de personas infectadas por el VHC (66).

- Bebés de madres infectadas por el VHC (72).

- Personas que acudan a centros sanitarios (odontológicos, estéticos, de acupuntura, podológicos, de tatuajes o piercings) donde no se cumplan los criterios de asepsia (66).

- Personas que compartan utensilios personales con pacientes infectados por el VHC, como, por ejemplo: cepillos de dientes, cuchillas de afeitar, cortaúñas, etc. (41).

- Personas con antecedentes de inyección de drogas o encarcelamiento (67,68).

De cara a evitar nuevas infecciones por el VHC, desde de los años 90 se realiza cribado de los hemoderivados para evitar la transmisión de la infección. Así mismo, se ha reducido considerablemente la transmisión de origen nosocomial con una correcta esterilización de material médico o con material de un solo uso. El origen actual de las nuevas infecciones procede de las poblaciones de mayor riesgo como los usuarios de drogas por vía parenteral, los HSH y los inmigrantes de países donde la infección es endémica.

En Europa y Estados Unidos el riesgo más elevado de infección por VHC corresponde al uso de drogas por vía intravenosa de forma no segura que representa el 50%-60% de las infecciones agudas por VHC (63,73,74). Aún así, en una proporción considerable de casos (de hasta el 40% en occidente) no se puede identificar un factor de riesgo en los pacientes infectados.

1.7 Trastorno por uso de sustancias y infección por hepatitis C

Los trastornos por uso de sustancias (TUS) designan al conjunto de síntomas somáticos, cognitivos y comportamentales que llevan al sujeto a autoadministrarse una sustancia de manera repetida, a pesar de reconocer las consecuencias negativas tanto orgánicas como

psicológicas y sociales que ello comporta. En el cerebro se producen cambios neurofisiológicos que se traducen en manifestaciones clínicas y conductas compulsivas que expresan una pérdida de la capacidad volitiva del sujeto (75). En España alrededor de un tercio de la población adulta admite haber consumido en algún momento de su vida alguna sustancia ilícita (Tabla 2) (76).

Tabla 2. Consumo de sustancias en la población española entre 15 y 64 años durante el año 2019/2020 (76).

Sustancia consumida	Vía de consumo	Consumo alguna vez en la vida	Consumo en el último mes
Cannabis	Fumada	37.5%	8%
Hipnosedantes	Oral	22.5%	8.6%
Cocaína en polvo	Inhalada, inyectada	10.9%	1.1%
Cocaína base	Fumada	1.4%	0.1%
Éxtasis	Oral, inhalada	5%	0.3%
GHB	Oral	0.9%	<0.1%
Anfetaminas	Oral, inhalada, inyectada	4.3%	0.3%
Metanfetaminas	Oral, inhalada, fumada, inyectada	1.2%	ND
Heroína	Inyectada, inhalada, fumada	0.7%	<0.1%

ND: dato no disponible

La infección por VHC es muy prevalente en pacientes con TUS, especialmente en aquellos con uso de drogas por vía inyectada (43,77,78). Se estima que en Europa de 2 a 3 millones de personas tienen historia de haber consumido drogas por vía inyectada y la prevalencia de anticuerpos anti-VHC en este colectivo es aproximadamente del 15% al 84% (79). Un estudio realizado en Cataluña mostró una prevalencia de anticuerpos anti-VHC del 79.8% en la población con uso de drogas por vía inyectada y una prevalencia de ARN VHC de 58.5% (80). Se dispone de poca información en población con uso de drogas no inyectadas. Un estudio realizado en 2001 que analizó 529 individuos con uso de drogas no inyectadas (heroína, cocaína o crack) evidenció una prevalencia de anticuerpos anti-VHC entre el 5% y el 29% según la zona del estudio (81).

Aproximadamente el 50-75% de los pacientes con TUS tienen comorbilidades con otros desórdenes psiquiátricos, una situación conocida como "patología dual" (82). El término de patología dual se usa para designar la co-ocurrencia de un TUS y al menos otro desorden psiquiátrico de forma independiente. Es necesario distinguir la patología dual de los desórdenes inducidos por sustancias. Si los síntomas del desorden psiquiátrico aparecen antes del TUS o después de un largo periodo de abstinencia el diagnóstico de patología dual debe considerarse (83). Estos individuos presentan un gran impacto social y clínico incluyendo un pronóstico más pobre y unos costes más altos en sanidad (82,84). En un estudio realizado en Estados Unidos en 2002, el 62% de 33,824 pacientes con infección por VHC tenían patología dual (85), pero hay poca información reciente al respecto. Los pacientes con patología dual presentan más conductas de riesgo que la población general por lo que tienen un riesgo considerable de infección por VHC. No hay estudios hasta la fecha para evaluar si la presencia de patología dual aumenta el riesgo de infección por VHC

en comparación con los pacientes con TUS. En esta línea, sería de gran utilidad identificar y analizar las barreras para acceder al tratamiento antiviral contra el VHC de esta población (77,86).

Los programas de cribado, tratamiento y prevención de la infección por VHC en los pacientes con TUS se centran principalmente en los sujetos con uso de drogas por vía intravenosa, sin incluir en la mayoría de los casos al resto de sujetos con TUS o con patología dual. Las recomendaciones de cribado en los pacientes con uso de drogas por vía intravenosa se basan en la alta prevalencia de infección por VHC, la demostración de que el conocimiento de su estado de infección induce cambios conductuales sostenidos que disminuyen el riesgo de transmisión (87,88), el potencial beneficio en salud pública de reducir la transmisión tratando a los potenciales transmisores (89–91) y los beneficios comprobados de la atención y el tratamiento para disminuir la morbilidad y mortalidad relacionadas con el VHC (28,92). Por todos estos motivos, la recomendación de cribado por el VHC en los pacientes con uso de drogas intravenosas es que se realice al menos una vez al año y tras los episodios de uso de drogas de alto riesgo (40).

Los estudios realizados con AAD pangenotípicos demuestran que estos tratamientos son eficaces y bien tolerados en pacientes con TUS, tanto con uso de drogas activo como pasado, incluyendo los pacientes que se encuentran en tratamiento sustitutivo con opiáceos (metadona, buprenorfina) (93–97). Las contraindicaciones para el uso de AADs en esta población son las mismas que las de la población general. A tener en cuenta las interacciones farmacológicas dado que los pacientes con TUS, sobre todo aquellos con patología dual, se encuentran frecuentemente bajo terapia con fármacos psicotrópicos (78,98).

En los sujetos con TUS existe un alto riesgo de reinfección por el VHC tras su eliminación o curación. Un metaanálisis mostró que el riesgo de reinfección por VHC fue de 5.9/100 personas-año entre las personas con uso recientes de drogas (por cualquier vía), 6.2/100 personas-año entre aquellos con uso reciente de drogas por vía intravenosa y de 3.8/100 personas-año entre aquellos en terapia con sustitutivos opiáceos. Un seguimiento a más largo plazo en el tiempo se asoció a un riesgo menor de reinfección hecho que sugiere que el riesgo de reinfección es más elevado los primeros meses post tratamiento (99).

A pesar de la buena tolerancia y eficacia de los AADs, las dudas sobre la adecuada adherencia a los AADs, el resultado terapéutico o el riesgo de reinfección posterior han obstaculizado la aceptación generalizada al tratamiento, hecho que suma una barrera más al correcto tratamiento y eliminación del VHC en esta población.

HIPÓTESIS

2 HIPÓTESIS

Los antivirales de acción directa contra la infección por el VHC son fármacos con elevada eficacia, bien tolerados y con escasas contraindicaciones, pero su acceso en los pacientes con trastorno por uso de sustancias es limitado. Este colectivo es en la actualidad uno de los reservorios del virus de la hepatitis C dado que presentan una prevalencia de infección más elevada y un acceso al sistema sanitario más restringido por la propia idiosincrasia de este grupo. Además, estos pacientes reciben habitualmente fármacos psicotrópicos. El tratamiento con dichos fármacos sigue siendo una de las pocas contraindicaciones que existen para el tratamiento del VHC con antivirales de acción directa.

Los factores anteriormente mencionados hacen necesario un abordaje especial de esta población.

Nuestra hipótesis sería que el desarrollo e implementación de un programa multidisciplinar y centralizado en el centro de atención y seguimiento (CAS) permitiría el cribado, diagnóstico y tratamiento del VHC en los individuos con trastorno por uso de sustancias (TUS). La centralización en el CAS, lugar que visitan a menudo por su adicción, permitiría la identificación, acceso al tratamiento y curación de los sujetos con infección crónica por VHC. Además, contribuiría a disminuir la prevalencia de infección por VHC en pacientes con TUS (tanto uso de vía parenteral como no uso de vía parenteral) que en este colectivo es más elevada que en la población general y disminuiría el riesgo de infección por VHC utilizando el tratamiento como prevención, en ausencia de una vacuna específica para la hepatitis C, evitando así reinfecciones.

OBJETIVOS

3 OBJETIVOS

El objetivo primario de esta tesis doctoral fue evaluar la utilidad de implementar un programa para el cribado, diagnóstico y tratamiento de la infección por el VHC centralizándolo en un CAS para facilitar la vinculación con el sistema sanitario de los pacientes con TUS. El programa se diseñó para acercar el sistema sanitario a este colectivo, de cara a valorar si de este modo se facilitaba el cribado, diagnóstico y tratamiento del VHC en esta población.

Objetivos secundarios:

1) Analizar las características de la población en términos sociodemográficos, psicológicos y de abuso de drogas así como evaluar la prevalencia de la infección por VHC.

2) Analizar la aceptación al tratamiento con AADs, su eficacia y contraindicaciones así como la adherencia al tratamiento antiviral en esta población.

3) Evaluar la adherencia al CAS y la incidencia de infección y reinfección por el VHC 18 meses después de la implementación del programa de cribado.

4) Analizar la eficacia y seguridad del tratamiento con AAD en combinación con fármacos antiepilépticos/psicotrópicos.

METODOLOGÍA

4 METODOLOGÍA

4.1 Primer estudio. Evaluar la utilidad de implementar un programa para el cribado, diagnóstico y tratamiento de la infección por el VHC centralizándolo en un CAS.

4.1.1 Diseño del estudio y pacientes

Estudio clínico prospectivo de cohortes diseñado para evaluar la atención en individuos con TUS o patología dual, incluyendo el cribado, diagnóstico y tratamiento con AAD del VHC dentro de los seis primeros meses después del diagnóstico. El estudio incluyó un seguimiento de 6 meses después de finalizar el tratamiento.

El estudio fue realizado en el CAS del hospital Vall d'Hebrón, Barcelona. A todos los individuos que acudieron al CAS desde noviembre 2018 a junio 2019 se les ofreció participar. Los criterios de inclusión fueron edad > 18 años y presentar TUS con o sin patología dual. Los criterios de exclusión fueron la presencia de deterioro cognitivo (basado en una puntuación de "mini-mental state examination" de < 27) o la presencia de barrera idiomática que interfiriera con la habilidad de entender el estudio. Haber sido diagnosticado o tratado previamente del VHC no fue un criterio de exclusión dado que la intención era estudiar las características de aquellos que se han infectado alguna vez *vs* los que nunca se han infectado. El proyecto (VHC-DAA-2018-01) fue aprobado por el comité ético del centro. Los participantes no recibieron ninguna compensación económica. Se obtuvo consentimiento informado escrito de todos los participantes.

4.1.2 Procedimiento

Después de firmar el consentimiento informado todos los participantes fueron sometidos a una evaluación psicológica para valorar la calidad de vida relacionada con la salud usando el cuestionario de salud Short-Form-36 Health Survey (SF-36), incluyendo la dimensión mental y física, y el estado de depresión con el inventario de depresión de Beck. Un psiquiatra recogió las características clínicas, sociodemográficas y adictivas de cada participante. A todos ellos se les realizó un análisis de sangre.

A los individuos con anticuerpos anti-VHC positivos y ARN VHC detectable se les realizó una evaluación clínica para la valoración de tratamiento del VHC en base a las recomendaciones de las guías internacionales. Si no presentaban contraindicación se les ofrecía tratamiento con AAD durante 8 o 12 semanas según el AAD elegido. Para facilitar el inicio y seguimiento del tratamiento con AAD, un hepatólogo se trasladaba al CAS dos veces por semana. De este modo visitaba a los pacientes y coordinaba su tratamiento con un equipo multidisciplinar que también incluía psiquiatras, psicólogos, enfermeras y asistentes sociales trabajando todos juntos para facilitar la vinculación del paciente con el sistema sanitario.

A los pacientes que aceptaban iniciar tratamiento con AAD se les facilitaba la medicación para las primeras 4 semanas. Posteriormente, eran citados cada 4 semanas en el CAS para ser visitados por el hepatólogo para asegurar la adherencia (determinada por el propio paciente), evaluar posibles efectos adversos y dispensar las 4 siguientes semanas de tratamiento con AAD. Al inicio de tratamiento y a cada visita se determinaban drogas en orina. Al finalizar tratamiento y a las 12 semanas tras finalizar el tratamiento los pacientes fueron visitados y se les realizó una analítica de sangre y un análisis de drogas en orina.

Dieciocho meses más tarde se contactó a todos los pacientes que aceptaron participar en el estudio en un primer momento para realizar una nueva analítica de cribado.

4.1.3 Instrumentos y variables

Características clínicas y sociodemográficas. Los datos sociodemográficos se recogieron al inicio (género, edad, nacionalidad, estado civil, vivienda, nivel educacional, empleo y antecedentes penales). En ese mismo momento se recogió también información clínica sobre antecedentes patológicos, TUS previo o actual (como alcohol, cannabis, benzodiacepinas, cocaína y heroína; vía de administración; edad de inicio del TUS; presencia de policonsumo definido como el consumo de tres o más sustancias) y tratamientos previos para el TUS. Los antecedentes familiares de TUS se excluyeron dado que se consideró que tenían escasa relevancia para el estudio actual. Se les preguntó a los pacientes si sabían si tenían o habían tenido alguna enfermedad infecciosa tal como VHC, VHB y VIH. La comorbilidad psiquiátrica con otros trastornos mentales (patología dual) fue evaluada por un psiquiatra y establecida por criterios clínicos siguiendo los criterios del DSM-5. Los trastornos mentales fueron agrupados en psicóticos, del ánimo, ansiosos y de personalidad. Todas las variables sociodemográficas y clínicas eran variables categóricas menos la edad.

Variables de laboratorio. Las analíticas de sangre incluyeron hemograma completo y un panel bioquímico estándar con perfil renal y perfil hepático. Se realizó un análisis no invasivo de fibrosis hepática mediante FIB-4 (basado en edad, número de plaquetas, AST y ALT). Los resultados del FIB-4 fueron interpretados según dos puntos de corte: <1.45 indicaba ausencia de cirrosis, >3.25 indicaba cirrosis, 1.45-3.25 fueron considerados no concluyentes. También se determinó el antígeno de superficie del VHB (HBsAg) y los anticuerpos contra el core del VHB (anti-HBc), anti-VIH y anti-VHC. Si los anticuerpos anti-VHC eran positivos se determinaba de manera refleja el ARN del VHC y el genotipo. El análisis de tóxicos en orina incluía benzodiacepinas, metadona, cocaína, opiáceos, anfetaminas y cannabis.

Cuestionarios para analizar depresión y calidad de vida. Se usó el inventario de depresión de Beck para analizar la presencia de síntomas depresivos durante las dos semanas previas. El inventario de depresión de Beck es un cuestionario que consta de 21 preguntas con respuestas múltiples. Un valor de 0 a 3 es asignado a cada respuesta. El punto de corte para síntomas depresivos es 10 y valores más altos se relacionan con mayor severidad de síntomas (100). El SF-36 se usó para medir la calidad de vida relacionada con la salud desde la perspectiva del paciente durante las últimas 4 semanas. Se calcularon dos dimensiones de calidad de vida relacionada con la salud: la mental y la física. Con el uso de algoritmos cada escala se transformó en una puntuación de 0 a 100, donde números más bajos indican mayor discapacidad.

4.1.4 Análisis estadístico

Se calcularon estadísticos descriptivos (media, desviación estándar, tablas de frecuencia) de las principales variables. Luego, los datos se analizaron a nivel bivariado. Se utilizó la prueba de chi-cuadrado para comparar variables categóricas y la prueba de la T de Student para variables continuas entre grupos clínicos. La prueba de chi-cuadrado no se consideró aplicable cuando una o más de las celdas tenían un recuento esperado <5.

Para reducir los resultados falsos positivos, se realizó la corrección de Bonferroni para múltiples pruebas según el número de pruebas en cada análisis bivariado para evitar el error tipo 1. Las variables que mantuvieron la significación estadística y se consideraron clínicamente relevantes se incluyeron en el análisis de regresión logística. Se utilizó un método de entrada condicional para seleccionar las variables en el modelo. Todas las hipótesis estadísticas fueron bilaterales y los valores de $p < 0.05$ se consideraron

estadísticamente significativos. Para todos los análisis se utilizó SPSS versión 20 (SPSS –inc., Armonk, NY, EE. UU.) para Windows.

4.2 Segundo estudio. Evaluar la interacción de AAD y fármacos antiepilépticos/psicotrópicos.

4.2.1 Diseño del estudio y pacientes

Descripción de pacientes con infección crónica por VHC que habían sido tratados con AAD a pesar de encontrarse en tratamiento con fármacos antiepilépticos/psicotrópicos. Los pacientes fueron buscados entre aquellos tratados en el hospital Vall d'Hebrón (Barcelona) y el hospital Marqués de Valdecilla (Santander). Se cruzaron bases de datos para identificar pacientes que habían recibido AAD y fármacos antiepilépticos/psicotrópicos alguna vez en la vida. De estos pacientes se seleccionaron los que cumplían los siguientes criterios de inclusión: sujetos adultos que habían recibido tratamiento concomitante con AAD y fármacos antiepilépticos/psicotrópicos y disponían de información sobre RVS.

4.2.2 Variables

Las variables obtenidas fueron edad del paciente; sexo; tipo, dosis e indicación de fármaco antiepiléptico/psicotrópico; tipo y tiempo de tratamiento con AAD; genotipo del VHC; presencia de cirrosis; niveles de ARN del VHC al inicio, final y 12 semanas post tratamiento.

RESULTADOS

5 RESULTADOS

5.1 Primer estudio. Evaluar la utilidad de implementar un programa para el cribado, diagnóstico y tratamiento de la infección por el VHC centralizándolo en un CAS.

5.1.1 Características de la muestra

Durante el periodo de reclutamiento, un total de 528 individuos acudieron al CAS y se les ofreció participar en el estudio. De éstos, se incluyeron 401 (75.9%) pacientes. Las razones para la exclusión fueron: negarse a participar en el estudio (n=86), negarse a la extracción de sangre (n=9), barrera idiomática (n=6) y presencia de deterioro cognitivo (n=26).

La muestra final de 401 participantes tenía una edad media de 45.4±11.5 años y 301 (75.1%) eran varones. En total, 253 participantes (63.1%) tenían patología dual y 148 (36.9%) tenían únicamente TUS sin comorbilidad psiquiátrica. Los TUS más frecuentes fueron alcohol (73.6%), cocaína (58.4%), cannabis (47.1%), heroína (38.2%) y benzodiacepinas (30.9%). Las características sociodemográficas, clínicas, psicométricas y terapéuticas de los pacientes con y sin patología dual se recogen en la Tabla 3. El grupo de pacientes con patología dual tenía un porcentaje más elevado de mujeres (32% vs 13%, p<0.001), españoles (87% vs 73%, p<0.001) y desempleados (80% vs 59%, p<0.001) con respecto a los pacientes sin patología dual. Además, este grupo tenía más antecedentes familiares de trastornos psiquiátricos (47% vs 20%, p<0.001), eran más dados al trastorno por uso de benzodiacepinas (38% vs 19%, p<0.001), habían requerido más tratamientos para el control del TUS (88% vs 74%, p<0.001) y habían sido hospitalizados en más ocasiones para desintoxicación (47% vs 18%, p<0.001). En general, los participantes con patología dual mostraron más síntomas

depresivos (según el inventario de depresión de Beck: 17 vs 11, p<0.001) y una peor calidad de vida relacionada con la salud, tanto en la dimensión física (p=0.02), como mental (p<0.001).

Las siguientes variables se asociaron de forma independiente a la presencia de patología dual: sexo femenino [Odds ratio (OR): 3.6], TUS por benzodiacepinas (OR 2.48), tratamientos previos para el control del TUS (OR 5.85), desempleo (OR 0.4) y la presencia de síntomas depresivos (OR 2.8) (Nagelkerke R^2=0.32; chi-cuadrado=64.27; p<0.001) (Tabla 4).

5.1.2 Hepatitis víricas e infección por VIH.

De entre los 401 participantes, 112 (27.9%) fueron positivos para anti-VHC y, de éstos, 42 (10.5% de la muestra) presentaron ARN VHC detectable. De los 70 participantes con serología anti-VHC positiva, pero ARN VHC indetectable, 34 (48.6%) habían sido tratados previamente para la infección por VHC. De los 42 participantes con ARN VHC detectable, ocho (19%) desconocían estar infectados. Los genotipos (GT) del VHC más prevalentes en los pacientes con ARN VHC detectable fueron GT1a (38.1%), GT3 (31%), GT1b (16.7%), GT4 (7.1%) y GT2 (2.4%).

De entre todos los participantes únicamente en 3 (0.75%) se detectaban HBsAg positivos. En total, en 44 (11%) se detectaron anticuerpos anti-VIH. Todos ellos ya habían sido diagnosticados previamente y 30 (68% de los infectados) estaban ya en tratamiento antirretroviral. La prevalencia de infección por VIH fue más elevada en el grupo de pacientes con patología dual (14.3% versus 5.4% p=0.007).

Tabla 3. Características basales de los participantes con y sin patología dual y seguimiento de aquellos con VHC.

	Total n=401	Sin patología Dual n=148	Patología Dual n=253	Valor *p*
Características sociodemográficas	**n(%)**	**n(%)**	**n(%)**	
Sexo masculino	301 (75%)	129 (87%)	172 (68%)	<0.001*,**
Edad media, años	45±12	45±12	46±11	0.69
Españoles	329 (82%)	108 (73%)	221 (87%)	<0.001*
Viven solos	126 (31%)	46 (31%)	80 (32%)	0.89
Educación primaria	225 (56%)	84 (57%)	141 (56%)	0.84
Desempleados	290 (72%)	87 (59%)	203 (80%)	<0.001*,**
Antecedentes penales	158 (39%)	54 (37%)	104 (41%)	0.36
Características del TUS				
Antecedentes médicos	273 (68%)	94 (64%)	179 (71%)	0.13
Historia psiquiátrica familiar	148 (37%)	29 (20%)	119 (47%)	<0.001*,**
Historia familiar de TUS	194 (49%)	66 (45%)	128 (51%)	0.30
Uso de opiáceos	152 (38%)	61 (41%)	91 (36%)	0.32
Uso de cocaína	233 (58%)	88 (60%)	145 (57%)	0.56
Uso de alcohol	292 (74%)	107 (74%)	185 (73%)	0.93
Uso de cannabis	187 (47%)	65 (45%)	122 (48%)	0.55
Uso de benzodiacepinas	123 (31%)	28 (19%)	95 (38%)	<0.001*
Uso de tabaco	319 (80%)	117 (79%)	202 (80%)	0.74
Policonsumo	195 (49%)	67 (46%)	128 (51%)	0.36
Uso de vía inyectada	93 (23%)	40 (27%)	53 (21%)	0.16
Uso de vía fumada	28 (7%)	8 (6%)	20 (8%)	0.32
Uso de vía esnifada	163 (42%)	57 (40%)	106 (44%)	0.16
Edad de inicio del TUS	21 ± 9	21 ± 9	21 ± 10	0.93
Historia de tratamiento				
Tratamiento médico previo para TUS	332 (83%)	109 (74%)	223 (88%)	<0.001*,**
Ingresos previos para deshabituación	146 (36%)	27 (18%)	119 (47%)	<0.001*,**
Características psicométricas				
Síntomas depresivos (BDI), media ± DS	15±10	11±9	17±10	<0.001*,**
Calidad de vida relacionada con la salud, dimensión física (SF-36)	46±11	48±10	45±11	0.02
Calidad de vida relacionada con la salud, dimensión mental (SF-36)	39±13	44±11	37±13	<0.001*
Marcadores serológicos				
Anti-VHC	112 (28%)	46 (31%)	63 (25%)	0.28
ARN VHC	42 (10%)	20 (14%)	22 (9%)	0.25
Anti-VIH	44 (11%)	8 (5%)	36 (14%)	0.007
Seguimiento de 42 pacientes ARN VHC positivo				
Pacientes que empezaron tratamiento	20 (47%)	8 (40%)	12 (60%)	0.34
Pacientes que finalizaron tratamiento	15 (78%)	6 (40%)	9 (62%)	N.A

Los datos están expresados como media±DS o como porcentaje (número)
* Estadísticamente significativo después de la corrección de Bonferroni. ** Estadísticamente significativo en el análisis multivariado.
Antecedentes médicos: cualquier antecedente médico reportado por el paciente (cardiovascular, endocrino, metabólico, renal, neurológico, etc.).
Policonsumo: Trastorno por uso de tres o más sustancias.
El trastorno por uso de sustancias engloba tanto el consumo activo como pasado.
La heroína y la cocaína pueden ser consumidas por vía inyectada, fumada o esnifada. El cannabis se consume fumado.

ARN, ácido ribonucleico; BDI, inventario de depresión de Beck (punto de corte para depresión, 10); N.A, chi-cuadrado no aplicable; TUS, trastorno por uso de sustancias; VHC, virus hepatitis C; VIH, virus de la inmunodeficiencia humana.

Tabla 4. Análisis multivariado para identificar factores independientemente asociados a patología dual.

A. Regresión logística en relación a la presencia de patología dual			Análisis bivariado	
	OR	IC 95%	OR No ajustado	IC 95%
Sexo femenino	3.6	1.5-8.5	3.1	1.8-5.4
Desempleado	0.4	0.2-0.8	0.4	0.2-0.6
Uso de Benzodiacepinas	2.5	1.1-5.4	2.5	1.5-4.1
Tratamiento médico previo para TUS	5.8	2.2-15.3	2.8	1.6-4.9
Síntomas depresivos (BDI)	2.8	1.5-5.4	2.8	1.7-4.7

El trastorno por uso de sustancias engloba tanto el consumo activo como pasado
BDI, inventario de depresión de Beck ; TUS, trastorno por uso de sustancias.

5.1.3 Resultados en relación a la presencia de anticuerpos anti-VHC.

Las características sociodemográficas, clínicas, psicométricas y terapéuticas en pacientes con y sin anticuerpos anti-VHC se presentan en la Tabla 5. No hubo diferencias significativas en la prevalencia de la infección por VHC en pacientes con o sin patología dual (9% vs 14%, p=0.25). Los pacientes con anticuerpos anti-VHC positivos tenían un nivel educacional más bajo (p=0.01) y un porcentaje más elevado de antecedentes penales (p<0.001). La infección por VIH era más frecuente en aquellos pacientes anti-VHC positivos (35.1% vs 1.7%, p<0.001). El TUS a cualquier sustancia, incluyendo uso de drogas no inyectadas (alcohol, cannabis, tabaco y benzodiacepinas), el policonsumo (p<0.001), el uso de drogas inyectadas (p<0.001) y una edad más joven al inicio del TUS (16±4 vs 23±10 años, p<0.001) se relacionó a un mayor riesgo de ser anti-VHC positivo. Además, la presencia de anticuerpos anti-VHC fue más común en participantes con TUS y trastornos de ansiedad (p=0.01) y personalidad

(p=0.01), en aquellos que habían recibido tratamientos previos para el control del TUS (p=0.007) y con ingresos previos para desintoxicación (p<0.001). Por lo que respecta a la lesión hepática, no se observaron diferencias significativas en los valores de FIB-4 en relación a la presencia de anti-VHC.

En el análisis multivariado, las siguientes variables se asociaron de forma independiente a la presencia de anticuerpos anti-VHC: el trastorno por uso de opiáceos (OR: 27.8), el trastorno por uso de cocaína (OR: 6.3), la presencia de antecedentes médicos (OR: 21.75), el antecedente de uso de drogas inyectadas (OR: 15) (Nagelkerke R^2=0.62, chi-cuadrado=303.69; p<0.001) (Tabla 6). Estos resultados deben ser tomados con precaución dado que puede haber colinealidad entre el trastorno por uso de opiáceos y el uso de drogas inyectadas. Aún así, ambas variables tienen relevancia clínica y por lo tanto se han mantenido en el modelo.

5.1.4 Infección por VHC y vinculación con el sistema sanitario.

De los 112 participantes con anticuerpos anti-VHC positivos 42 (37.5%) presentaban ARN VHC detectable. En la tabla 5 se resumen las principales diferencias observadas entre los sujetos con ARN VHC detectable o indetectable. La presencia de patología dual fue similar en ambos grupos (52% *versus* 63% p=0.28). Los pacientes ARN VHC detectable fueron más jóvenes (41.1±7.3 vs 46.1±8.3 años p=0.001), habían recibido menos tratamientos previos para el TUS (85.7% vs 98.6% p=0.01) y tenían valores de AST más elevados (72 IU/L vs 26IU/L p<0.001) que aquellos con ARN VHC indetectable. No hubo diferencias significativas entre estos grupos en el análisis multivariado. Se determinó el FIB-4 en todos los participantes, sin encontrar diferencias entre los dos grupos. En total 8 participantes con serología anti-VHC positiva presentaron valores de FIB-4 sugestivos de fibrosis avanzada (FIB-4 >3.25),

porcentaje que tendió a ser superior entre aquellos con viremia detectable (12% vs 4%, p=0.14). Ninguno de los sujetos tenía historia de descompensación hepática previa.

A pesar del manejo centralizado, únicamente 20 de los 42 pacientes candidatos a tratamiento, es decir, con ARN VHC detectable, acudieron a la primera visita con el hepatólogo. Los pacientes no acudieron por las siguientes razones: 11 perdieron el seguimiento médico, 6 volvieron a sus países de origen, 2 no quisieron ser tratados, 2 eran seguidos por hepatólogos en otros centros y 1 ingresó en prisión.

Al comparar aquellos pacientes ARN VHC detectable que no empezaron tratamiento con AAD con aquellos que sí lo hicieron, se evidenció que los pacientes que no lo iniciaron habían consumido más cocaína en el último mes (2.64±3.74 vs 0.55±1.8 g/semana; p=0.014), tenían un nivel académico más bajo (52.6% vs 22.7%; p=0.047) y tenían un nivel más alto de desempleo (26.3% vs 4.5% p=0.049). No se encontraron otras diferencias para ninguna de las demás variables sociodemográficas o clínicas.

Veinte pacientes iniciaron tratamiento con AAD para el VHC, pero uno se perdió en la semana 8 de tratamiento. De los 19 restantes, 17 tuvieron una elevada adherencia al tratamiento (>90%), uno suspendió el tratamiento 28 días antes de finalizarlo y otro se olvidó dosis durante un total de 6 días. Al final los 19 sujetos tratados terminaron el tratamiento con ARN VHC indetectable. La respuesta virológica sostenida (RVS) a la semana 12 se pudo evaluar en 15 casos y todos ellos alcanzaron RVS. Los 4 sujetos restantes, perdieron el seguimiento. En la figura 5 se muestra el diagrama de flujo de los pacientes diagnosticados, tratados y curados. En total se programaron 90 visitas hasta la semana 12 post-tratamiento. En 27 (30%) de estas visitas los pacientes no se presentaron o aparecieron algunos días después de la cita.

Tabla 5. Características basales de los participantes en relación a la presencia de anticuerpos anti-VHC o ARN VHC.

	Anti-VHC positivo n=112	Anti-VHC negativo n=289	*p*	ARN VHC detectable n=42	ARN VHC indetectable n=70	Valor *p*
Características sociodemográficas	n(%)	n(%)		n(%)	n(%)	
Sexo masculino	91 (81%)	210 (73%)	0.075	29 (69%)	62 (89%)	0.01
Edad media, años	44±8	46±13	0.18	41±7	46±8	0.001*
Españoles	86 (77%)	243 (84%)	0.09	27 (64%)	59 (84%)	0.02
Educación primaria	75 (67%)	150 (52%)	0.01	15 (36%)	22 (31%)	0.64
Desempleados	91 (81%)	199 (69%)	0.01	36 (86%)	55 (79%)	0.35
Antecedentes Penales	81 (72%)	77 (27%)	<0.001*	29 (69%)	52 (74%)	0.55
Trastorno por uso de sustancias						
Antecedentes médicos	104 (93%)	169 (59%)	<0.001*	39 (93%)	65 (93%)	1.00
Uso de opiáceos	104 (94%)	48 (17%)	<0.001*	39 (93%)	65 (93%)	1.00
Uso de cocaína	100 (90%)	133 (46%)	<0.001*	36 (88%)	64 (91%)	0.54
Uso de alcohol	67 (61%)	225 (78%)	<0.001*	24 (59%)	43 (62%)	0.69
Uso de cannabis	74 (67%)	113 (40%)	<0.001*	27 (66%)	47 (67%)	0.89
Uso de benzodiacepinas	60 (54%)	63 (22%)	<0.001*	19 (46%)	41 (59%)	0.21
Uso de tabaco	101 (90%)	218 (76%)	0.001*	35 (83%)	66 (94%)	0.06
Policonsumo	98 (88%)	97 (34%)	<0.001*	35 (85%)	63 (90%)	0.46
Uso de vía inyectada	81 (72%)	12 (4%)	<0.001*	32 (76%)	49 (70%)	0.48
Edad de inicio del TUS	16±4	23±10	<0.001*	16±4	17±5	0.65
Patología dual	66 (59%)	187 (65%)	0.28	22 (52%)	44 (63%)	0.28
Trastornos psicóticos	23 (21%)	42 (15%)	0.14	6 (14%)	17 (24%)	0.21
Trastornos del ánimo	31 (28%)	103 (36%)	0.13	11 (26%)	20 (29%)	0.79
Trastornos ansiosos	8 (7%)	57 (20%)	0.01	4 (10%)	4 (6%)	0.45
Trastornos de personalidad	24 (21%)	30 (10%)	0.01	9 (21%)	15 (21%)	1.00
Edad de inicio de los síntomas psiquiátricos	24±15	19±10	0.01	20±11	18±10	0.48
Historia de tratamiento						
Tratamiento médico previo para TUS	97 (87%)	235 (81%)	0.007	36 (86%)	69 (99%)	0.01
Ingresos previos para deshabituación	70 (63%)	119 (47%)	<0.001*	21 (50%)	37 (53%)	0.77
Características psicométricas						
Síntomas depresivos (BDI)	17±12	15±9	0.15	20±13	15±12	0.18
Calidad de vida relacionada con la salud, dimensión física (SF-36)	43±9	47±11	0.02	45±9	43±10	0.39
Calidad de vida relacionada con la salud, dimensión mental (SF-36)	33±10	39±10	0.57	33±10	40±12	0.02
Bioquímica y estimación de la lesión hepática						
AST	43±49	31±31	0.006	72±69	26±9	<0.001
ALT	42±49	27±19	<0.001*	76±64	21±17	<0.001
Plaquetas	225±67	258±72	<0.001*	225±72	226±65	0.94
FIB4	2±1	1±2	0.18	2±1	1±1	0.08
FIB4 > 3.25	8 (7%)	12 (4%)	0.23	5 (12%)	3 (4%)	0.14

* Estadísticamente significativo después de la corrección de Bonferroni.
Antecedentes médicos: cualquier antecedente médico reportado por el paciente (cardiovascular, endocrino, metabólico, renal, neurológico, etc.).
Policonsumo: Trastorno por uso de tres o más sustancias.
El trastorno por uso de sustancias engloba tanto el consumo activo como pasado.
FIB4>3.25 indica cirrosis

ALT, alanina aminotransferasa; ARN, ácido ribonucleico; AST, aspartato aminotransferasa; BDI, inventario de depresión de Beck (punto de corte para depresión, 10); TUS, trastorno por uso de sustancias; VHC, virus hepatitis C.
Los datos están expresados como media±DS o como porcentaje (número)

Tabla 6. Análisis multivariado para identificar factores independientemente asociados a presencia de anti-VHC positivos.

Regresión logística en relación a la presencia de anti-VHC positivos			Análisis bivariado	
	OR	IC 95%	OR No ajustado	IC 95%
Antecedentes médicos	21.7	6.7-70.3	9.2	4.3-19.7
Uso de opiáceos	27.8	9.5-80.9	64.1	29.3-140.3
Uso de cocaína	6.3	1.9-20.1	10.3	5.3-20.1
Uso de vía inyectada	14.9	5.7-39.1	64.8	31.6-132.7

Antecedentes médicos: cualquier antecedente médico reportado por el paciente (cardiovascular, endocrino, metabólico, renal, neurológico, etc.).
El trastorno por uso de sustancias engloba tanto el consumo activo como pasado

El único efecto adverso detectado durante el tratamiento contra la hepatitis C con AAD fue un ligero aumento en la ansiedad y astenia, pero ninguno de los pacientes requirió suspender la terapia antiviral ni modificar su tratamiento psiquiátrico concomitante.

A 15 pacientes se les realizó despistaje de tóxicos en durante el tratamiento con AAD. Once (73%) de ellos dieron positivo para metadona o benzodiacepinas, seis (40%) para metadona o benzodiacepinas junto con alguna droga ilegal (cocaína, opiáceos o anfetaminas) y tres (20%) únicamente para alguna droga ilegal.

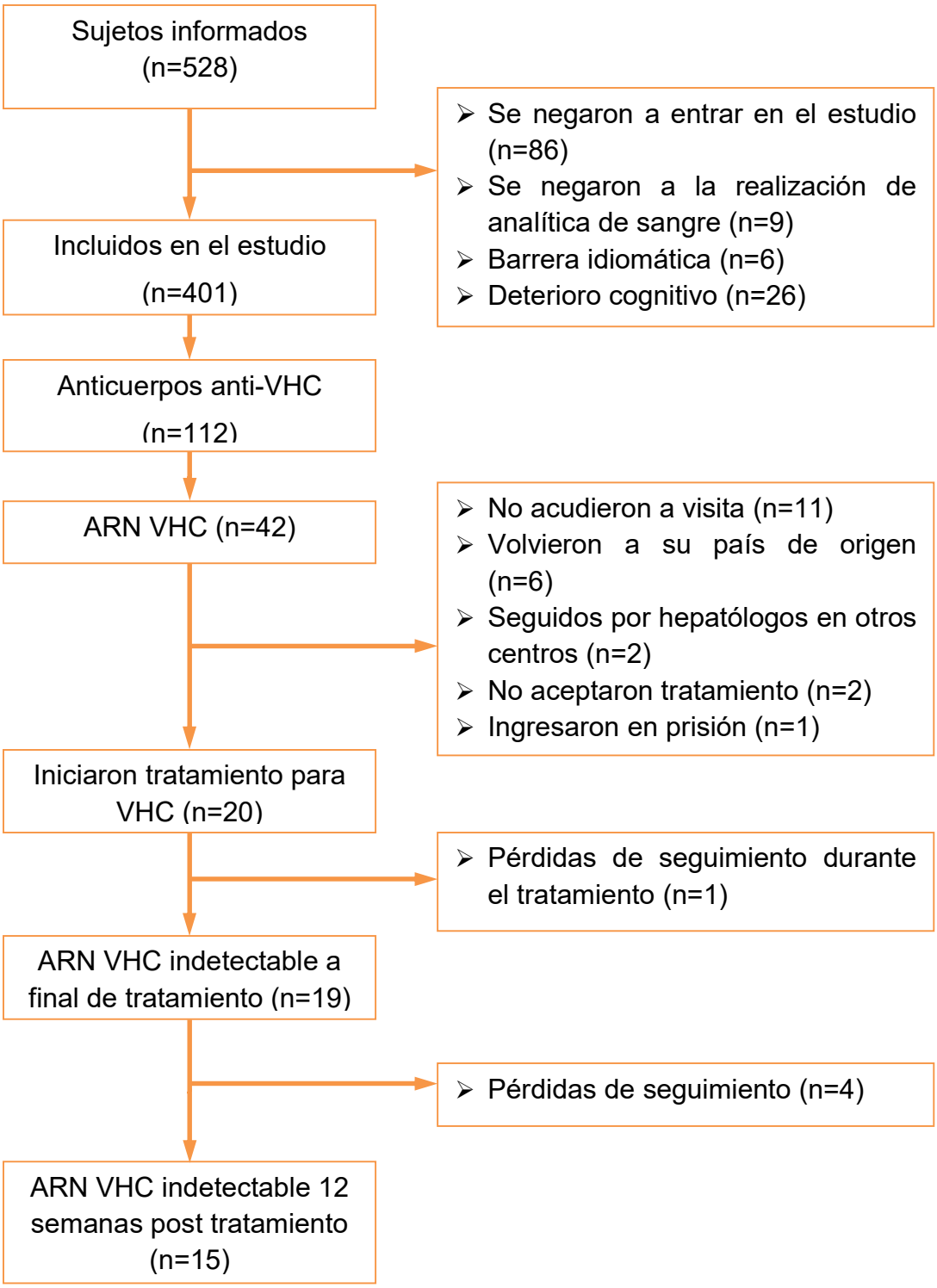

Figura 5. Diagrama de flujo de la participación en la primera parte del estudio.

5.1.5 Adherencia al CAS e incidencia de infección y reinfección por el VHC 18 meses después de la implementación del programa de cribado.

Dieciocho meses después de la implementación del programa de cribado (de Mayo 2020 en adelante) se intentó contactar con los 401 participantes del estudio. Únicamente 242 (60.3%) de ellos seguían adheridos al centro y 176 (72%) aceptaron ser cribados de nuevo para la hepatitis C. En total, 58 (33%) de los 176 sujetos presentaron serología positiva para el VHC. De estos 58, 56 ya eran previamente conocidos y dos casos fueron nuevos diagnósticos.

El ARN VHC se detectó en 6 (3.4%) pacientes, cuatro de ellos ya conocidos del primer cribado y no habían aceptado tratamiento, y dos (1.1%) eran nuevas infecciones. De los 15 pacientes tratados en la primera parte del estudio y que habían logrado RVS solo 8 seguían adheridos al centro y no se detectaron reinfecciones. Los resultados de este segundo estudio de cribado se muestran en la figura 6.

La adherencia al seguimiento en el CAS fue superior en los participantes de mayor edad (47±11 vs 44±12 años, p=0.02), en aquellos con uso de opiáceos (37% vs 24%, p=0.008) y en aquellos con uso de drogas inyectadas (27% vs 18%, p=0.03). También los participantes con consumo de cocaína fueron menos adherentes al CAS (37% vs 47%, p=0.049). Por el contrario, la presencia de patología dual mejoró la adherencia al seguimiento (69% vs 54%, p=0.003). La diferencia entre los sujetos que mantuvieron la adherencia al seguimiento en el CAS entre el primer y el segundo despistaje de infección por VHC se muestra en la tabla 7.

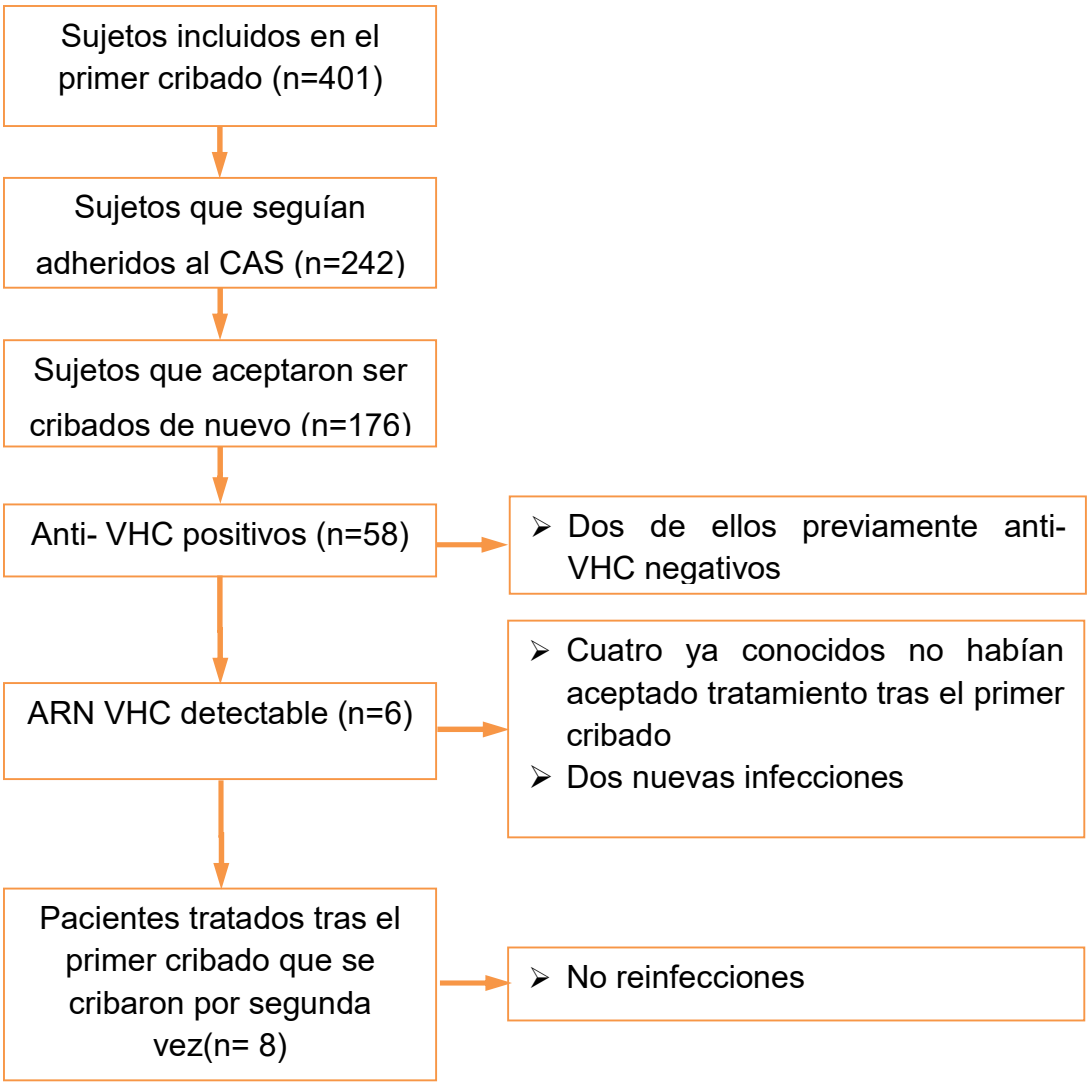

Figura 6. Diagrama de flujo de la participación en el estudio 18 meses más tarde.

Tabla 7. Características basales de los pacientes adherentes y no adherentes al CAS dieciocho meses después del estudio inicial.

	Adherentes n=242	No Adherentes n=159	Valor p
Características sociodemográficas	**n (%)**	**n (%)**	
Sexo masculino	176 (73%)	125 (79%)	0.151
Edad media, años	46.5 ± 11.1	43.6 ± 12.1	0.02*
Trastorno por uso de sustancias			
Uso de opiáceos	89 (37%)	38 (24%)	0.008*
Uso de cocaína	87 (37%)	74 (47%)	0.049*
Uso de alcohol	123 (51%)	95 (60%)	0.76
Uso de cannabis	46 (19%)	33 (21%)	0.622
Uso de benzodiacepinas	27 (11%)	13 (8%)	0.350
Policonsumo	118 (49%)	78 (49%)	0.906
Uso de vía inyectada	65 (27%)	28 (18%)	0.03*
Edad de inicio del TUS	21.5 ± 9.8	20.3 ± 8.9	0.231
Patología dual	167 (69%)	86 (54%)	0.003*
Trastornos del ánimo	94 (39%)	41 (26%)	0.007*
Trastornos psicóticos	46 (19%)	19 (12%)	0.043*
Trastornos ansiosos	39 (16%)	27 (17%)	0.921
Trastornos de personalidad	33 (14%)	20 (13%)	0.928

Los datos están expresados como media±DS o como porcentaje (número)
* Estadísticamente significativo después de la corrección de Bonferroni.
Policonsumo: Trastorno por uso de tres o más sustancias.
El trastorno por uso de sustancias engloba tanto el consumo activo como pasado.
TUS, trastorno por uso de sustancias.

5.2 Segundo estudio. Evaluar la interacción de AAD y fármacos antiepilépticos/psicotrópicos

Entre el hospital Vall d'Hebrón (Barcelona) y Marqués de Valdecilla (Santander) se identificaron un total de 334 pacientes que habían recibido tratamiento con AAD y fármacos antiepilépticos/psicotrópicos alguna vez en la vida. De entre ellos, 5 pacientes habían recibido concomitantemente ambos tipos de fármacos, a pesar de que la coadministración de estos fármacos no está recomendada debido a potenciales interacciones farmacológicas.

Todos los pacientes alcanzaron respuesta a final de tratamiento así como RVS a las 12 semanas. No se reportaron efectos adversos ni necesidad de modificación de dosis. Las características de estos 5 pacientes se resumen en la tabla 8.

5.2.1 Descripción de los casos

El paciente número 1 era un hombre de 40 años que recibía tratamiento con oxcarbazepina 300mg dos veces al día por un trastorno psicótico y de personalidad. Su psiquiatra consideró que parar el tratamiento no era adecuado debido a su labilidad. Otras medicaciones concomitantes: clorazepato 50mg al día, clotiapina 40mg al día, levetiracetam 500mg dos veces al día, zuclopentixol 25mg cuatro veces al día.

El paciente número 2 era un hombre de 39 años que recibía tratamiento con oxcarbazepina 600mg tres veces al día por epilepsia. El neurólogo intentó un cambio de oxcarbazepina a levetiracetam para evitar interacciones con los AAD, pero una semana después del cambio el paciente sufrió varias crisis comiciales por lo que se reinstauró el tratamiento previo con oxcarbazepina. No había otras medicaciones concomitantes.

El paciente número 3 era un hombre de 54 años en tratamiento con fenitoína 100mg dos veces al día por epilepsia, además de infección por VIH. El control de la epilepsia había sido complicado hasta que se inició la fenitoína por lo que, a pesar de que el neurólogo estaba dispuesto a intentar un cambio de medicación, el paciente se negó. Otras medicaciones concomitantes: dolutegravir 50mg al día, abacavir 60mg al día, lamivudina 300mg al día y clonazepam 0.5mg al día.

El paciente número 4 era un hombre de 38 años en tratamiento con oxcarbazepina 600mg dos veces al día por un trastorno psicótico y de personalidad. De nuevo, su psiquiatra consideró que parar el tratamiento no era adecuado debido a que la estabilidad del

paciente era muy lábil. Otras medicaciones concomitantes: clonazepam 2mg tres veces al día, paroxetina 20mg al día, perfenazina 8mg al día y quetiapina 200mg al día.

El paciente número 5 era un hombre de 43 años en tratamiento con eslicarbazepina 400mg tres veces al día por epilepsia. El neurólogo cambió el tratamiento con eslicarbazepina por brivaracetam para evitar interacciones con los AAD, pero debido a la aparición de efectos adversos al brivaracetam, se reinició la eslicarbazepina. Otras medicaciones concomitantes: topiramato 75mg dos veces al día, sertralina 100mg al día, clobazam 25mg al día, enalapril 20mg al día y bisoprolol 5mg al día.

Tabla 8. Características de los pacientes.

Pcte	Gen	Edad	FAE	Indicación FAE	G VHC	ARN VHC	Cirrosis	AAD	ARN VHC semana 4 tto	ARN VHC final tto	ARN VHC 12 semanas post tto
1	H	40	Oxcarbazepina 300mg BID	Psicotrópico	1b	10^6	No	GLE/PIB 8 semanas	10^4	indetec	indetec
2	H	39	Oxcarbazepina 600mg TID	Epilepsia	1b	10^8	No	LPV/SOF 12 semanas	10^1	indetec	indetec
3	H	54	Fenitoína 100mg BID	Epilepsia	4	10^6	Si	SOF/VEL 12 semanas	n.d.	indetec	indetec
4	H	38	Oxcarbazepina 600mg BID	Psicotrópico	3	10^4	No	SOF/VEL 12 semanas	n.d.	indetec	indetec
5	H	43	Eslicarbazepina 400mg TID	Epilepsia	3	10^6	No	GLE/PIB 8 semanas	indetec	indetec	indetec

BID, dos veces al día; FAE, fármaco antiepiléptico/psicotrópico; G, genotipo; Gen, género; GLE/PIB, glecaprevir/pibrentasvir; indetec, indetectable; LPV/SOF, ledipasvir/sofosbuvir; n.d., no disponible; Pcte, paciente; SOF/VEL, sofosbuvir/velpatasvir; TID, tres veces al día; tto, tratamiento.

DISCUSIÓN

6 DISCUSIÓN

Esta tesis doctoral describe el diseño e implementación de un programa multidisciplinar en el CAS del hospital Vall d'Hebrón para facilitar el acceso al sistema sanitario, cribado, diagnóstico y tratamiento de la infección por VHC de los pacientes con TUS, una población con un alto riesgo de infección por VHC y así poder conseguir el objetivo fijado por la OMS de eliminar el VHC con el consiguiente impacto en la reducción de la mortalidad asociada a esta infección.

El trabajo describe las características de estos pacientes y la experiencia en su cribado, diagnóstico y seguimiento. Se enfocó especialmente en determinar si había diferencias entre los participantes con únicamente TUS y aquellos con patología dual. Los resultados demostraron que la presencia de patología dual no aumenta el riesgo de infección por VHC ni interfiere con el acceso al sistema sanitario o con el tratamiento en comparación con aquellas personas que únicamente presentaban TUS. Las tasas similares de infección por VHC entre ambos grupos se podrían explicar si se tiene en cuenta que el principal factor para la adquisición de VHC es un comportamiento de riesgo relacionado con el uso de sustancias y no con la patología psiquiátrica (85,101). Los pacientes con patología dual representaron el 63% de la cohorte, un resultado similar al observado en otros estudios (102,103).

El cribado mostró que un 27.9% de los participantes presentaban anticuerpos anti-VHC y 10.5% de ellos tenían ARN VHC detectable. La prevalencia de ARN VHC detectable en el estudio en pacientes con TUS fue 20 veces más alta que la reportada en la población general española (59,60), pero más baja que la indicada en otros estudios de pacientes con TUS (54,81,104), mayormente debido a la alta representación de usuarios de drogas por vía

parenteral en los otros estudios. No se encontraron diferencias en la prevalencia de ARN VHC detectable entre los pacientes con patología dual y aquellos con solo TUS.

En el estudio, los pacientes ARN VHC detectable fueron más jóvenes y habían recibido menos tratamientos previos para el control del TUS que aquellos con viremia indetectable. La explicación para estos resultados podría ser que los pacientes de más edad han tenido más oportunidades de entrar en contacto con el sistema sanitario y ser diagnosticados y tratados de sus enfermedades (105). Los ingresos hospitalarios ofrecen una oportunidad para vincular estos pacientes al sistema sanitario y por lo tanto al diagnóstico y tratamiento del VHC, como ha sido demostrado en otros estudios (106).

Con la introducción de los AAD y su elevada efectividad y seguridad, el principal problema en la población con VHC es el acceso al sistema sanitario, un reto bien ilustrado con los resultados de este estudio. Como se ha evidenciado, el diagnóstico y manejo de la infección por VHC sigue siendo difícil en los pacientes con TUS a pesar del uso de un programa centralizado y multidisciplinar para acercarse más al paciente. A todas las personas de la cohorte se les ofreció cribado del VHC mediante la realización de una analítica de sangre con determinación refleja del ARN VHC. La necesidad de realizar una analítica en algunos casos fue el motivo para declinar la participación en el estudio (7% de aquellos que rechazaron cribado). Aunque el porcentaje no es muy elevado, éste es un factor modificable que se puede mejorar. El uso de métodos alternativos como los test en sangre seca han demostrado una alta sensibilidad y especificidad (80,107) y podría ser una manera de incrementar las tasas de cribado en poblaciones difíciles, como los sujetos con TUS.

La falta de cribado es la primera barrera contra la erradicación de la infección por VHC y puede ser uno de los obstáculos más importantes para lograr los objetivos de la OMS (65). En España, el porcentaje de pacientes con ARN VHC detectable en la población general que

desconocen estar infectados por el VHC se ha estimado del 29.4% (108). Otros estudios realizados en pacientes con TUS han descrito que entre el 35% y el 43% de ellos desconocen estar infectados (80,109). En la muestra del estudio de este trabajo, únicamente un 19% de los pacientes con viremia detectable desconocían estar infectados. A pesar de que esto es una mejora, todavía existe un reservorio considerable de infección potencialmente transmisible que tiene que ser diagnosticada. Un cribado etario que incorpore la determinación de anticuerpos anti-VHC y ARN del VHC reflejo en aquellas personas a las que se les realiza una analítica de sangre por otros motivos en urgencias o en consultas externas podría tener valor para mejorar la tasa de cribado. Un estudio realizado en las urgencias del hospital Vall d'Hebrón (Barcelona) entre 2020 y 2021 cribó 13479 pacientes y vinculó al sistema sanitario aquellos pacientes con ARN VHC detectable para ser tratados. Este estudio demostró que el cribado en urgencias era coste-efectivo, logrando reducir la mortalidad relacionada con el hígado en un 56% y evitar complicaciones hepáticas en un 50%-67% con un ahorro de costos relacionados de 247,942€ (110).

Las dificultades de acceso al sistema sanitario y al tratamiento evidenciadas en este trabajo han sido descritas también en otros estudios, donde el desempleo y especialmente el bajo nivel educacional se han asociado a unas tasas más bajas de adherencia al sistema sanitario (111–113). En esta cohorte, estos factores así como el consumo de altas cantidades de cocaína fueron más frecuentes en los participantes que rechazaron tratamiento con AAD que en aquellos que lo aceptaron. Estos hallazgos no son sorprendentes dado que los usuarios de cocaína son más compulsivos y suelen tener adicciones más severas que les llevan a resultados clínicos más pobres (114). Por otro lado, un bajo nivel educativo interfiere en el uso de recursos y disminuye la conciencia de cualquier riesgo (115).

En España, el sistema sanitario es universal y está financiado públicamente por lo que todos sus ciudadanos tienen derecho al diagnóstico y tratamiento. Teniendo esto en cuenta, el bajo porcentaje de pacientes con TUS que inician tratamiento para el VHC es todavía más preocupante. De los 42 pacientes con ARN VHC detectable elegibles para tratamiento con AAD, 20 (47.6%) fueron tratados: 15 (36%) lograron RVS y 5 se perdieron durante el seguimiento. Estos resultados se asemejan a los descritos en otro estudio realizado en nuestro país que evaluaba la aceptabilidad del tratamiento del VHC dentro de un programa de tratamiento de opiáceos, donde el 38% de 249 pacientes elegibles para tratamiento con AAD alcanzaron RVS (98). Estos resultados indican que el inicio y la adherencia al tratamiento en estos pacientes debería mejorar con un seguimiento más estrecho y programas motivacionales, pero también tiene que ir acompañado de esfuerzos preventivos como programas educacionales, asesoramiento y programas de intercambio de jeringuillas (116).

Por lo que respecta al tratamiento con AAD, se ofreció tratamiento y se trataron pacientes tanto con consumo activo de drogas como con consumo previo. Únicamente el consumo de cocaína en el último mes se asoció a una menor tasa de inicio de AAD, no observándose diferencias con el consumo de otras drogas, la vía de consumo o la presencia de patología dual. El único efecto adverso detectado durante el tratamiento del VHC con AAD fue un ligero aumento en la ansiedad y astenia, hechos que no modificaron el curso de tratamiento con AAD ni obligaron a cambiar el tratamiento psiquiátrico de base. Dichos resultados están en línea con los evidenciados en otros estudios en los que la presencia de consumo activo de drogas no influye en la adherencia al tratamiento, en la RVS, ni en la aparición de eventos adversos en comparación con aquellos con consumo pasado de drogas (96).

Dieciocho meses después del primer cribado, se contactó nuevamente con los 401 participantes iniciales, para realizar un re-cribado y determinar el grado de adherencia al CAS y la incidencia de nuevas infecciones y reinfecciones por VHC. Con este seguimiento se observó que, a pesar de usar un modelo centralizado en el CAS para el cribado, diagnóstico y tratamiento, una alta proporción de pacientes con TUS no aceptaron ser cribados. Esta baja tasa de cribado es un problema importante dado que la prevalencia e incidencia de VHC sigue siendo alta en esta población, por lo que se debe incrementar y dirigir los esfuerzos para crear nuevas formas de micro-eliminación. Como se ha comentado antes, el uso de métodos como los test en sangre seca han demostrado una alta sensibilidad y especificidad (80) pero se tiene que encontrar la manera de acercarlos a los pacientes dado que la adherencia al CAS mostró una tasa de abandono del 40% en nuestro estudio. Una alternativa podría ser la promoción del autocribado con la posibilidad de que las personas pudieran auto-testarse. Reconocemos que el grado de abandono pudo verse aumentado por la pandemia de SARS-CoV2, pero a los pacientes se les dio todas las facilidades para mantenerse en contacto con el CAS durante esa época. La adherencia fue inferior en aquellos sujetos más jóvenes y en los consumidores de cocaína, nuevamente por tratarse de pacientes más compulsivos y con adicciones más severas (114). Por otro lado, aquellos en tratamiento médico (por estar en tratamiento sustitutivo de opiáceos o en tratamiento psiquiátrico por patología dual) presentaron unas tasas de adherencia al CAS más elevadas durante el seguimiento.

Entre los pacientes que acudieron para inicio de tratamiento con AAD, ninguno de ellos presentaba interacciones farmacológicas que contraindicaran el tratamiento. Aún así y dado que esta población es propensa al uso de fármacos antiepilépticos/psicotrópicos, hecho que sigue siendo todavía una de las pocas contraindicaciones para el uso de AAD (40), se realizó

una búsqueda activa de pacientes tratados con AAD y fármacos antiepilépticos/psicotrópicos de forma concomitante en nuestro entorno. Datos recientes en la literatura demuestran que la polifarmacia y las interacciones farmacológicas continúan siendo un problema importante incluso con los AAD más recientes (117–119). Un estudio observacional, retrospectivo, de cohortes evaluó las medicaciones concomitantes y las interacciones farmacológicas en 3,181 pacientes con infección por VHC tratados con AAD pangenotípicos (117). Con la ayuda de la herramienta para evaluar interacciones creada por la universidad de Liverpool, los autores clasificaron las interacciones farmacológicas en interacciones potenciales (18.1%), interacciones débiles (4.8%) y interacciones que suponían contraindicación (1.8%), en todos los casos con fármacos para tratamiento de patologías cardiovasculares o del sistema nervioso central. Evidenciaron que un 4.2% de los pacientes tuvieron que discontinuar su tratamiento de base durante el tratamiento con AAD. Por lo tanto, las interacciones medicamentosas forzaron la suspensión de tratamientos crónicos en un porcentaje elevado de pacientes y eso no siempre es posible, especialmente en aquellos tratados con fármacos antiepilépticos/psicotrópicos. En nuestra cohorte se encontraron cinco pacientes que habían sido tratados con AAD concomitantemente con fármacos antiepilépticos/psicotrópicos a pesar de las formales contraindicaciones. Todos ellos lograron RVS sin la necesidad de modificar dosis y sin desarrollar efectos adversos. Dado que la información de estos casos se obtuvo de las historias clínicas no se dispone de las concentraciones plasmáticas de AAD ni de niveles seriados del ARN del VHC. Aún así, estos casos reportados indican resultados alentadores para el tratamiento del VHC en pacientes en tratamiento con fármacos antiepilépticos/psicotrópicos.

Esta tesis tiene algunas limitaciones. Una de ellas es el pequeño porcentaje de participantes con ARN VHC detectable, hecho que ha limitado el poder estadístico de algunos análisis.

Como el estudio se realizó dentro de la práctica clínica diaria, la muestra contenía usuarios de drogas tanto por vía inyectada como no inyectada y pacientes previamente tratados para el VHC, pudiendo explicar todos estos factores el bajo porcentaje de pacientes virémicos. Otra limitación fue que el tratamiento con AAD no se pudo iniciar en la mitad de los pacientes con ARN VHC detectable, hecho mayormente debido a la pérdida de seguimiento. Además, el registro de algunas características sociodemográficas y clínico-epidemiológicas de los participantes se baso en autoinformes, por lo tanto, podría existir algún sesgo de recuerdo. Por otro lado, el estudio de las interacciones farmacológicas con fármacos antiepilépticos/psicotrópicos se ha basado en una búsqueda retrospectiva entre todos los pacientes tratados con AAD de dos grandes hospitales por lo que no se dispone de datos prospectivos ni se han podido analizar niveles plasmáticos de AAD ni la cinética del ARN de VHC, dado que no se realiza en la práctica clínica habitual. Además, dado que el tratamiento concomitante de estos fármacos con los AAD está contraindicado ha sido difícil encontrar un elevado número de pacientes.

Los puntos fuertes de esta tesis incluyen el diseño prospectivo del primer estudio, en un escenario real de práctica clínica diaria, con un elevado número de participantes de una unidad especializada así como su posterior seguimiento dieciocho meses después. La muestra incluye pacientes con TUS, tanto por vía inyectada como por vía no inyectada, así como pacientes con patología dual, población con escasa representación en la literatura. Además, se realizó un manejo centralizado en el CAS con un equipo multidisciplinar que permitió a los participantes un acceso más completo y especializado a diferentes niveles, a pesar de que dicho manejo no logró unas altas tasas de tratamiento. La evaluación incluyó datos de las características psiquiátricas analizadas por personal experto mediante escalas validadas. Las variables relacionadas con el VHC fueron bien documentadas por análisis de

laboratorio fiables. Por otro lado, una búsqueda exhaustiva retrospectiva, ha permitido identificar pacientes que han recibido tratamiento concomitante con AAD y fármacos antiepilépticos/psicotrópicos, a pesar de las contraindicaciones, demostrando en todos los casos la curación de la infección. Estos resultados son prometedores y permitirán tratar a estos pacientes.

CONCLUSIONES

7 CONCLUSIONES

1. Los resultados de esta tesis evidencian que, a pesar de implementar un programa para el cribado, diagnóstico y tratamiento de la infección por el VHC centralizada en un CAS, siguen existiendo importantes barreras para la atención de la infección por el VHC. Las barreras identificadas están relacionadas con el cribado precoz y acceso al tratamiento, factores que dificultan la eliminación del VHC en este grupo.

2. Más de la mitad de los participantes en el estudio tenían patología dual, característica que no parece aumentar el riesgo de infección por VHC ni interfiere con el acceso al sistema sanitario o con el tratamiento del VHC en relación a los pacientes con TUS.

3. La prevalencia de anticuerpos anti-VHC en la cohorte fue del 27.9% y de ARN VHC detectable en un 10.5%, prevalencia 20 veces más alta que la reportada en la población general. Los pacientes ARN VHC detectable eran más jóvenes y habían recibido menos tratamientos previos para el control del TUS en comparación con aquellos con ARN VHC indetectable, si bien no hubo diferencias significativas en el análisis multivariado.

4. La aceptación del tratamiento fue relativamente baja, menos de la mitad de los pacientes elegibles iniciaron tratamiento a pesar de las facilidades. El desempleo, el bajo nivel educacional y el consumo de cocaína impactaron negativamente en el inicio del tratamiento. En aquellos que iniciaron el tratamiento la adherencia fue relativamente buena (75%) y no se evidenciaron efectos adversos. Una barrera al tratamiento del VHC, especialmente en los pacientes con patología psiquiátrica y dual, son las interacciones entre los AADs y los fármacos antiepilépticos/psicotrópicos, ampliamente usados en esta población. Los hallazgos descritos en esta tesis muestran que en algunas situaciones el tratamiento es posible con elevadas tasas de curación.

5. La adherencia al CAS durante el seguimiento fue del 60%. Se observó que 4 de cada 10 participantes abandonaron el seguimiento, principalmente sujetos más jóvenes y los consumidores de cocaína.

6. En conclusión, la dificultad para el cribado y el acceso al sistema sanitario y tratamiento para el VHC así como las interacciones farmacológicas son los obstáculos principales para la eliminación del VHC en la población con TUS. Es crucial abordar estas barreras para lograr los objetivos de la OMS para la eliminación del VHC.

LÍNEAS DE FUTURO

8 LÍNEAS DE FUTURO

Para lograr el objetivo de la OMS de eliminar el VHC es importante abordar las barreras identificadas en el cribado y tratamiento de las poblaciones con mayor prevalencia de VHC, como son los pacientes con TUS, dado que estas poblaciones representan el reservorio de la infección.

Sobre el cribado de los pacientes, existen en la actualidad test rápidos de diagnóstico de la infección por VHC que no requieren de venopunción ni de la presencia cercana de un laboratorio. Es necesario normalizar el uso de estos test en los sitios de mayor afluencia de las poblaciones de riesgo: CAS, puntos de administración de metadona, centros penitenciarios, centros de atención de enfermedades de transmisión sexual y centros de atención al inmigrante, entre otros. Además, se debería valorar la necesidad y coste-efectividad de la implementación de un programa de cribado universal, dado que ha quedado demostrado que hay un amplio número de sujetos que desconocen estar infectados.

Si se logra el cribado y diagnóstico de la infección por VHC de forma descentralizada, es necesario también acercar el tratamiento al paciente para favorecer su inicio y evitar así su pérdida en el sistema. Para ello, es necesario que el tratamiento con AAD deje de ser de prescripción hospitalaria y limitado a ciertos especialistas dado que existen en la actualidad tratamientos pangenotípicos que han demostrado ser seguros y eficaces en la gran mayoría de los pacientes infectados. Únicamente deberían de ser remitidos al especialista aquellos pacientes con interacciones farmacológicas o con enfermedad hepática crónica avanzada.

Estos esfuerzos en el cribado y tratamiento deben ir acompañados de programas para evitar la transmisión del virus. Para ello es necesario concienciar a la población con programas

educacionales, centros de reducción de daños y programas de intercambio de jeringuillas entre otros.

Otra barrera sobre la que es necesario actuar es la persistencia de algunas interacciones farmacológicas que todavía contraindican el tratamiento con AAD. Estudios farmacocinéticos y de vida real son necesarios para guiar a los clínicos en el tratamiento de los pacientes con interacciones medicamentosas.

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ANEXOS

10 ANEXOS

10.1 Artículos científicos derivados de esta tesis doctoral

10.1.1 Barriers to linkage to care in hepatitis C patients with substance use disorders and dual diagnoses, despite centralized management.

Grau-López L, **Marcos-Fosch C**, Daigre C, Palma-Alvarez RF, Rando-Segura A, Llaneras J, et al. Barriers to linkage to care in hepatitis C patients with substance use disorders and dual diagnoses, despite centralized management. Therap Adv Gastroenterol [Internet]. 2021;14:17562848211016564.

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Barriers to linkage to care in hepatitis C patients with substance use disorders and dual diagnoses, despite centralized management

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Abstract

Background: Hepatitis C virus (HCV) management is a challenge in patients with substance use disorder (SUD). This study aimed to describe an HCV screening and linkage to care program in SUD patients, and analyze the characteristics of this population in relation to HCV infection, particularly the impact of psychiatric comorbidities (dual diagnosis).

Methods: This study was a prospective clinical cohort study using a collaborative, multidisciplinary model to offer HCV care (screening, diagnosis, and therapy) to individuals with SUD attending a dedicated hospital clinic. The characteristics of the participants, prevalence of HCV infection, percentage who started therapy, and adherence to treatment were compared according to the patients' consumption characteristics and presence of dual diagnosis. HCV screening, diagnosis, treatment initiation, and sustained virologic response were analyzed.

Results: 528 individuals attended the center (November 2018–June 2019) and 401 (76%) accepted screening. In total, 112 (28%) were anti-HCV-positive and 42 (10%) had detectable HCV RNA, but only 20 of the latter started HCV therapy. Among the 253 (63%) patients with a dual diagnosis, there were no differences in HCV infection prevalence *versus* patients with SUD alone ($p = 0.28$). Dual diagnosis did not lead to a higher risk of HCV infection or interfere with linkage to care or treatment.

Conclusion: This study found a high prevalence of dual diagnosis and HCV infection in SUD patients, but dual diagnosis was not associated with an increased risk of acquiring HCV or more complex access to care. Despite use of a multidisciplinary management approach, considerable barriers to HCV care remain in this population that would need more specific focus.

Keywords: addiction and dual diagnosis center, direct-acting antiviral agents, dual diagnosis, Hepatitis C virus, substance use disorder

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Introduction

Hepatitis C virus (HCV) is the most prevalent viral hepatitis in Western countries and a major cause of chronic liver disease.[1] Recent epidemiological studies in the adult population of Spain have estimated that the prevalence of HCV infection with detectable HCV RNA is between 0.35% and 0.41%,[2,3] and around 29% of these individuals are unaware of their infection.[4] Since the introduction of oral direct-acting antiviral agents

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(DAAs) the clinical care of patients with HCV-related liver disease has advanced considerably, enabling HCV cure in almost all cases regardless of viral genotype, degree of liver fibrosis, or comorbidity.[5] These huge improvements in HCV treatment have led the World Health Organization (WHO) to encourage elimination of HCV infection by 2030 by increasing the diagnosis, therapy, and prevention of this condition.[6]

HCV infection is highly prevalent in people with substance use disorders (SUDs), especially those with a history of injecting drugs.[5,7,8] An estimated 2 or 3 million individuals have a history of injecting drug use in Europe alone, and their anti-HCV antibody prevalence ranges from 15% to 84%.[9] A study in people who inject drugs in Catalonia (Spain) showed an overall HCV seroprevalence of 79.8%, and viremic infection in 58.5%.[10] However, there is little updated information for individuals using non-injected drugs. A study conducted in 2001 reported that the prevalence of anti-HCV antibodies in a sample of 529 non-injecting drug users (heroin, cocaine, or crack) ranged from 5% to 29%.[11]

Approximately 50–75% of individuals with SUDs have comorbidities with other psychiatric disorders, a situation known as dual diagnosis.[12] These individuals report a greater social and clinical impact, including a poorer prognosis and higher healthcare costs.[12,13] In a study performed in the United States in 2002, 62% of 33,824 patients with HCV infection had dual diagnosis,[14] but there is little recent information in this line. Dual diagnosis patients engage in more risky behaviors than the general population and have a higher probability of reinfection; hence, they are at considerable risk for HCV infection. Barriers to starting therapy in this population must be understood to improve HCV care and achieve HCV elimination.[7,15]

Considering the above and the limited available data on HCV in non-injecting drugs users and dual diagnosis patients, the objective of this study was to describe an HCV screening, diagnosis, and treatment program to facilitate linkage to care in all patients with SUDs attending a dedicated addiction and dual diagnosis center (ADDC). The characteristics of the participating individuals, the prevalence of HCV infection, the percentage of patients who started HCV therapy, and adherence to treatment were investigated in those with and without a dual diagnosis.

Methods

Study design and patients

This was a prospective clinical cohort study designed to investigate HCV care in individuals with SUD or dual diagnosis, including HCV screening, diagnosis, and therapy with DAAs within the first 6 months after the diagnosis. The study included a prospective follow-up period of 6 months.

The study was conducted at the ADDC of Vall d'Hebron Hospital, Barcelona (Spain). All patients who attended the center from November 2018 to June 2019 were asked to participate. The inclusion criteria were age older than 18 years and a diagnosis of SUD with or without dual diagnosis. Patients with cognitive impairment (based on a Mini-Mental State Examination score <27) or low Spanish or English language proficiency that interfered with their ability to understand the study proposal were excluded. Having previously been diagnosed and cured of HCV was not an exclusion criterion as we were interested in studying the characteristics of those ever infected *versus* those never infected. The project (VHC-DAA-2018-01) was approved by the Ethics Committee of Vall d'Hebron Hospital. Patients did not receive any financial compensation. Written informed consent was obtained from all participants.

Procedure

After providing informed consent, all patients underwent a psychological evaluation to assess health-related quality of life (HRQoL) using the Short Form-36 Health Survey (SF-36), including the mental and physical dimensions, and depression status using the Beck Depression Inventory (BDI). A psychiatrist collected the sociodemographic and clinical features of each participant. A blood sample was obtained.

Patients who tested anti-HCV positive and had detectable HCV RNA underwent a clinical evaluation to assess suitability for treatment based on international guideline recommendations. Those eligible were offered treatment for 8 or 12 weeks

according to the prescribed DAA scheme. To facilitate the start and follow-up of DAA treatment, a hepatologist went to the addiction center twice a week to visit the patients and coordinate their treatment with a multidisciplinary team that additionally included psychiatrists, psychologists, nurses, and assistants working together to facilitate linkage to care.

Patients accepting treatment were provided with the first 4 weeks of DAAs and were subsequently seen at 4-week intervals by the hepatologist to ensure adherence (determined by self-report), evaluate possible adverse events, and dispense the next 4 weeks of DAAs. Drug determination in urine was performed at the beginning of treatment and at each visit. At completion of treatment, and at week 12 after completion, patients attended a medical visit, a blood sample was obtained, and a new drug urinalysis was performed.

Instruments and variables

Sociodemographic and clinical features. Demographic data were collected at the time of enrollment (sex, age, nationality, civil status, housing, educational level, employment status, and criminal record). Information regarding clinical variables, such as self-reported medical conditions (e.g. cardiac, endocrine, metabolic, renal, and neurologic diseases, termed *any medical history* in the analysis), previous and current SUDs (such as alcohol, cannabis, benzodiazepines, cocaine and heroin; route of drug administration; age at start of SUD; polysubstance consumption defined as use of three or more substances), and previous SUD treatments, was also collected. Family history of substance use was excluded, as it was considered to have limited clinical relevance for the current study. Patients were asked of any known infectious disease such as HCV, HBV, or HIV. Psychiatric comorbidity with other mental disorders (dual diagnosis) was evaluated by a psychiatrist and established by clinical judgment, following the DSM-5 criteria. Mental disorders were grouped into psychotic, mood, anxiety, and personality disorders. All sociodemographic and clinical factors were categorical variables except for age.

Laboratory assessment. Blood tests included a complete blood count and standard biochemical panel. Non-invasive liver fibrosis assessment used the FIB-4 (based on age, platelet count, AST and ALT). FIB-4 results were interpreted according to two cut-off values: <1.45 indicated absence of cirrhosis, >3.25 indicated cirrhosis, 1.45–3.25 were considered inconclusive. HBsAg, anti-HIV, and anti-HCV antibodies were determined. In individuals testing positive for anti-HCV antibodies, HCV RNA and HCV genotype were determined. Drug urinalysis included benzodiazepines, methadone, cocaine, opioids, amphetamines, and cannabinoids.

Questionnaires to assess depression and quality of life. The Spanish version of the Beck Depression Inventory (BDI-I) was used to assess the presence of depressive symptoms during the previous 2 weeks. The BDI-I is a 21-question multiple-choice self-report inventory. A value of 0–3 is assigned to each answer. The cut-off for depressive symptoms is 10, and higher total scores indicate more severe symptoms.[16] The SF-36 was used to measure functional health and well-being from the patient's perspective during the last 4 weeks. Two summary measures of HRQoL were calculated: the physical component and mental component. Using algorithms, each scale is transformed into a 0–100 score, in which lower scores indicate greater disability.

Statistical analysis

Descriptive statistics (mean, standard deviation, frequency tables) of the main variables were calculated. The data were then analyzed at the bivariate level. The chi-square test was used to compare categorical variables and the Student *t* test for continuous variables between clinical groups. The chi-square test was not considered applicable when one or more of the cells had an expected count <5.

To reduce false-positive results, the Bonferroni correction for multiple tests was performed according to the number of tests in each bivariate analysis in order to avoid type 1 error. Variables that retained statistical significance and were considered clinically relevant were included in the logistic regression analysis. A conditional entrance method was used to select variables in the model. All statistical hypotheses were two-sided and p-values < 0.05 were considered statistically significant. SPSS version 20 (SPSS Inc., Armonk, NY, USA) for Windows was used for all analyses.

Results

Sample recruitment and sample features

During the recruitment period, 528 patients attended the ADDC and were asked to participate. Ultimately, 401 (75.9%) patients were included. Reasons for exclusion were refusal to take part in the study ($n=86$), refusal to have blood drawn ($n=9$), language barrier ($n=6$), and cognitive impairment ($n=26$).

The final sample of 401 patients had a mean age of 45.4 ± 11.5 years and 301 (75.1%) were men. In total, 253 patients (63.1%) had a dual diagnosis and 148 (36.9%) had only SUD without psychiatric comorbidities. The most frequent SUDs involved alcohol (73.6%), cocaine (58.4%), cannabis (47.1%), heroin (38.2%), and benzodiazepines (30.9%). The sociodemographic, clinical, psychometric, and therapeutic features of patients with and without dual diagnosis are summarized in Table 1. The dual diagnosis group had a higher percentage of women (32%), Spanish natives (87.4%), and unemployed individuals (80.2%). In addition, these patients had a family history of psychiatric disorders more often (47%), were more prone to sedative use disorder (37.5%), had required more medical treatments for SUD control (88.8%), and had been previously hospitalized more often for detoxification (56.2%). Overall, dual diagnosis patients showed more depressive symptoms (according to the BDI-I) and had a poorer HRQoL.

The following variables were independently associated with dual diagnosis status: female sex [Odds ratio (OR):1.50], benzodiazepine use disorder (OR 2.48), previous medical treatment for SUD (OR 5.85), unemployment (OR 0.40), and depressive symptoms (OR 1.10) (Nagelkerke $R^2=0.32$; chi-square = 64.27; $p<0.0001$) (Table 2).

Viral hepatitis and HIV infection

Among the 401 participants, 112 (27.9%) had anti-HCV antibodies and, of these, 42 (10.5% of the sample) had detectable HCV RNA. Of the 70 anti-HCV-positive patients with undetectable HCV RNA, 34 (48.6%) had been previously treated for HCV infection. Eight of the 42 patients (19%) testing HCV RNA positive were unaware of the infection. The most prevalent HCV genotypes (G) in patients with detectable HCV RNA were G1a (38.1%), G3 (31%), G1b (16.7%), G4 (7.1%), and G2 (2.4%). HIV prevalence was higher in the dual diagnosis group (14.3% *versus* 5.4% $p=0.007$).

Results in relation to the presence of anti-HCV antibodies

Sociodemographic, clinical, psychometric, and therapeutic features in patients with and without anti-HCV antibodies are presented in Table 3. There were no significant differences in the prevalence of HCV infection between patients with and without a dual diagnosis. Patients testing anti-HCV-positive had a lower educational level and a higher percentage of criminal records. HIV infection was more frequent in anti-HCV positive patients (35.1% *versus* 1.7%, $p<0.0001$). Use of any substance including non-injecting drug use (alcohol, cannabis, tobacco, and benzodiazepine), polysubstance use, injecting drug use, and early onset of SUD were related to a higher risk of anti-HCV-positive status. In addition, anti-HCV antibodies were more common in SUD patients who had anxiety or personality disorders, previous medical treatment for SUD, and previous detoxification hospitalizations. Regarding liver injury, no significant differences were seen in FIB-4 levels between anti-HCV-positive than anti-HCV-negative patients.

On multivariable analysis, the following variables were independently associated with anti-HCV antibody positive status: opioid use disorder (OR: 27.8), cocaine use disorder (OR: 6.3), any medical history (OR: 21.75), and injecting drug use history (OR: 15) (Nagelkerke $R^2=0.62$; chi-square = 303.69; $p<0.0001$) (Table 2). The current results should be cautiously interpreted because there may be collinearity between opioid use disorder and injecting drug use. However, both variables are clinically relevant, and therefore they were maintained in the model.

Active hepatitis C infection and linkage to care

Among the 112 individuals testing positive for anti-HCV antibodies, HCV RNA was detected in 42 (37.5%) cases. No significant differences were found regarding dual diagnosis between HCV RNA-positive and HCV RNA-negative individuals (52% *versus* 63% $p=0.25$). HCV RNA-positive individuals were younger (41.1 ± 7.3 *versus* 46.1 ± 8.3 $p=0.001$), had received fewer previous

Table 1. Baseline characteristics of patients with and without a dual diagnosis and follow-up of those with hepatitis C.

Sociodemographic features	Total *n* = 401	No dual diagnosis *n* = 148	Dual diagnosis *n* = 253	*p*
	n(%)	*n*(%)	*n*(%)	
Males (%)	301 (75)	129 (87)	172 (68)	<0.0001*,**
Mean age, years	45 ± 12	45 ± 12	46 ± 11	0.69
Spanish (%)	329 (82)	108 (73)	221 (87)	<0.0001*
Living alone (%)	126 (31)	46 (31)	80 (32)	0.89
Primary education (%)	225 (56)	84 (57)	141 (56)	0.84
Unemployed (%)	290 (72)	87 (59)	203 (80)	<0.0001*,**
Criminal records (%)	158 (39)	54 (37)	104 (41)	0.36
Substance use disorder features				
Any medical history (%)	273 (68)	94 (64)	179 (71)	0.13
Family psychiatric history (%)	148 (37)	29 (20)	119 (47)	<0.0001*,**
Family SUD history (%)	194 (49)	66 (45)	128 (51)	0.30
Opioid use (%)	152 (38)	61 (41)	91 (36)	0.32
Cocaine use (%)	233 (58)	88 (60)	145 (57)	0.56
Alcohol use (%)	292 (74)	107 (74)	185 (73)	0.93
Cannabis use (%)	187 (47)	65 (45)	122 (48)	0.55
Benzodiazepine use (%)	123 (31)	28 (19)	95 (38)	<0.0001*
Tobacco use (%)	319 (80)	117 (79)	202 (80)	0.74
Polysubstance use (%)	195 (49)	67 (46)	128 (51)	0.36
Injected drug use (%)	93 (23)	40 (27)	53 (21)	0.16
Smoked drug use (%)	28 (7)	8 (6)	20 (8)	0.32
Sniffed drug use (%)	163 (42)	57 (40)	106 (44)	0.16
Age of onset of SUD	21 ± 9	21 ± 9	21 ± 10	0.93
Treatment history				
Previous medical treatment for SUD (%)	332 (83)	109 (74)	223 (88)	<0.0001*,**
Previous inpatient detoxification (%)	146 (36)	27 (18)	119 (47)	<0.0001*,**
Psychometric features				
Depressive symptoms (BDI), mean ± SD	15 ± 10	11 ± 9	17 ± 10	<0.0001*,**
HRQoL physical component summary (SF-36)	46 ± 11	48 ± 10	45 ± 11	0.02
HRQoL mental component summary (SF-36)	39 ± 13	44 ± 11	37 ± 13	<0.0001*
Serological markers				
Anti-HCV (%)	112 (28)	46 (31)	63 (25)	0.28

(continued)

Table 1. (continued)

Sociodemographic features	Total $n=401$	No dual diagnosis $n=148$	Dual diagnosis $n=253$	p
	n(%)	n(%)	n(%)	
HCV RNA (%)	42 (10)	20 (14)	22 (9)	0.25
Anti-HIV (%)	44 (11)	8 (5)	36 (14)	0.007
Follow-up characteristics in 42 HCV RNA-positive patients				
Patients who started treatment	20 (47%)	8 (40%)	12 (60%)	0.34
Patients who completed treatment	15 (78%)	6 (40%)	9 (62%)	N.A.

*Statistically significant after Bonferroni correction.
**The result is statistically significant after multivariate analysis.
Any medical history: self-reported medical conditions (e.g. cardiac, endocrine, metabolic, renal, or neurologic diseases).
Polysubstance use: Three or more substance use disorders.
Substance use disorders account for current and previous use.
Injected, smoked and sniffed drug use: cocaine and heroin can be consumed in any way, and cannabis is only smoked.
Data are expressed as the mean ± SD or as the percentage (number).
BDI, Beck depressive inventory (depression cut-off, 10); HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; N.A., chi-square was not applicable; RNA, ribonucleic acid; SUD, substance use disorder.

Table 2. Multivariable analysis identifying factors independently associated with (a) dual diagnosis (b) anti-HCV antibody positivity.

a. Logistic regression according to the presence of dual diagnosis			Bivariate analysis	
	OR	95% CI	Unadjusted OR	95% CI
Sex	3.6	1.5–8.5	3.1	1.8–5.4
Unemployed	0.4	0.2–0.8	0.4	0.2–0.6
Benzodiazepine use	2.5	1.1–5.4	2.5	1.5–4.1
Prior medical SUD treatment	5.8	2.2–15.3	2.8	1.6–4.9
Depressive symptoms (BDI)	2.8	1.5–5.4	2.8	1.7–4.7
b. Logistic regression according to anti-HCV positivity			**Bivariate analysis**	
	OR	95% CI	Unadjusted OR	95% CI
Any relevant medical condition	21.7	6.7–70.3	9.2	4.3–19.7
Opioid use	27.8	9.5–80.9	64.1	29.3–140.3
Cocaine use	6.3	1.9–20.1	10.3	5.3–20.1
Injected drug use	14.9	5.7–39.1	64.8	31.6–132.7

Any medical history: self-reported medical conditions (e.g. cardiac, endocrine, metabolic, renal and neurologic diseases).
Substance use disorders account for current and previous use.
BDI, Beck Depression Inventory; CI, confidence interval; OR, odds ratio; SUD, substance use disorders.

SUD medical treatments (98.6% *versus* 85.7% $p=0.007$), and had more pronounced liver injury [higher AST (72 IU/L *versus* 25 IU/L, $p<0.0001$) and ALT levels (75 IU/L *versus* 21 IU/L, $p<0.0001$)] than HCV RNA-negative patients (Table 3). There were no significant differences between these groups on multivariable analysis. The FIB-4 score was determined in all participants,

Table 3. Baseline characteristics of patients according to the presence of anti-HCV antibody or HCV RNA.

Sociodemographic features	Anti-HCV negative $n=289$	Anti-HCV positive $n=112$	p	HCV RNA negative $n=70$	HCV RNA positive $n=42$	p
	n(%)	n(%)		n(%)	n(%)	
Males (%)	210 (73)	91 (81)	0.075	62 (89)	29 (69)	0.01
Mean age, years	46 ± 13	44 ± 8	0.18	46 ± 8	41 ± 7	0.001*
Spanish (%)	243 (84)	86 (77)	0.09	59 (84)	27 (64)	0.02
Primary education (%)	150 (52)	75 (67)	0.01	22 (31)	15 (36)	0.64
Unemployed (%)	199 (69)	91 (81)	0.01	55 (79)	36 (86)	0.35
Criminal records	77 (27%)	81 (72%)	<0.0001*	52 (74%)	29 (69%)	0.55
Substance use disorder						
Any medical history (%)	169 (59)	104 (93)	<0.0001*	65 (93)	39 (93)	1.00
Opioid use (%)	48 (17)	104 (94)	<0.0001*	65 (93)	39 (93)	1.00
Cocaine use (%)	133 (46)	100 (90)	<0.0001*	64 (91)	36 (88)	0.54
Alcohol use (%)	225 (78)	67 (61)	<0.0001*	43 (62)	24 (59)	0.69
Cannabis use (%)	113 (40)	74 (67)	<0.0001*	47 (67)	27 (66)	0.89
Benzodiazepine use (%)	63 (22)	60 (54)	<0.0001*	41 (59)	19 (46)	0.21
Tobacco use (%)	218 (76)	101 (90)	0.001*	66 (94)	35 (83)	0.06
Polysubstance use (%)	97 (34)	98 (88)	<0.0001*	63 (90)	35 (85)	0.46
Injected drug use (%)	12 (4)	81 (72)	<0.0001*	49 (70)	32 (76)	0.48
Age of onset of SUD	23 ± 10	16 ± 4	<0.0001*	17 ± 5	16 ± 4	0.65
Dual diagnosis (%)	187 (65)	66 (59)	0.28	44 (63)	22 (52)	0.28
Psychotic disorders (%)	42 (15)	23 (21)	0.14	17 (24)	6 (14)	0.21
Mood disorders (%)	103 (36)	31 (28)	0.13	20 (29)	11 (26)	0.79
Anxiety disorders	57 (20%)	8 (7%)	0.01	4 (6%)	4 (10%)	0.45
Personality disorders	30 (10%)	24 (21%)	0.01	15 (21%)	9 (21%)	1.00
Age at psychiatric symptoms onset	19 ± 10	24 ± 15	0.01	18 ± 10	20 ± 11	0.48
Treatment history						
Previous medical treatment for SUD (%)	235 (81)	97 (87)	0.225	69 (99)	36 (86)	0.01
Previous inpatient detoxification (%)	119 (47)	70 (63)	<0.0001*	37 (53)	21 (50)	0.77

(continued)

Table 3. (continued)

Sociodemographic features	Anti-HCV negative $n=289$	Anti-HCV positive $n=112$	p	HCV RNA negative $n=70$	HCV RNA positive $n=42$	p
	n(%)	n(%)		n(%)	n(%)	
Psychometric features						
Depressive symptoms (BDI)	15 ± 9	17 ± 12	0.15	15 ± 12	20 ± 13	0.18
HRQoL physical score (SF-36)	47 ± 11	43 ± 9	0.02	43 ± 10	45 ± 9	0.39
HRQoL mental score (SF-36)	39 ± 10	33 ± 10	0.57	40 ± 12	33 ± 10	0.02
Liver function tests						
AST	31 ± 31	43 ± 49	0.006	26 ± 9	72 ± 69	<0.0001
ALT	27 ± 19	42 ± 49	<0.0001*	21 ± 17	76 ± 64	<0.0001
Platelets	258 ± 72	225 ± 67	<0.0001*	226 ± 65	225 ± 72	0.94
FIB-4	1 ± 2	2 ± 1	0.18	1 ± 1	2 ± 1	0.08
FIB-4 >3.25 (%)	12 (4)	8 (7)	0.23	3 (4)	5 (12)	0.14

*Statistically significant after Bonferroni correction.
Any medical history: self-reported medical conditions (e.g. cardiac, endocrine, metabolic, renal or neurologic diseases).
Polysubstance use: three or more substance use disorders.
Substance use disorders account for current and previous use.
FIB-4 >3.25 indicated cirrhosis.
Data are expressed as the mean ± SD or as the percentage.
ALT, alanine transaminase; AST, aspartate transaminase; BDI, Beck depressive inventory (depression cut-off, 10); HCV, hepatitis C virus; HRQoL, health-related quality of life (lower scores indicate more disability); RNA, ribonucleic acid; SUD, substance use disorder.

with no significant differences between the clinical groups. FIB-4 was >3.25 in 3 of the 20 patients who started antiviral therapy. None of them had a history of liver decompensation.

Despite the centralized management, only 20 of the 42 treatment-eligible participants attended the first visit with the hepatologist. Patients did not attend for the following reasons: 11 were lost to follow-up, six returned to their country of origin, two did not want to start treatment, two were followed by hepatologists in other centers, and one was imprisoned.

In the comparison of HCV RNA-positive patients who did not start DAA treatment and those who did, patients who did not start reported use of a larger amount of cocaine during the last month (2.64 ± 3.74 *versus* 0.55 ± 1.8 g/week; $p=0.014$), had a lower academic level (52.6% *versus* 22.7%; $p=0.047$), and were more often unemployed (26.3% *versus* 4.5% $p=0.049$). No differences were found for any of the other sociodemographic or clinical variables, or for dual diagnosis status.

Twenty patients started HCV treatment, but one patient was lost to follow-up at week 8 of therapy. Treatment adherence was excellent in 17 patients, whereas one patient stopped treatment 28 days before completion, and one other missed doses for a total of 6 days. In all 19 treated patients, HCV RNA was undetectable at treatment end. Fifteen patients attended the week 12 post-treatment visit and all had achieved sustained virological response (SVR), but the remaining four were lost to follow-up (Figure 1). In total, 90 visits had been scheduled up to week 12 post-treatment. Patients did not show up or showed up some days later in 27 (30%) of these visits.

The only adverse effects detected during HCV treatment were a mild increase in anxiety and asthenia, but none of the patients required

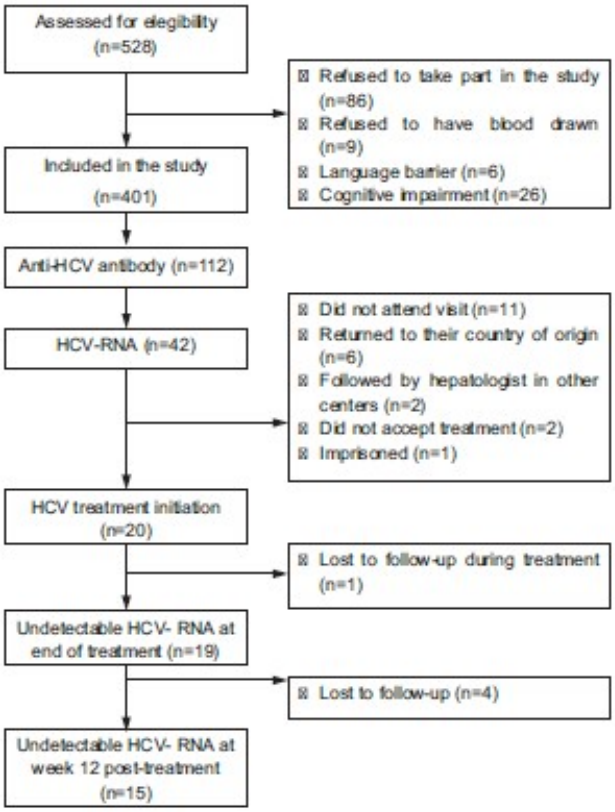

Figure 1. Flow chart study enrollment.

discontinuation or modification of their concomitant psychiatric medication

Fifteen patients were tested for active drug use during antiviral therapy. Eleven of them tested positive for methadone or benzodiazepines, six for methadone or benzodiazepines plus certain illegal drugs (cocaine, opioids, or amphetamines), and three for illegal drugs alone.

Discussion

In accordance with the WHO effort to eliminate HCV infection worldwide, our hospital launched a multidisciplinary program to facilitate HCV screening and linkage to care in SUD patients, a population at high risk for acquiring this infection. This study describes the characteristics of these patients and the initial experience in screening, diagnosing, and treating them. We particularly focused on determining whether there would be differences as related to HCV between patients with SUD alone and those with dual diagnoses. The results show that dual diagnosis status did not lead to a higher risk of HCV infection or interfere with linkage to care or treatment compared with SUD alone. The similar rates of HCV infection between both groups of patients could be explained if the main factor for acquisition of hepatitis C is risk behavior related to substance abuse and not own psychiatric disease.[14,17] Patients with dual diagnoses accounted for 63% of the cohort, a value consistent with findings from previous studies performed in similar settings.[18–21]

On screening, anti-HCV antibody tested positive in 27.9% of patients, and 10.5% of them had detectable HCV RNA. The HCV RNA prevalence found here in SUD patients is 20 times higher than the values reported in the general Spanish population,[2,3] but it is lower than values reported in other SUD studies,[6,11,22] mainly because of the contribution of injecting drug users in these previous reports. We found no differences in the prevalence of HCV viremia between individuals with a dual diagnosis and those with SUD alone.

In our study, HCV RNA-positive patients were younger and had received fewer previous medical treatments for SUD than those testing negative. These findings are reasonable, as older patients are likely to have had more frequent contact with medical care, and therefore more opportunities to be diagnosed and treated for all their diseases.[23] Hospital admission offers an opportunity to link these individuals to HCV care, as has been shown in a previous study.[24]

Now that DAAs have provided effective antiviral treatment, the main issue in the HCV-infected population is improving access to care, a challenge well illustrated by the data from this study. We found that HCV diagnosis and management remains difficult in the SUD population despite the use of a centralized, multidisciplinary approach for care. All patients in the cohort were offered HCV testing based on reflex HCV RNA testing by venipuncture which, in some cases, discouraged study participation (7% of those who refused screening). Although the percentage is not extremely high, this is a modifiable factor that can be improved. Point-of-care HCV RNA testing by non-invasive dried blood spot analysis has shown high sensitivity and specificity[10,25] and could be a feasible way to increase screening rates in the SUD population.

Lack of screening is the first barrier against eradication of HCV infection and may be one of the most important obstacles to achieving the WHO objective.[26] In Spain, the percentage of HCV RNA-positive individuals in the general population unaware of their infection has been estimated at 29.4%.[27] Studies conducted in SUD patients have reported values of 35% to 43%.[10,28] In our sample, only 19% of HCV RNA-positive patients with SUD were unaware of the infection. This may be because of the current heightened awareness and management of this infection in our hospital outpatient clinics. Although this is an improvement, there remains a considerable reservoir of potentially transmissible infection that should be brought to light. A universal screening approach incorporating anti-HCV or HCV RNA reflex testing in emergency rooms and outpatient clinics when blood tests are performed for other purposes could be of value in this regard.

The difficulties to linkage to care and treatment seen here have been reported in other studies, where unemployment and, particularly, low educational level have been associated with low healthcare retention rates.[29–31] In our cohort, these factors associated with failure to treat, as well as the use of large amounts of cocaine, were more common in patients refusing than accepting DAA therapy. These findings are not surprising. Cocaine users are more impulsive and often have a severe addiction, which leads to poorer clinical outcomes.[32] A low educational level interferes with the use of resources and decreases awareness of any risk.[33]

Spain has a publically funded universal healthcare system in which everyone is entitled to treatment. With this in mind, the low percentage of SUD patients starting HCV therapy is worrisome. Among the 42 patients eligible for DAA therapy, 20 (47.6%) were treated: 15 (36%) achieved SVR, and five were lost to follow-up. These findings are in line with a study conducted in Spain assessing HCV therapy in an opioid treatment program, where 38% of 249 patients eligible for DAAs achieved SVR.[34] These results indicate that treatment uptake needs to be enhanced in these patients by close follow-up and motivational programs, but it should also be accompanied by preventive efforts such as educational interventions, counseling, and needle exchange programs.[35]

Our study has several limitations. One concern is the small percentage of participants with detectable HCV RNA in our sample, which limited the power of some analyses. As the study was performed in daily clinical practice, the sample contained both injecting and non-injecting drug users, and previous treatment for HCV infection was not an exclusion criterion, factors that could explain this low percentage. A further limitation was that treatment could not be started in half the HCV RNA-positive individuals, mainly because

they did not return to the ADDC and were lost to follow-up. Finally, self-reported instruments were used for certain factors studied; hence, there could be some recall bias.

The strengths of our study include its prospective design, real-world setting of daily practice, and enrollment of a large sample including all patients seen in a dedicated unit; that is, SUD patients using non-injecting as well as injecting drugs and dual diagnosis patients, a population with scarce data in the literature. In addition, centralized management with a multidisciplinary team provided more complete access and specialized care on several levels for these patients, although it did not achieve a high rate of treatment. The extensive evaluations included data on the psychiatric characteristics assessed by trained staff using validated instruments. Finally, HCV-related variables were well documented by reliable laboratory analyses.

In summary, the results of this study highlight a high prevalence of dual diagnosis and HCV in SUD patients. However, in general, dual diagnosis was not associated with a higher risk of HCV infection or more complex linkage to care for this condition. We found that despite centralized management by a multidisciplinary team, there are still considerable barriers to HCV care in this population, particularly regarding early screening and treatment. It is essential to address these barriers to achieve the WHO objective of HCV elimination.

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Author contributions

Lara Grau-López: conceptualization, methodology, validation, investigation, resources, data curation, writing original draft, visualization. **Cristina Marcos-Fosch**: conceptualization, methodology, validation, investigation, resources, data curation, writing original draft, visualization. **Constanza Daigre**: formal analysis, investigation, data curation. **Raúl Felipe Palma-Alvarez**: investigation, data curation. **Ariadna Rando-Segura**: investigation, data curation. **Jordi Llaneras**: investigation, data curation. **Marta Perea-Ortueta**: investigation, data curation. **Francisco Rodriguez-Frias**: investigation, data curation. **Nieves Martínez-Luna**: investigation, data curation. **Mar Riveiro-Barciela**: conceptualization, methodology, writing review and editing. **Josep Antoni Ramos-Quiroga**: methodology, writing review and editing. **Joan Colom**: resources, investigation. **Rafael Esteban**: conceptualization, methodology, writing review and editing. **Maria Buti**: conceptualization, methodology, validation, writing review and editing, supervision, project administration, funding acquisition.

Conflict of interest statement

Lara Grau-López: No personal or financial conflicts of interest.

Cristina Marcos-Fosch: No personal or financial conflicts of interest.

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10.2 Artículos científicos publicados durante la realización de la tesis doctoral

10.2.1 Etiologies and Features of Acute Viral Hepatitis in Spain.

Llaneras J, Riveiro-Barciela M, Rando-Segura A, **Marcos-Fosch C**, Roade L, Velázquez F, et al. Etiologies and Features of Acute Viral Hepatitis in Spain. Clin Gastroenterol Hepatol [Internet]. 2020 Jul;

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Etiologies and Features of Acute Viral Hepatitis in Spain

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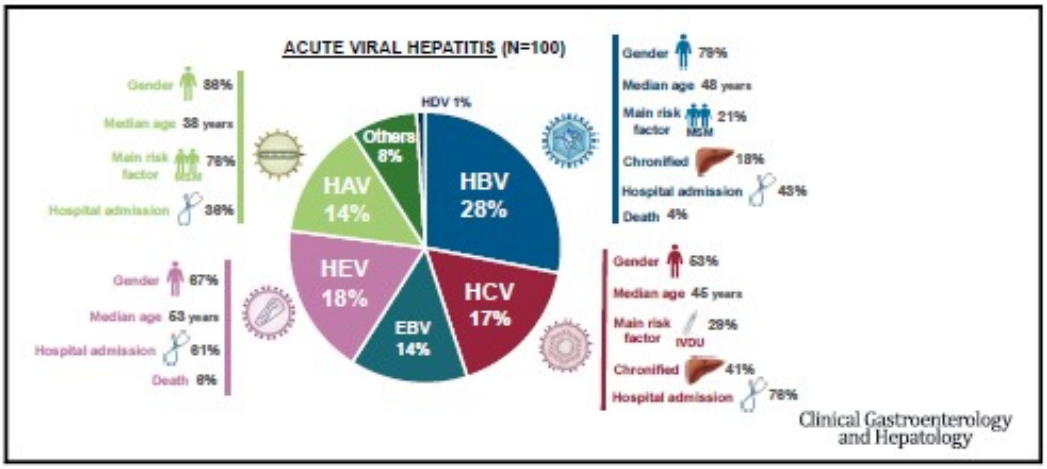

BACKGROUND AND AIM: Etiologies of acute viral hepatitis in high-income countries change with migration of populations, lifestyle changes, and emergence of new pathogens. We analyzed etiologies, characteristics, and outcomes of patients with acute viral hepatitis at a tertiary hospital in Spain.

METHODS: We analyzed data from all patients with acute hepatitis (n = 100; 71% male; median age, 42 years; 72% Spanish nationals), older than 16 years, diagnosed in the emergency department of an academic hospital in Barcelona, Spain, from January 2014 through December 2018. Blood samples were collected and patients with serum levels of alanine aminotransferase more than 10-fold the upper limit of normal and markers viral infection were considered to have acute viral hepatitis. We collected clinical information from patients, and samples were analyzed for IgM antibody to hepatitis B (HB) core antigen, HB surface antigen, antibody against hepatitis C virus (HCV), HCV RNA, IgM against hepatitis E virus (HEV), HEV RNA, and IgM against hepatitis A virus (HAV). Patients were followed until resolution of infections or evidence of chronic infection.

Abbreviations used in this paper: ALT, alanine aminotransferase; anti-HCV, antibodies against hepatitis C virus; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; IgM anti-HAV, IgM antibody to HAV; IgM anti-HBc, IgM antibody to hepatitis B core antigen; IgM anti-HEV, IgM antibody to HEV; MELD, Model for End-Stage Liver Disease MSM, men who have sex with men.

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RESULTS: The most common etiologies of acute hepatitis were HBV infection (28%), HEV infection (18%), HCV infection (17%), and HAV infection (14%). The main risk factors of the cohort were sexual risk contact and intravenous drug use; 79% of cases of HAV had sexual risk behavior. Twenty-nine percent of patients with acute HAV infection and 29% of patients with HBV infection were immigrants to Spain. Fifty-four patients were hospitalized; jaundice and HCV infection were associated with hospital admission. Three patients died (2 from acute liver failure related to acute HBV infection or HBV and HDV co-infection). Chronic infections developed in 5/28 patients (18%) with acute HBV infection and 7/17 patients (41%) with acute HCV infection.

CONCLUSIONS: Despite universal vaccination against HBV in Spain, HBV remains the most frequent cause of acute viral hepatitis in our emergency department. Almost one-third of cases of acute HBV and HAV infections were immigrants, possibly from countries with suboptimal vaccination programs. A high proportion of patients with acute hepatitis have HEV infection (18%); acute HAV infection was associated with sexual risk behavior.

Keywords: ALT; MELD; Features; Europe; Socioeconomic Factor.

Acute hepatitis is a common syndrome defined by increased levels of hepatic transaminases and impaired liver function. Viral infection is a frequent cause of acute hepatitis, and classically, 5 viruses are associated with this condition: hepatitis A virus (HAV) and hepatitis E virus (HEV), which are related to oral transmission, and hepatitis B virus (HBV), hepatitis D virus (HDV), and hepatitis C virus (HCV), mainly transmitted by parenteral mechanisms. In addition, several nonhepatotropic viruses can cause acute hepatitis, with liver involvement being a part of the disseminated disease. The most common of these are herpes virus, cytomegalovirus, and Epstein-Barr virus.

In general, the main pathogens associated with acute viral hepatitis infection worldwide are HAV and HBV.[1,2] but the causes of this condition can vary depending on geographical and socioeconomic factors. Enteric hepatitis viruses transmitted by the oral route (HEV and HAV) predominant in low-income countries, and are associated with poor dietary hygiene, whereas HBV and HCV predominate in high-income countries, and are linked with sexual risk behavior and intravenous drug use.[3] Nonetheless, the etiology of acute viral hepatitis in high-income countries may be changing because of implementation of extended vaccination programs, migratory movements from less economically favored countries, immunosuppressant conditions, and lifestyle changes.

Patients with acute viral hepatitis are usually asymptomatic, but the disease can lead to impaired liver function, acute liver injury, and even acute liver failure, which is associated with high morbidity and mortality, and sometimes requires liver transplantation.[4,5] In addition, a considerable percentage of patients with acute HCV infection and HBV/HDV superinfection progress to chronic infection. A recent report has shown that HEV can also progress to chronicity in patients receiving immunosuppressive drugs, in particular in the transplantation setting.[6] In some scenarios, such as acute HBV infection, the chronicity rate is linked to the age at which acute infection occurred, with more than 95% of newborns developing chronic infection in contrast to <5% of adults.[7,8]

There are few available descriptive studies on the prevalence of acute viral hepatitis in tertiary hospitals in high-income countries, and the results in those that exist show significant differences.[9–11] In a previous study performed 25 years ago in our center, HAV and HCV were the main causes of acute hepatitis, followed by HBV, whereas no cases of HEV were diagnosed in the cohort studied.[12] The changes in life habits, emergence of universal vaccination programs, and other factors mentioned previously seem to have led to changes in the current prevalence of the causes of these infections. A greater knowledge of more recently recognized pathogens such as HEV, more accurate and faster diagnostic testing, and the development of more effective treatments imply an improvement in the morbidity and mortality of patients with viral hepatitis. Hence, continuous study of the etiological changes occurring is of value to know where to focus preventive strategies and the diagnostic and therapeutic efforts to control these diseases.

The objectives of this study were to investigate the viral etiologies of a contemporary cohort of acute hepatitis patients in a tertiary hospital in a high-income country, and analyze the demographic, clinical, and laboratory features, and the clinical outcomes of the affected patients.

Patients and Methods

This is a prospective study conducted at the emergency room of an academic hospital in Barcelona, Spain (January 2014-December 2018), including all cases of acute viral hepatitis. Inclusion criteria were adult patients (≥16 years of age) with evidence of acute hepatitis; that is, alanine aminotransferase (ALT) 10-fold above the upper limit of normality and serologic or virologic markers of an acute viral etiology. In all cases, a

comprehensive workup was carried out to rule out biliary obstruction (abdominal ultrasound or computed tomography), drug-induced liver injury (exclusion of potentially toxic drugs within the previous 3 months), autoimmune hepatitis (immunoglobulin G quantification and analysis of anti-tissue antibodies, including antinuclear, anti-smooth muscle, and antimitochondrial antibodies), and inherited liver diseases (ceruloplasmin, serum copper concentration, serum iron concentration, transferrin saturation level, and serum ferritin level).

Data on sex, age, race, drug and alcohol consumption, sexual behavior, and lifestyle were collected at emergency room admission in all cases. Clinical features, such as jaundice, ascites, hepatomegaly, and encephalopathy, were also recorded and Model for End-Stage Liver Disease (MELD) and MELD-Sodium scores were calculated for each patient.[13–15] Complete blood analyses (cell count, biochemistry, and coagulation study), viral serologies, and virologic markers were performed. Serum samples were tested by commercial enzyme immunoassays for hepatitis B surface antigen (HBsAg), IgM antibody to hepatitis B core antigen (IgM anti-HBc), IgM antibody to HAV (IgM anti-HAV), antibodies against HCV (anti-HCV), and IgM antibody to HEV (IgM anti-HEV). HCV RNA and HEV RNA were also tested. HBsAg, IgM anti-HBc, IgM anti-HAV, and anti-HCV were tested by electrochemiluminescent assay (Elecsys and cobas e analyzers; Roche Diagnostics, Basel, Switzerland). IgM anti-HEV was tested by the Mikrogen assay (recomWell; Mikrogen, Neuried, Germany), which has a sensitivity of 93.3% and specificity of 96.9%.[16] HCV RNA was determined by real-time reverse-transcription polymerase chain reaction (cobas HCV) and HEV RNA by real-time polymerase chain reaction (cobas HEV) on a 6800 system (Roche Diagnostics), with a lower limit of detection of 12 IU/mL and 18.6 IU/mL, respectively.

Criteria to Establish the Etiology of Acute Viral Hepatitis

Acute HAV was diagnosed based on positive testing for IgM anti-HAV.[17] Acute HBV was established on detection of IgM anti-HBc with or without HBsAg.[18–20] Differentiation between acute HBV and acute exacerbation of chronic HVB was based on the presence of IgM anti-HBc and HBsAg-negative status on previous testing.[21] Acute HCV was diagnosed by seroconversion to anti-HCV in previously negative cases or by detectable HCV RNA in patients previously positive for anti-HCV, but with undetectable HCV RNA.[22] Acute HEV was established on positive testing for IgM anti-HEV with or without HEV RNA.[6,23]

Patients were followed up until resolution of the infection. If ALT and viral markers remained elevated, follow-up was maintained until the infection became chronic. Resolution of viral hepatitis was defined as HBsAg loss, or undetectable HCV RNA or HEV RNA, plus normal ALT levels within the first 6 months after acute infection by HBV, HCV, or HEV, respectively. In acute hepatitis due to HAV or nonhepatotropic viruses, resolution was defined by normalization of transaminase levels. The diagnosis of chronic HBV or HCV was based on persistently positive HBsAg or HCV RNA 6 months after the acute infection.[18,22] Chronic HEV was established by the presence of HEV RNA 3 months after the acute HEV diagnosis.[6] Hospital admissions, acute liver failure, liver transplantation requirement, and death were recorded.

What You Need to Know

Background

Etiologies of acute viral hepatitis in high-income countries change with migration of populations, lifestyle changes, and emergence of new pathogens. The authors analyzed etiologies, characteristics, and outcomes of patients with acute viral hepatitis at a tertiary hospital in Spain.

Findings

Hepatitis B virus (HBV) infection is the most frequent cause of acute viral hepatitis in the emergency department studied. Almost one-third of cases of acute HBV and hepatitis A virus infections were in immigrants. Eighteen percent of patients with acute hepatitis had hepatitis E virus infection. Acute hepatitis A virus infection was associated with sexual risk behavior.

Implications for patient care

HBV is still the leading cause of acute viral hepatitis in an emergency department in an economically developed European country.

Statistics

Normally distributed quantitative variables were compared by the Student *t* test and expressed as the mean ± SD. Variables with a non-normal distribution were analyzed using the Mann-Whitney *U* test and expressed as the median and interquartile range. Categorical variables were compared using the chi-square or Fisher exact test when frequencies were <5% and expressed as frequencies and percentages. Logistic regression analysis was performed for multivariate study of qualitative variables. P values <.05 were considered statistically significant. All analyses were done using Stata Statistical Software release 14 (StataCorp, College Station, TX).

Results

In total, 100 consecutive cases of acute viral hepatitis were included: 28 patients (28%) had HBV infection, 18 (18%) had HEV, 17 (17%) had HCV, and 14 (14%) had

HAV. One patient, a known HBsAg carrier, was diagnosed with HDV superinfection. Fourteen (14%) patients had acute hepatitis due to Epstein-Barr virus, and 8 (8%) had other viral etiologies, such as influenza virus and cytomegalovirus. Epidemiological and clinical characteristics are shown in Table 1.

Epidemiological and Clinical Characteristics

Most patients were men (71%), and the median age was 42 (interquartile range, 31–55) years. Patients with acute hepatitis by hepatotropic viruses were older than those with nonhepatotropic viruses (47 years of age vs 30 years of age; $P < .001$). In addition, patients with acute HAV were younger than those with other hepatotropic viruses (36 of age vs 50 of age; $P = .003$). There were no differences according to sex between the various viral etiologies ($P = .25$).

Most patients with acute viral hepatitis were born in Spain (72%). Twenty-nine percent of acute HAV and the same percentage of acute HBV infections occurred in immigrants, mainly those from South America and North Africa, likely due to the lack or low coverage of HAV and HBV vaccination programs in their countries of origin. Four of the 18 (22%) acute HEV infections occurred in immigrants. Overall, the main risk factor for infection was sexual contact, followed by intravenous drug use (Table 1). Eleven of the 14 (79%) cases of acute HAV were related to sexual risk behavior (men who have sex with men [MSM]).

Jaundice was present in 61 (61%) patients: 56 of the 61 (92%) cases caused by hepatotropic viruses and only 5 of 22 (23%) by nonhepatotropic virus ($P < .001$). Acute hepatitis A and B were the etiologies most often associated with jaundice, present in 86% and 79% of cases, respectively ($P = .385$). ALT levels were higher in patients infected by hepatotropic viruses than in those with nonhepatotropic viruses (1711 IU/L vs 630 IU/L; $P < .001$). Acute HAV cases showed the highest median ALT levels (2026 IU/L) and acute HEV the lowest ALT levels (1166 IU/L), but the difference was not statistically significant ($P = .14$). Bilirubin levels were higher than >6 mg/dL more often in patients with acute HAV and HBV, but differences relative to patients with other hepatotropic viruses were not significant. No statistically significant differences in MELD or MELD-Sodium scores were observed between the different viral etiologies at the time of the diagnosis.

Clinical Outcomes

Fifty-four (54%) patients were hospitalized: 13 (76%) with acute HCV, 11 (61%) with acute HEV, and 12 (43%) with acute HBV. On multivariate regression analysis, the factors independently associated with hospital admission were HCV infection (odds ratio, 6.7; 95% confidence interval, 1.4–31) and the presence of jaundice (odds ratio, 4.5; 95% confidence interval, 1.2–16). Clinical outcomes are summarized in Table 2.

Two (2%) patients had developed acute liver failure and presented with hepatic encephalopathy at admission: 1 with acute HBV, and the other with HBV plus HDV superinfection. The patient with HDV superinfection died, and the other patient with liver failure underwent liver transplantation with a good prognosis. A third patient, who had high comorbidity, died from complications associated with acute HEV infection.

Over 6 months of follow-up, 12 of 64 (19%) patients with acute viral hepatitis and a potential to progress to chronicity (ie, HBV, HCV, or HEV) developed chronic infection: 5 (18%) of 28 acute HBV and 7 (41%) of 17 acute HCV cases. Among these cases, differentiation between acute HBV and acute exacerbation of chronic HBV was based on the presence of a risk factor, previous HBsAg-negative status, absence of liver disease, and detectable IgM antibodies against HBc. Two of the 5 patients with HBV infection that became chronic had histological evidence of cirrhosis at 1 year after the acute infection, and 2 others had significant fibrosis. HBsAg remained detectable for more than 15 months in all cases. Longer follow-up showed that in 3 cases HBsAg became undetectable at months 19, 25, and 36, respectively. The 2 remaining cases are still HBsAg-positive (Table 3). At admission for the acute infection, neither the presence of jaundice ($P = .28$) nor the ALT levels ($P = .24$), bilirubin levels ($P = .09$), or prothrombin time ($P = .53$) showed an association with later chronification. All patients who progressed to chronic HCV were subsequently treated with direct-acting antivirals and achieved sustained virologic response. None of the acute HEV cases developed chronic HEV infection. The single patient with acute HDV superinfection died during the acute phase. Older age was the only significant variable related to chronification of the infection (odds ratio, 1.1; 95% confidence interval, 1.01–1.12).

Discussion

The results of this study show that HBV remains a major cause of acute viral hepatitis in Spain, affecting 28% of patients in the 2014–2018 period, a figure higher than the 20% recorded in 1994 in our setting.[12] These HBV results are unexpected in a country where systematic HBV vaccination was introduced in 1991 in preadolescents and in 1981 in newborns.[24] However, analysis of the demographics showed that none of the acute HBV cases occurring in individuals younger than 35 years of age were in Spanish nationals. The affected patients were Spaniards older than 35 years of age and immigrants from countries without universal HBV vaccination. Although many patients with acute HBV were immigrants, the most important associated risk factor for this infection was sexual risk practices (MSM and heterosexual individuals). No cases of acute HBV were associated with the use of intravenous drugs.

Table 1. Baseline Characteristics and Laboratory Findings by Viral Etiologies of the Subjects Included

	Total (N = 100)	HBV (n = 28)	HDV (n = 1)	HCV (n = 17)	HEV (n = 18)	HAV (n = 14)	EBV (n = 14)	Others (n = 8)	*P* Value
Baseline characteristics									
Male	71 (71)	22 (79)	1 (100)	9 (53)	12 (67)	12 (86)	8 (57)	7 (88)	.26
Age, y	42 (31–55)	48 (37–56)	77	45 (35–51)	53 (45–61)	38 (26 –45)	20 (18–26)	32 (26–40)	<.001
Birthplace									.48
Spain	72 (72)	20 (71)	1 (100)	10 (58)	14 (78)	10 (71)	9 (64)	8 (100)	
South America	17 (17)	5 (18)	0	2 (12)	2 (10)	3 (21)	5 (36)	0	
North Africa	5 (5)	3 (11)	0	2 (12)	0	0	0	0	
East Europe	3 (3)	0	0	2 (12)	1 (6)	0	0	0	
Asia	3 (3)	0	0	1 (6)	1 (6)	1 (8)	0	0	
Sexual risk behavior									<.001
MSM	18 (18)	6 (21)	0	1 (6)	0	11 (79)	0	0	
Heterosexual	7 (7)	5 (18)	0	2 (12)	0	0	0	0	
Intravenous drug users	6 (6)	0	0	5 (29)	1 (6)	0	0	0	<.001
Nosocomial risk factor	5 (5)	0	1 (100)	4 (24)	0	0	0	0	<.001
Clinical characteristics									
Jaundice	61 (61)	22 (79)	1 (100)	11 (65)	10 (59)	12 (86)	3 (21)	2 (25)	<.001
Hepatomegaly	22 (22)	8 (29)	0	4 (24)	6 (35)	0	4 (29)	0	.16
Encephalopathy	2 (2)	1 (4)	1 (100)	0	0	0	0	0	.03
Prothrombin time, %	86 (74–95)	87 (75–98)	13	86 (82–95)	87 (73–100)	81 (65–88)	89 (76–94)	82 (76–92)	.46
ALT, IU/L	1455 (611–2156)	1877 (746–2302)	3359	1562 (1040–2106)	1166 (533–2149)	2026 (1657–2959)	630 (558–849)	615 (414–1378)	.002
AST, IU/L	865 (481–1518)	1273 (481–1507)	2553	873 (662–1609)	687 (524–1201)	1407 (592–2086)	503 (392–643)	416 (242–774)	.01
Total bilirubin, mg/dL	4.6 (1.5–8.5)	6.6 (2–10.8)	5	5.7 (1.6–8.5)	2.5 (1.7–4.6)	6.9 (5–11.2)	1.7 (1–2.5)	1 (0.7–3.4)	.002
Direct bilirubin, mg/dL	3 (0.8–6.6)	5.4 (0.7–7.3)	3	4.7 (2.5–7.1)	1.7 (0.9–3)	5.6 (4.5–9.2)	1.2 (0.4–2)	1.3 (0.4–2.4)	.005
MELD score	13 (9–17)	16 (9–19)	24	15 (12–17)	12 (8–12)	15 (13–18)	11 (9–14)	11 (9–15)	.01
MELD-Na score	16 (13–19)	17 (13–22)	20	16 (14–18)	14 (10–17)	18 (17–20)	15 (11–17)	14 (13–17)	.16

NOTE. Values are as n (%) or median (interquartile range).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease-Sodium; MSM, men who have sex with men.

Table 2. Clinical Evolution by Hepatotropic Viral Etiologies

	Total	HBV (n = 28	HDV (n = 1	HCV (n = 17	HEV (n = 18	HAV (n = 14	*P* Value
Hospital admission	54/100 (54)	12 (43)	1 (100)	13 (76)	11 (61)	5 (36)	.09
Acute liver failure	2/100 (2)	1 (4)	1 (100)	0	0	0	
Death	3/100 (3)	1 (4)	1 (100)	0	1 (6)	0	.05
Chronification	12/64 (19)[a]	5 (18)	0	7 (41)	0	0	
Liver transplant	1/100 (100)	1 (4)	0	0	0	0	

NOTE. Values are n/n (%) or n (%).
HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.
[a]Only in relation to viral etiologies that can become chronic.

In the present study, the enteric hepatotropic viruses, HEV and HAV, were the second and third most common causes of acute hepatitis, respectively. The HEV detection rate in our setting has increased considerably compared with that of the previous study (18% vs 0%),[12] which may be attributable to the significant improvements in diagnostic testing and faster results, enabling diagnosis in the emergency department. There did not seem to be any relationship between immigrant status or sexual risk behavior and acute HEV infection. In addition to better diagnostic tests for HEV, all patients with acute hepatitis are now tested for both HEV RNA and IgM anti-HEV, which confers a high probability of detecting the virus. It is also possible that dietary changes, with increased consumption of raw or undercooked pork meat and wild game, could have contributed to the large incidence of acute HEV infections observed.

In contrast, 11 of the 14 (79%) acute HAV patients practiced sexual risk behavior (all were MSM). This supports evidence reported in previous studies of an increase in acute hepatitis A outbreaks associated with sexual practices in young MSM.[25–27] An association has been found between HCV outbreaks and the Gay Pride Festival,[28] but we were unable to establish a temporal relationship with this factor in our HAV cases. It has been suggested that universal vaccination against HAV may be cost-effective considering the epidemiological changes in this infection.[29] Currently, vaccination against HAV is only recommended in persons at a high risk of infection by this virus, and it is not included in the universal vaccination schedule in Spain. The high incidence of new HAV infections in young people could justify universal vaccination or at least extension of the HAV vaccine recommendations to at-risk populations such as MSM or sex workers, among others.

Fifty-four (54%) patients were hospitalized, and 37 of them (69%) had jaundice on admission. Patients diagnosed with acute HCV were hospitalized more often, likely because HCV RNA testing to diagnose HCV requires more time than conventional serology. Knowledge of the profiles of patients with different hepatitis etiologies may allow early discharge from the emergency department without admission requirements.[4]

In our series, none of the acute hepatitis C patients received therapy, and HCV progressed to chronicity in 40% of cases, a value similar to those reported rates in symptomatic cases, and it contrasts with higher rates in asymptomatic cases.[30] In the chronic phase, all patients were treated with direct-acting antivirals, and all achieved sustained virologic response. In patients with acute hepatitis B, 18% developed chronic infection, a percentage significantly higher than has been reported.[18] An unusual feature of these cases was the rapid progression of liver disease: 4 of the 5 patients who developed chronic infection had clinical or histological features of moderate fibrosis or cirrhosis at 1 year after the acute infection. Their specific characteristics are summarized in Table 3. None of these patients were immunocompromised, receiving immunosuppressive treatment, or had known previous liver disease.

It can be difficult to differentiate an episode of acute hepatitis from an acute exacerbation of chronic HBV. The presence of anti-HBc IgM is very suggestive of acute HBV, but some chronic patients with an acute exacerbation can also have low IgM anti-HBc levels.[21] In our patients, the presence of an obvious temporary risk factor for acute infection, no HBsAg detection in a previous control, and the presence of anti-HBc IgM support the diagnosis of acute hepatitis with progression to chronic hepatitis in these 5 cases. In addition, during long term follow-up, 3 of the 5 chronic HBV cleared HBsAg, a factor that supports the diagnosis of acute hepatitis. However, the HBsAg loss occurred after 18 months of acute hepatitis, which leads us to that these 3 cases were acute HBV that became chronic. We were unable to identify the reason for the rapid progression of liver damage, a feature that requires further study.

The main limitation of this study is that it was performed with data obtained in the emergency department of an academic hospital. This implies that the rural population was not represented and that there may have been a trend toward including patients with more marked symptoms, who are more likely to consult in the emergency room. In addition, children and adolescents were not included. However, a large number of cases were collected during the study period, and the results reflect the situation of individuals living in an urban setting.

Table 3. Characteristics of the Patients With AHB That Progressed to Chronicity

Sex, Age	Risk Factor	Previous HBsAg (Year of Determination)	Previous Liver Disease	Date of AHB diagnosis	HBsAg/IgM Anti-HBc	HBeAg	Platelets (× 10^9/L)	ALT (IU/L)	Total Bilirubin (mg/dL)	Liver Biopsy (Months After AHB)[a]	Treatment	Last HBsAg Positive Determination Follow-Up	Last HBsAg Control
Male, 37 y	Accidental puncture with infected patient	Negative (2016)	Normal US (2016)	June 2017	Positive /Positive	Positive	284	479	2.2	F2 (7 mo)	No	15 mo	Negative at 19 mo of follow-up
Male, 49 y	MSM/IVDU	Negative (2016)	No	March 2017	Positive/ positive	Positive	192	403	1.3	F4 (8 mo)	Tenofovir (Nov 2017)	20 mo	Negative at 25 mo of follow-up
Male, 42 y	MSM	Negative (2010)	Hepatic steatosis	May 2017	Positive/ positive	Positive	266	371	2.1	F0 (10 mo)	No	Persistently positive (36 mo of follow-up)	
Female, 61 y	Accidental puncture with infected patient	Not available	Hepatic steatosis	May 2016	Positive/ positive	Positive	222	485	1.3	F2 (13 mo)	No	29 mo	Negative at 36 mo of follow-up
Male, 54 y	Heterosexual contact	Negative (2013)	No	February 2016	Positive/ positive	Positive	263	1431	12.9	F4 (12 mo)	Tenofovir (January 2017)	Persistently positive (48 mo of follow-up)	

AHB, acute hepatitis B; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM anti-HBc, IgM antibody to hepatitis B core antigen; IVDU, intravenous drug user; MSM, men who have sex with men; US, ultrasonography.
[a]Metavir fibrosis stage biopsy.

In summary, HBV infection remains a common cause of acute viral hepatitis in a high-income country such as Spain. Migration from countries without universal HBV vaccination programs could have contributed to this persistent prevalence, which stresses the need to intensify HBV vaccination worldwide. A large number of patients with acute HEV were observed, suggesting the need for routine testing of this virus. It is important to monitor the characteristics of acute viral hepatitis and trends in the patients' life habits, as several issues related to HAV and HEV hepatitis seem to be unresolved even in high-income countries.

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Conflicts of interest
These authors disclose the following: F. Rodriguez-Frias has served as a speaker for Roche and Gilead. Mar Riveiro-Barciela has received grant support from Gilead and has served as a speaker for Gilead, Grifols, and MSD. Maria Buti has served as an advisor and speaker for Gilead, MSD, and AbbVie. Rafael Esteban is an advisor and speaker for Gilead, MSD and AbbVie. The remaining authors disclose no conflicts.

10.2.2 Nucleos(t)ide analogue therapy: The role of tenofovir alafenamide.

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SUPPLEMENT ARTICLE

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Nucleos(t)ide analogue therapy: The role of tenofovir alafenamide

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Abstract

Chronic hepatitis B virus (HBV) infection remains an important global health problem, and may be difficult to manage in clinical practice. Nucleos(t)ide analogues (NAs) with a high barrier to resistance (entecavir [ETV], tenofovir disoproxil fumarate [TDF] and tenofovir alafenamide [TAF]) are the most frequently used HBV treatments because of their long-term effectiveness and tolerability. ETV may be less effective in patients with lamivudine-resistant strains, and TDF is associated with impaired renal function and reductions in bone mineral density. TAF, a new tenofovir prodrug, has been developed to overcome the less favourable safety profile of TDF. TAF is more stable in plasma, and higher tenofovir levels are achieved within cells at lower doses than with TDF. Several registration and real-life studies, performed up to week 144 of treatment, have shown that TAF is at least as effective as TDF, with higher rates of ALT normalization and significantly fewer kidney disturbances and changes in bone mineral density. No emergence of drug resistance has been found with TAF use. The main limitation to prescribing TAF is its price. The European Association for the Study of the Liver has suggested selecting TAF or ETV instead of TDF in patients >65 years old and in those with a risk of osteoporosis or renal abnormalities, and to prescribe TAF rather than ETV in patients previously exposed to NAs.

KEYWORDS

chronic hepatitis B, hepatitis B virus, nucleos(t)ide analogues, TAF, tenofovir

1 | INTRODUCTION

Hepatitis B virus (HBV) was discovered more than 50 years ago, and an effective HBV vaccine has been available for over 30 years.[1] Nevertheless, chronic HBV infection remains an important global health problem affecting more than 257 million people worldwide[2] and causing more than 780 000 deaths per year.[3] Although HBV treatment has progressed and improved over the years, a cure has not been achieved. Current antiviral therapies effectively reduce viral replication, but they have no or little influence on the HBV reservoir in hepatocytes.[3]

The main goal of HBV therapy is to prevent the progression of liver disease and the development of cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) through suppression of viral replication.[1] There are two main strategies for treating chronic HBV infection: nucleos(t)ide analogues (NAs) and pegylated interferon-α.[1] There are six different types of NAs, and those with a high genetic barrier (entecavir [ETV], tenofovir disoproxil fumarate [TDF]

Abbreviations: ALT, alanine aminotransferase; BMD, bone mineral density; EASL, European association of the study of the liver; eGFR, estimated glomerular filtration rate; ETV, Entecavir; HBB, hepatocellular carcinoma; HBV, hepatitis B virus; NA, nucleos(t)ide analogues; TAF, Tenofovir alafenamide; TDF, Tenofovir disoproxil fumarate.

and recently approved tenofovir alafenamide [TAF])[1] are the recommended first-line HBV regimens because of their favourable safety profiles and high long-term antiviral effectiveness, resulting in undetectable HBV DNA levels in most patients.[1,4] These agents strongly inhibit the HBV polymerase, suppressing viral replication. ETV and TDF have been shown to be highly effective in phase III trials and real-life studies, with high rates of HBV DNA suppression (94%-99% in up to 10 years of follow-up) in both HBeAg-negative and -positive patients.[1,5] However, HBsAg loss is rare, with annual rates of <1%.[5] While there are no significant differences between ETV and TDF for the suppression of HBV DNA, ETV may be less effective in patients with lamivudine-resistant strains, a limitation that does not occur with TDF, which is associated with no drug resistance.[1,4]

This article reviews the effectiveness and safety of tenofovir alafenamide (TAF) for the treatment of patients with chronic HBV infection.

Key points

- ETV, TDF and TAF are the recommended NA treatments for HBV because of their high long-term efficacy and tolerability.
- TDF use is associated with impaired renal function and reductions in bone mineral density, and ETV may be less effective in patients with lamivudine-resistant strains.
- TAF as or more effective than TDF and ALT normalization rates are higher.
- Kidney disturbances and bone mineral density changes are much milder with TAF than with TDF.
- No emergence of HBV drug resistance has been seen with TAF after 144 weeks of treatment.

2 | TAF: A NEW TENOFOVIR PRODRUG

Tenofovir was first described in 1993 with the name (R)-RMPA. To ensure oral bioavailability of the molecule, a diester of tenofovir was formulated with fumarate resulting in the drug TDF. Following intracellular metabolism to its active form, tenofovir diphosphate, TDF inhibits reverse transcription of HBV and HIV.[6] TDF was marketed to treat HIV infection in 2001 and HBV infection in 2008. Although the high antiviral activity of TDF has been confirmed in patients with chronic HBV infection and no resistance over 10 years of use, long-term treatment is associated with impaired renal function, reductions in bone mineral density (BMD) and increases in markers of bone turnover.[5]

TAF, a new phosphonate tenofovir prodrug, was developed to improve the suboptimal safety profile of TDF. Intracellular metabolic activation of TAF occurs in peripheral blood mononuclear cells and liver cells where it is converted into tenofovir-alanine and then hydrolysed to tenofovir before being phosphorylated to obtain tenofovir diphosphate, the final active metabolite of both TAF and TDF.[7] Compared to TDF, TAF is more stable in plasma and remains mainly intact when penetrating virally infected cells, which leads to higher levels of intracellular tenofovir diphosphate at lower drug doses. Thus, systemic exposure to tenofovir is more than 90% lower with TAF than with TDF and the safety profile is considerably better.[7] TAF was found to decrease HBV DNA levels at week 4 at all doses (8, 25, 40 or 120 mg)[8] similar to TDF at 300 mg. Based on these results, the 25-mg dose was selected for clinical development of TAF as treatment of HBV infection.[8]

3 | EFFICACY OF TAF IN CHRONIC HBV INFECTION

In two identically designed double-blind, phase-III international trials, adults with chronic HBV infection and compensated liver disease were randomized 2:1 to receive 25 mg TAF or 300 mg TDF for 96 weeks, followed by an open-label TAF phase through week 144. A total of 1298 patients were enrolled, 873 HBeAg positive and 425 HBeAg negative.[9,10] The protocol was amended to extend the double-blind phase from 96 weeks to 144 weeks, followed by an open-label phase through week 384. However, before the amendment, 540 patients entered the open-label phase on week 96 (360 patients remained on TAF and 180 switched from TDF to TAF). Patients' baseline characteristics were similar between the groups: mean age 40 years old, 63% men, 78% Asian, mainly genotypes C (48%) and D (26%), mean HBV DNA 7.0 log10 IU/mL, 25% previously treated with NAs and 10% with cirrhosis.

At week 96, viral suppression was similar in HBeAg-positive patients receiving TAF or TDF (73% vs 75%, respectively, $P = .47$) and in HBeAg-negative patients (90% vs 91%, $P = .84$).[11] However, in both studies, the percentage of patients with normal alanine aminotransferase (ALT) levels at week 96 was significantly higher in patients receiving TAF than in those who received TDF (75% vs 68%, respectively, $P = .017$).[11] Patients treated with TAF had a significantly smaller mean decrease in hip and lumbar spine BMD (−0.33% vs −2.51%; $P < .001$ and −0.75% vs −2.57%; $P < .001$), respectively, and a significantly smaller median change in the estimated glomerular filtration rate (eGFR) by the Cockcroft-Gault method (−1.2 vs −4.8 mL/min; $P < .001$) than patients receiving TDF.[11]

While there were high rates of virological control in both TAF- and TDF-treated HBeAg-negative and -positive patients at week 144, at year 3, the percentage of patients with ALT normalization was greater in patients receiving TAF (71% vs 59%, $P = .052$ in HBeAg negative and 64% vs 53%, $P = .010$ in HBeAg positive). The serological response rate in HBeAg-positive participants was similar with both treatments, with HBeAg loss in 24% of patients at 3 years. Adverse events and severe events were similar for both treatments. A greater median decrease in creatinine clearance was observed with TDF, while there was only a slight decrease in the TAF group (−6 vs −1.2 mL/min; $P < .001$). Similarly, the mean decrease in hip (−2.5% vs −0.4%, $P < .001$) and spine (−2.0% vs −0.5%, $P < .001$) BMD was significantly higher in the TDF than in the TAF group.[12]

Finally, HBV DNA was undetectable in 84% of the 180 patients who switched to open-label TAF at week 96 (TDF → TAF),[13] and the ALT normalization rate was higher in TDF → TAF patients at 1 year following the switch (45% vs 29% by AASLD criteria; $P = .043$). None of the patients achieved HBsAg loss. At week 144, the median GFR had improved in the TDF → TAF group, (+4.2 [−3.3,+9] mL/min), while those remaining on TDF showed a persistent decrease in median eGFR (−0.9 [−6.6,+6.0] mL/min) $P < .001$). Hip and spine BMD significantly increased in the TAF switch group (+0.98% and + 2.04% from baseline, respectively), while values remained the same in the ongoing TDF group.

Another phase III double-blind study assessed the efficacy and safety of switching to TAF vs continued TDF treatment in chronic HBV patients with viral suppression on long-term TDF.[14] A total of 488 patients were randomized (1:1) to TAF 25 mg or TDF 300 mg for 48 weeks, and they all then received open-label TAF 25 mg until week 96. Virological suppression was similar at weeks 48 and 96 in both groups, and ALT normalization rates increased in both groups at week 96. Bone and renal safety was similar to that in the previous study.

Several real-life studies have been performed with TAF. Kaneko et al reported a similar reduction in HBV DNA levels in a study including 14 treatment-naïve patients with chronic HBV treated with TAF and 45 with TDF for 48 weeks, while eGFR was significantly decreased with TDF (−5.34 ± 7.69 mL/min/ 1.73 m2; $P < .001$).[15] Most studies have been performed in TDF-treated patients who switched to TAF. Like in registration studies, the antiviral effect was maintained for HBV DNA.[16] Real-life studies showed that decreases in eGFR and BMD were not only inhibited by switching to TAF, but even improved.[9,16,17] The results of several switch studies from TDF to TAF are shown in Table 1.

4 | EFFICACY OF TAF IN NA-EXPERIENCED PATIENTS

The two previous phase-III trials contained 386 NA-experienced patients (265 [30%] in the TAF group and 121 [28%] in the TDF group). Previous therapy was mainly ETV and lamivudine.[9,10] The virological response at weeks 96 and 144 was similar whatever the previous therapy. Several small studies in clinical practice have shown that switching from ETV to TAF is more effective and associated with higher HBV DNA suppression rates than remaining on ETV.[18] Some of these studies have also reported a significant ALT normalization rate after switching to TAF.[13,14]

5 | USE OF TAF IN SPECIAL POPULATIONS

5.1 | Elderly

No clinically relevant differences in the pharmacokinetics of TAF according to age or ethnicity have been identified.[19] The effectiveness and safety of TAF is similar in geriatric and younger patients.[20] Dose adjustment is not required in patients aged 65 years and older.[19]

5.2 | Paediatric population

The pharmacokinetics of TAF and tenofovir were evaluated in HIV-1 infected, treatment-naïve adolescents who received TAF (10 mg) given with elvitegravir, cobicistat and emtricitabine as a fixed-dose combination tablet. No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between adolescent and adult HIV-1-infected individuals. The safety and efficacy of TAF in children <12 years old or weighing <35 kg have not been established.[19]

5.3 | Women of childbearing age and family planning

Telbivudine and TDF are considered to be safe options during pregnancy, and TDF is the first choice therapy.[1] Data on TAF in pregnant or breastfeeding women are limited. However, substantial data on TDF in pregnant women have not shown any malformations or feto/neonatal toxicity. In one study in China, 26 pairs of mothers and infants were enrolled to receive TAF, while another 26 pairs received TDF. TAF concentrations were below the lower limits (0.5 ng/mL) in cord blood and breast milk samples from the TAF group, while the median tenofovir concentration was 4.98 (IQR 0.73-7.24) ng/mL and 12.83 (IQR 7.46-29.46) ng/mL in cord blood and breast milk samples from the TDF group respectively. None of the infants had congenital malformations at birth, confirming that TAF seems to be safe during the 3rd trimester of pregnancy and during breastfeeding, however, larger groups and long-term cohort studies are still need.[21] In the meantime, TAF may be considered during pregnancy if necessary, but should not be used during breastfeeding.[19]

5.4 | Patients with impaired kidney function

TAF is secreted by the kidney. No clinically relevant differences in TAF or tenofovir pharmacokinetics have been observed between healthy individuals and patients with severe renal impairment (eGFR >15 and <30 mL/min) in studies on TAF.[19] TAF dose adjustment is not required in patients with eGFR ≥15 mL/min or in those with eGFR <15 mL/min receiving haemodialysis. During haemodialysis sessions, TAF should be administered after the treatment session has been completed.[19] There are no dosing recommendations for patients with eGFR <15 mL/min who are not receiving haemodialysis.

5.5 | Patients with hepatic impairment

Total plasma concentrations of TAF and tenofovir are lower in patients with severely impaired hepatic function than in those with

TABLE 1 Results of studies focusing on treatment switch from TDF to TAF

Study	N	Population characteristics	Groups compared	HBV DNA suppression	ALT normalization	Changes in Creatinine Clearance (mL/min)	Changes in Bone mineral density
Pan et al 2017[27]	181		Baseline vs 48 weeks after switching to TAF	88% vs 89% P = NS	78% vs 89% P < .001	−4.8 vs −1.2[a] P < .001	0% vs −3.4%[d] P < .001
Gaine et al 2018[16]	101	1 or more TDF risk factors[e]	Baseline vs 48 weeks after switching to TAF	P = NS	ND	+3[a] P < .001	Hip +0.97%[b] P = .002 Spine +2.18%[b] P < .001
Buti et al 2019[28]	358	1 or more TDF risk factors[e]	Patients on TDF who continued on TDF vs switched to TAF for 48 weeks	97% vs 97% P = .96	ND	−2.7 vs +1.8[a] P < .0001	+6.8% vs −3%[d] P < .0001
Lee et al 2019[29]	45		Baseline vs 12 weeks after switching to TAF	ND	−12.93[c] P < .002	P = .6	ND
Lim et al 2019[17]	174	Patients with HBV resistant to entecavir and/or adefovir	Patients on TDF who continued on TDF vs switched to TAF for 48 weeks	98% vs 99% P = .99	79% vs 92% P = .06	4.5% vs 8.2%[b] P = .06	0.08% vs 1.84%[b] P = .01
Kaneko et al 2019[15]	36		Baseline vs 24 weeks after switching to TAF	P = NS	ND	−7.32 vs +2.89[c] P = .02	ND
Ahn et al 2020[30]	288	Asians with 1 or more TDF risk factors[e]	Patients on TDF who continued on TDF vs switched to TAF for 48 weeks	97% vs 97% P = NS	73% vs 76% P = NS	−2.7 vs +2.6[a] P < .0001	P < .0001
Lampertico et al 2020[14]	488		Patients on TDF for 48 weeks switched to TAF for 48 weeks more vs TAF for 96 weeks	94% vs 95% P = .686	74% vs 56% P = .051	−0.39 vs +0.51[a] P = .871	Hip 0.18% vs 1.16%[b] P < .001 Spine 1.7% vs 2.3%[b] P = .097

[a]Median change mL/min.
[b]Mean % change.
[c]Mean change mL/min.
[d]Median % change in C-type collagen sequence.
[e]Age > 60 yr, osteoporosis of hip/spine, ≥Stage 2 chronic kidney disease (CKD), albuminuria (UACR > 30 mg/g), hypophosphatemia (PO4 < 2.5 mg/dL) or comorbidities associated with CKD (eg HTN, DM, obesity); ND: testing not done; NS: not significant.

normal function. When corrected for protein binding, free plasma TAF concentrations are similar in both groups.[19] The efficacy and safety of TAF in patients with decompensated chronic hepatitis B seem to be similar to that of compensated patients based on the limited data with this agent.[22]

6 | USEFULNESS OF TAF IN REAL LIFE

In certain countries, the main limitation to the prescription of TAF in patients with chronic HBV is the price of the drug, which is usually more expensive than ETV or TDF, which are both generic. To overcome the safety limitations of TDF, the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines have proposed selecting TAF or ETV rather than TDF in patients >65 years old and in those with a risk of osteoporosis or renal abnormalities, and to prescribe TAF rather than ETV in patients who have received NAs.

Sixty-six per cent of 565 chronic HBV patients receiving TDF in two European centres met the EASL criteria to switch to TAF or ETV.[23] It should be noted that most of the patients in the cohort were NA experienced, and TAF should be prescribed if possible in these cases.

A study in 1037 patients in the USA found that TAF was prescribed in 38% for prevention rather than for adverse clinical changes in renal and bone function, [24] while in a Greek study the main reasons for starting TAF were renal (54%), BMD (35%) and both renal and BMD (11%) disorders/risks.[25]

All these data suggest that TAF is more often initiated indifferent countries based on cost than for its efficacy and safety, even though some studies have found TAF to be cost-effective.[26]

In summary, the initiation of TAF is important to overcome drug safety issues in patients with chronic HBV. The antiviral effectiveness of this agent is at least as potent as TDF, but it is associated with significantly lower rates of changes in renal function and BMD. Like TDF, TAF results in little or no emergence of drug resistance.

CONFLICT OF INTEREST

Maria Buti—Has received research grants from Gilead and has served as an advisor for Gilead, Bristol-Myers Squibb and Novartis. No personal conflicts of interest. Cristina Marcos-Fosch—No personal of financial conflicts of interest. Rafael Esteban—Has received research grants from Gilead and has served as an advisor for Gilead, Bristol-Myers Squibb and Novartis. No personal conflicts of interest.

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10.2.3 Naïve hepatitis B e antigen-negative chronic hepatitis B patients are at risk of carotid atherosclerosis: A prospective study.

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ORIGINAL ARTICLE

Prospective Study

Naïve hepatitis B e antigen-negative chronic hepatitis B patients are at risk of carotid atherosclerosis: A prospective study

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Abstract

BACKGROUND

There is an increased risk of atherosclerosis in patients with chronic hepatitis C or human immunodeficiency virus, but there is scarce data on hepatitis B virus infection. The hypothesis of this study is that hepatitis B virus infection increases the risk of carotid plaques and subclinical atherosclerosis in naïve hepatitis B e antigen (HBeAg) negative subjects.

AIM

To assess the rate of carotid plaques and subclinical atherosclerosis in naïve HBeAg negative subjects in comparison with a cohort of healthy controls.

METHODS

Prospective case-control collaborative study conducted in two tertiary hospitals. Four hundred and two subjects prospectively recruited at the outpatient clinic were included from May 2016 to April 2017: 201 naïve HBeAg-negative hepatitis

B virus-infected [49 chronic hepatitis B (CHB) and 152 inactive carriers(ICs)] and 201 healthy controls. Anthropomorphic and metabolic measures, liver stiffness and carotid Doppler ultrasound were performed. Subclinical atherosclerosis was established on an intima-media thickness increase of ≥1.2 mm and/or the presence of carotid plaques. Normally distributed quantitative variables were compared with the Student *t* test and those with a non-normal distribution with the Mann-Whitney *U* test. Categorical variables were compared between groups using the χ^2 or Fisher exact test.

RESULTS

Carotid plaques were found more often in CHB (32.7%) than ICs (17.1%) or controls (18.4%) ($P = 0.048$). Subclinical atherosclerosis was also increased in CHB (40.8%) *vs*ICs (19.1%) or controls (19.4%) ($P = 0.003$). No differences in the risk of atherosclerosis were observed between controls and ICs. The factors independently associated with the presence of carotid plaques were age [odds ratio(OR) 1.43, $P < 0.001$] and CHB (OR 1.18, $P = 0.004$) and for subclinical atherosclerosis, age (OR 1.45, $P < 0.001$), CHB (OR 1.23, $P < 0.001$) and diabetes (OR 1.13, $P = 0.028$). In the subset of young subjects (< 50 years), carotid plaques (12.5% *vs* 1.1%, $P = 0.027$) and subclinical atherosclerosis (12.5% *vs* 2.2%, $P = 0.058$) were more frequent among CHB than ICs.

CONCLUSION

Untreated HBeAg-negative CHB is an independent risk factor for carotid plaques and subclinical atherosclerosis, while ICs present a similar risk to controls.

Key Words: Hepatitis B virus; Carotid plaques; Subclinical atherosclerosis; Cardiovascular risk; Endothelial dysfunction; Intima-media thickness

Core Tip: This prospective case-control collaborative study aimed to assess whether chronic infection by hepatitis B was associated with risk of carotid plaques and subclinical atherosclerosis. Overall, 402 subjects were recruited, 201 naive hepatitis B e antigen-negative hepatitis B virus-infected and 201 healthy controls Patients with hepatitis B e antigen-negative chronic hepatitis B presented a higher rate of carotid plaques than non-infected controls,but no differences were observed between controls and hepatitis B inactive carriers. These results suggest that hepatitis B infection may have a role as a cardiovascular risk factor in patients with chronic hepatitis B.

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INTRODUCTION

More than 257 million people worldwide are infected with hepatitis B virus (HBV)[1], and more than 780000 die each year due to the infection[2]. Chronic HBV infection is a dynamic condition that passes through several phases, being the hepatitis B e antigen (HBeAg)-negative form the most common in Western countries[1]. Currently, patients are classified as HBeAg-negative chronic hepatitis B (CHB) when they have increased HBV DNA and alanine aminotransferase (ALT) levels and liver fibrosis and/or necroinflammation or as HBeAg-negative chronic infection/inactive carriers (ICs)when they have low HBV DNA and normal ALT levels and associated with absent or mild liver damage[3].

were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. It was approved by the Ethics Committee of both hospitals (PR(AG)245/2015).

Informed consent statement: Informed verbal consent was obtained from all individual participants included in the study and recorded at the medical records.

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An increased risk of cardiovascular events has been associated with some viral infections like hepatitis C virus (HCV)[4] or human immunodeficiency virus (HIV)[5] as well as autoimmune diseases[6]. The cause of atherosclerosis in these patients is not fully explained by conventional risk factors, and endothelial dysfunction has been suggested as the underlying mechanism causing the early atherosclerotic process. This endothelial dysfunction is mainly associated with the persistent inflammatory state linked to these diseases (HCV, HIV and autoimmune diseases). In fact, eradication of HCV infection has shown a positive impact on carotid atherosclerosis[7]. Both the presence of carotid plaques or measurement of the intima-media thickness (IMT) are accepted and validated surrogate markers for early diagnosis of subclinical atherosclerosis leading to increased cardiovascular risk[8].

Chronic HBV infection has been associated with a propensity to mount proinflammatory immune reactions[9,10], including higher oxidative stress[11], that may predispose to a higher subclinical atherosclerosis.

The aim of this study was to assess whether the stage of HBeAg-negative chronic HBV infection impacts the presence of both carotid plaques and subclinical atherosclerosis. Another aim was to evaluate if the risk of both carotid plaques and subclinical atherosclerosis in HBeAg-negative patients differ to those of healthy controls.

MATERIALS AND METHODS

Patients

Two hundred and one patients with chronic HBV infection and naïve to antiviral therapy were prospectively recruited at the outpatient clinics of two tertiary hospitals (Di.Bi.M.I.S., University of Palermo, Italy and Vall d'Hebron Hospital, Spain) from May 2016 to April 2017. Inclusion criteria were hepatitis B surface antigen (HBsAg) positive for more than 6 mo, HBeAg-negative and no prior exposure to antiviral therapy. Exclusion criteria were previous cardiovascular events (acute myocardial infarction or ischemic stroke), liver transplantation, HCV, hepatitis D or HIV coinfection, history of hepatocellular carcinoma or evidence of liver disease of mixed etiology (autoimmune hepatitis, Wilson's disease, hemochromatosis, α1-antitriypsin deficiency). In addition, 201 healthy individuals matched for sex, age and body mass index were recruited as controls at the outpatient clinics from the same centers. In particular, no patient had a history of previous cardiovascular events, evidence of HBV infection (HBsAg and anti-HBc negative), HCV or HIV, or history of rheumatic or oncological disease. Importance of selection of naïve patients was crucial in view of the effect of antiviral therapy in both liver immunity and carotid plaques in subjects with HCV treated with direct-acting antivirals[7].

Naïve patients with HBV infection were classified into CHB and IC according to the recommendations of European Association for the Study of the Liver[3]: HBeAg-negative CHB was established on HBV DNA > 2000 IU/mL plus fluctuating or persistently elevated ALT levels and/or histological evidence of at least moderate fibrosis and/or necroinflammation; HBeAg-negative chronic infection or IC state was established on persistently normal ALT levels plus HBV DNA < 2000 IU/mL or HBV DNA 2000-20000 IU/mL plus evidence of mild or absent hepatic necroinflammation and fibrosis. Diagnosis of liver cirrhosis was established by liver biopsy (Ishak score 5 or 6) or transient elastography values > 13.1 kPa[12]. This study was conducted in accordance with the Declaration of Helsinki guidelines and the principles of Good Practice and was approved by the Ethics Committee of both hospitals (PR(AG) 245/2015).

Baseline clinical and laboratory assessment

Data on demographics (sex, age and race), toxic exposure (alcohol, tobacco), cardiovascular risk factors (on-treatment arterial hypertension, diabetes and dyslipidemia) and anthropomorphic characteristics (height, weight, and waist circumference) were prospectively collected at the time of enrollment. A blood test was performed including hematology and a standard biochemical panel as well as insulin level, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, HBV serology (quantitative HBsAg, anti-HBc, HBeAg and anti-HBe) and HBV virology. HBV DNA was determined using the COBAS 6800 HBV test (Roche Diagnostics, Mannheim, Germany), with a lower limit of quantification of 20 IU/mL and lower limit of detection of 10 IU/mL. Antibodies against HCV, hepatitis D virus and HIV were also tested.

Central obesity was defined as a waist circumference greater than 102 cm in men and 88 cm in women. Insulin resistance was determined with the homeostasis model assessment[13]. The nonalcoholic fatty liver disease (NAFLD) score was also calculated, and values > 0.675 were considered suggestive of advanced NAFLD-related fibrosis[14]. Liver elastography (Fibroscan® 502 Touch, Echosens, Paris, France), including the control attenuation parameter (CAP) as a marker to quantify hepatic steatosis, was carried out in all patients. CAP was chosen as marker of liver steatosis because it has been pointed out as more accurate than other scores such as Hepatic Steatosis Index in patients with chronic infection by HBV[15].

Carotid artery evaluation

Carotid Doppler ultrasound study (Vivid I, General Electric, GE Healthcare, Horten, Norway, equipped with a 3.5-10 MHz linear transducer) was performed to determine the IMT. B-mode ultrasound with a semi-automatic edge-detection algorithm was used to measure the medium and maximum IMT on the far wall of both the right and left side of the common carotid artery at 1 cm before the bifurcation, measuring at least 250 mm of a straight arterial segment. The presence of an atheroma plaque was established based on the Manheim criteria, as a focal structure that encroached into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or demonstrated a thickness > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface[16]. The presence of plaques was investigated in the common carotid artery and internal and external carotid arteries. Subclinical atherosclerosis was established on an increased IMT (≥ 1.2 mm) and/or detection of a carotid plaque[16]. To avoid interobserver variability, ultrasound measurements were performed by operators specifically trained in carotid ultrasound cardiovascular risk assessment. Moreover, measurement of the IMT at the common carotid artery presented high reproducibility and interobserver agreement in previous multicenter studies[17].

Statistical analysis

Normally distributed quantitative variables were compared with the Student *t* test and those with a non-normal distribution with the Mann-Whitney *U* test. Quantitative variables were expressed as the median and interquartile range or mean and standard deviation depending on the group size. Categorical variables were compared between groups using the χ^2 or Fisher exact test, as appropriate.Variables with a *P* value < 0.10 in the univariate model were analyzed in a multivariate logistic regression model. Quantitative variables were also introduced as categorical (median or mean of the overall cohort) in order to increase the potency of the models. In the case of homeostasis model assessment, values from included patients were contrasted with the normal from general population[18]. Odds ratios (ORs) and 95% confidence intervals were calculated for the independent predictive factors of carotid plaques and subclinical atherosclerosis. Only patients with available data for all the variables considered in the analysis were included in the multivariate logistic regression models.

Because enrollment of patients with CHB was difficult due to the limitation to naïve subjects, the number of CHB and ICs differed. For this reason, a propensity score analysis matched by sex, age and main cardiovascular risk factors was carried out by using the package of R[19]. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS, version 26.0 (SPSS Inc, Armonk, NY, United States).

RESULTS

Baseline characteristics of patients

In total, 402 individuals were enrolled: 201 chronic HBV-infected and 201 healthy controls. Overall, 218 (54.2%) were males, and the more common cardiovascular risk factors were active or former smokers (33.3%), alcohol intake (25.8%) and dyslipidemia (19.9%). Both alcohol intake and central obesity were more common in the control group. Table 1 shows the baseline characteristics of the included cohorts of patients.

In the HBV-infected group, 152 (75.6%) were ICs and 49 (24.4%) CHB. In the latter, 12 (24.4%) patients had liver cirrhosis. Baseline characteristics according to the classification of HBV infection were summarized in Table 1. Most patients were Caucasian (68.2%), and the median age was 47 years. Demographical features did not differ between the two groups. Dyslipidemia was more common in ICs than in patients with CHB, whereas the prevalence of the remaining cardiovascular risk factors was similar. ALT, HBV DNA and HBsAg values as well as liver stiffness were significantly higher

Table 1 Baseline characteristics of included subjects and comparison between infected and non-infected subjects and among patients infected by hepatitis B virus according to the phase of the infection (chronic hepatitis B *vs* inactive carriers)

	Controls	Chronic hepatitis B	Inactive carriers		
	n = 201	*n* = 49	*n* = 152	*P* value[1]	*P* value[2]
Age, yr	48.1 ± 10.2	48.4 ± 12.0	46.5 ± 13.4	0.29	0.28
Male sex (%)	103 (51.2)	31 (64.6)	84 (54.9)	0.13	0.16
Race (%)				< 0.001	0.48
Caucasian	186 (92.5)	35 (72.9)	102 (66.7)		
Asian	2 (1.0)	6 (12.5)	11 (7.2)		
African	0 (0)	6 (12.5)	28 (18.3)		
Hispanic	13 (6.5)	1 (2.1)	12 (7.8)		
Cardiovascular risk factors (%)					
Tobacco exposure	74 (36.8)	15 (31.3)	45 (29.6)	0.09	0.48
Alcohol intake[3]	70 (34.8)	11 (22.9)	23 (15.4)	< 0.001	0.17
Hypertension	40 (19.9)	11 (22.9)	27 (17.8)	0.46	0.28
Diabetes	4 (2.0)	4 (8.3)	6 (3.9)	0.08	0.2
Dyslipidemia	46 (22.9)	3 (6.3)	31 (20.4)	0.08	0.02
Central obesity	52 (25.9)	10 (20.8)	27 (17.9)	0.04	0.4
BMI, kg/m^2	25.3 ± 3.6	26.0 ± 3.9	25.2 ± 4.0	0.76	0.22
Liver cirrhosis (%)	0 (0)	12 (24.4)	0 (0)	< 0.001	< 0.001
ALT, IU/mL	22.6 ± 12.7	59.7 ± 48.6	25.6 ± 16.7	< 0.001	< 0.001
GGT, IU/mL	30.4 ± 30.9	60.7 ± 87.9	31.5 ± 63.3	0.24	< 0.001
LDL, mg/dL[4]	131.9 ± 38.3	116.9 ± 30.7	118.1 ± 32.6	0.002	0.82
Triglycerides, mg/dL	108.0 ± 56.7	96.4 ± 46.3	106.8 ± 59.1	0.54	0.26
C-reactive protein, mg/dL[5]	0.29 ± 0.42	0.84 ± 1.90	1.00 ± 9.00	0.42	0.88
HOMA index[5]	2.05 ± 1.84	4.20 ± 3.50	3.40 ± 3.90	< 0.001	0.18
HBsAg, logIU/mL	-	3.6 ± 0.8	2.9 ± 1.2	-	0.001
HBV DNA, logIU/mL	-	4.4 ± 1.8	2.4 ± 1.1	-	< 0.001
Transient elastography, kPa	4.5 ± 1.4	11.3 ± 10.9	5.5 ± 2.4	< 0.001	< 0.001
CAP, dB/m	246.5 ± 54.5	227.4 ± 55.0	227.2 ± 56.2	0.001	0.98

Data are expressed as the median (interquartile range) or as the n (%).
[1]Comparison between hepatitis B virus-infected and non-infected controls.
[2]Comparison between patients with chronic hepatitis B and inactive carriers.
[3]Significant alcohol intake was defined as > 30 g per day for men and > 20 g per day for women.
[4]These data were available in 132 non-infected subjects.
[5]This data was available in 83 non-infected subjects. ALT: Alanine transaminase; CAP: Control attenuation parameter; GGT: Gamma glutamyltransferase; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; BMI: Body mass index; LDL: Low-density lipoprotein; HOMA: Homeostasis model assessment.

in patients with CHB.

Carotid plaques and subclinical atherosclerosis in HBV-infected group in comparison with the control group

No differences were observed between the HBV-infected group and the control group in terms of gender and age, although some cardiovascular risk factors such as central obesity and dyslipidemia were more common among non-HBV infected individuals (Table 1). In fact, although increased values of liver stiffness were observed in patients with HBV infection, CAP levels were higher in subjects within the control group.

Table 2 Factors associated with the presence of carotid plaques and subclinical atherosclerosis

	Subclinical atherosclerosis			Carotid plaques		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
		OR (95%CI)	*P* value		OR (95%CI)	*P* value
Age, years	< 0.001			< 0.001		
Age > 50 years	< 0.001	1.45 (1.24-1.48)	< 0.001	< 0.001	1.43 (1.21-1.44)	< 0.001
Male sex	0.004		0.336	0.003		0.212
Central obesity	0.008		0.073	0.007		0.141
Tobacco exposure	0.003		0.081	0.002		0.187
Alcohol intake[1]	0.109		-	0.073		0.929
Arterial hypertension	< 0.001		0.949	< 0.001		0.690
Diabetes mellitus	0.004	1.13 (1.03-1.59)	0.028	0.01		0.082
Dyslipidemia	0.001			< 0.001		0.095
Chronic hepatitis B	0.001	1.25 (1.11-1.41)	< 0.001	0.016	1.18 (1.06-1.34)	0.004
Transient elastography, kPa	0.01		0.090	0.073		0.438
Transient elastography > 5.7 kPa	0.008			0.048		
CAP, dB/m	< 0.001		0.989	< 0.001		0.577
CAP > 238 dB/m	< 0.001			< 0.001		
AST, IU/mL	0.115		-	0.152		-
AST > 27 IU/mL	0.102			0.131		
GGT, IU/mL	< 0.001		0.067	0.001		0.947
GGT > 36 IU/mL	< 0.001			0.001		
Triglycerides, mg/dL	0.011		0.059	0.018		0.957
Triglycerides > 106 mg/dL	0.009			0.009		
LDL, mg/dL	0.651		-	0.180		-
HOMA index	0.038		0.073	0.278		0.105
HOMA index > 1.2	0.150			0.489		
HOMA index > 3	0.002			0.018		

Data are given as mean ± SD or as n (%).

[1]Significant alcohol intake was defined as > 30 g per day for male and > 20 g per day for female. At the multivariate logistic regression model only patients with available data for all the variables were included. The cut-off for inclusion was a *P* value < 0.10 in the univariate model. AST: Aspartate transaminase; CAP: Control attenuation parameter; GGT: Gamma glutamyltransferase; CI: Confidence interval; OR: Odds ratio; HOMA: Homeostasis model assessment; LDL: Low-density lipoprotein.

Overall, patients with HBV infection presented higher rates of both carotid plaques (20.9% *vs* 18.4%) and subclinical atherosclerosis (24.4% *vs* 19.4%), though these differences did not reach statistical significance ($P = 0.31$ and $P = 0.14$, respectively). When the three groups were analyzed separately, taking into account the state of HBV infection, we learnt that patients with CHB had higher rates of carotid plaques (32.7%) and subclinical atherosclerosis (40.8%) than controls (18.4% and 19.4%, respectively), as shown in Figure 1. However, the rates were similar when only ICs and controls were compared (carotid plaques: 17.1% *vs* 18.4%, $P = 0.446$; subclinical atherosclerosis: 19.1% *vs* 19.4%, $P = 0.525$). Although the typical cardiovascular risk factors were linked with both carotid plaques and subclinical atherosclerosis on the univariate analysis, on the multivariate (Table 2) the only factors independently associated with the presence of subclinical atherosclerosis were older age (OR 1.45, $P < 0.001$), diagnosis of CHB (OR 1.23, $P < 0.001$) and diabetes (OR 1.13, $P = 0.028$). Similar results were observed

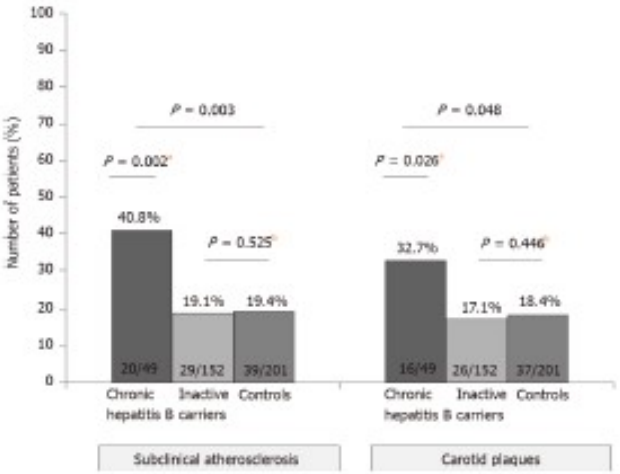

Figure 1 Rate of carotid plaques and subclinical atherosclerosis (defined as intima-media thickness ≥ 1.2 mm and/or presence of atheroma plaques) in the overall cohort. *$P < 0.05$; †$P < 0.01$.

regarding the carotid plaques, with age over 50 years (OR 1.43, $P < 0.001$) and CHB (OR 1.18, $P = 0.004$) as independent risk factors.

Though this is a prospective study, due to the different number of HBV-infected subjects included in each group, a propensity score analysis including all patients with CHB ($n = 49$) and a cohort with the same number of IC and controls, balanced by age, sex and main cardiovascular risk factors, was carried out. The multivariate analysis of this propensity score revealed similar results as shown the analysis performed with the overall cohort, with older age (OR 1.30, $P = 0.01$) and CHB state (OR 1.26, $P = 0.03$) as independent risk factors associated with the presence of carotid plaques (Table 3).

Carotid plaques and subclinical atherosclerosis in CHB and HBV ICs

Overall, 49 (24.4%) patients had subclinical atherosclerosis, including 42 (20.9%) with carotid plaques, 19 (9.5%) with increased IMT (≥ 1.2 mm) and 12 (6%) with both findings. The prevalence of both subclinical atherosclerosis ($P = 0.003$) and carotid plaques ($P = 0.019$) was higher in patients with CHB than ICs (Figure 2). Liver cirrhosis was associated with an increased risk of subclinical atherosclerosis (42.0% *vs* 23.0%) although the difference did not reach statistical significance ($P = 0.13$). The impact of CHB on the presence of subclinical atherosclerosis remained when patients were stratified by age (Figure 2). In those ≤ 50 years, the prevalence of subclinical atherosclerosis was 12.5% in CHB patients and only 2.2% in ICs ($P = 0.058$). In patients aged over 50 years, those with CHB also had a higher prevalence of subclinical atherosclerosis (68.0% *vs* 45.8%, $P = 0.051$). Age was strongly associated with the presence of subclinical atherosclerosis ($P < 0.001$). On multivariate analysis, factors independently associated with the presence of subclinical atherosclerosis were older age (OR 1.11, $P < 0.001$), increased values of gamma-glutamyltransferase (OR 5.9, $P = 0.007$) and CHB (OR 3.35, $P = 0.017$). When age was introduced as a categorical variable (threshold of 50 years), both CHB and age remained as predictive factors of subclinical atherosclerosis (Table 4).

In terms of carotid plaques, impact of CHB was especially important in patients aged ≤ 50 years (Figure 2). On the multivariate analysis, only age (age > 50 years, OR 1.45, 95% confidence interval 1.30-1.62, $P < 0.001$) and increased gamma-glutamyltransferase levels (gamma-glutamyltransferase > 36 IU/mL, OR 1.19, 95% confidence interval 1.04-1.37, $P = 0.012$) independently impacted the presence of carotid plaques.

Four patients with CHB and liver cirrhosis presented a NAFLD score > 0.675, suggesting significant fibrosis. Two of them had subclinical atherosclerosis, but none had a history of diabetes, and their body mass index was < 25 kg/m^2 and CAP < 250 dB/m. Otherwise, they presented an HBV DNA > 2000 IU/mL, suggesting that fibrosis was likely related to CHB.

Table 3 Factors associated with the presence of carotid plaques in a propensity score matched by age, sex and main cardiovascular risk factors

	Groups of study			Univariate analysis	Multivariate analysis	
	Chronic hepatitis B, *n* = 49	Inactive carriers, *n* = 49	Controls, *n* = 49	*P* value	OR (95%CI)	*P* value
Age, yr	48.4 ± 12.0	48.7 ± 13.0	47.1 ± 11.3	0.78		
Age > 50 yr (%)	25 (51.0)	24 (49.0)	23 (46.9)	0.92	1.30 (1.12-1.50)	0.01
Male sex (%)	31 (64.6)	31 (63.3)	31 (63.3)	1		0.72
Caucasian race (%)	35 (72.9)	32 (65.3)	38 (77.6)	0.41		-
Cardiovascular risk factors (%)						
Tobacco exposure	15 (31.3)	13 (26.5)	16 (32.7)	0.80		0.71
Hypertension	11 (22.9)	10 (20.4)	11 (22.4)	0.96		0.40
Diabetes	4 (8.3)	5 (10.2)	3 (6.1)	0.76		0.57
Dyslipidemia	3 (6.3)	3 (6.1)	5 (10.2)	0.68		0.54
Central obesity	10 (20.8)	10 (20.4)	10 (20.4)	1		0.06
BMI, kg/m^2	26.0 ± 3.9	26.3 ± 4.9	26.4 ± 3.8	0.90		0.16
ALT, IU/mL	48.6 ± 9.4	26.9 ± 9.4	25.2 ± 9.6	< 0.001		0.08
GGT, IU/mL	60.7 ± 87.9	42.7 ± 106.0	37.7 ± 50.9	0.45		0.07
LDL, mg/dL[1]	116.9 ± 30.7	120.3 ± 32.6	112.7 ± 35.3	0.72		0.87
Triglycerides, mg/dL	96.4 ± 46.3	99.0 ± 57.5	115.3 ± 77.1	0.30		0.41
HOMA index[2]	4.2 ± 3.5	4.7 ± 5.8	2.6 ± 2.6	0.14		0.40
Transient elastography, kPa	11.3 ± 10.9	5.7 ± 3.0	5.0 ± 7.9	< 0.001		0.80
CAP, dB/m	227.4 ± 55.0	232.1 ± 48.6	251.5 ± 62.8	0.095		0.49
Chronic hepatitis B state (%)	49 (100)	0 (0)	0 (0)	< 0.001	1.26 (1.09-1.47)	0.03

[1]Only available for 34 controls.

[2]Only available for 25 non-infected controls. ALT: Alanine transaminase; CAP: Control attenuation parameter; GGT: Gamma glutamyltransferase; BMI: Body mass index; LDL: Low-density lipoprotein; CI: Confidence interval; OR: Odds ratio; HOMA: Homeostasis model assessment.

DISCUSSION

The results of this prospective collaborative study including well-characterized HBeAg negative chronic HBV infection show that CHB is independently associated with the presence of both carotid plaques and subclinical atherosclerosis. These results suggest that HBV infection may have a role as a cardiovascular risk factor in naïve patients with CHB.

There are few studies assessing the potential effect of HBV infection on development of carotid atherosclerosis, and they are all cross-sectional with a limited number of HBsAg-positive populations (Supplementary Table 1). In two of these studies, an association was observed between HBsAg positivity and early atherosclerosis[11,20]. The severity of liver disease was not determined in any of these studies, and therefore no data on the possible impact of CHB was reported. In our cohort, similar to HCV and HIV, patients with HBV infection had greater risk of subclinical atherosclerosis and carotid plaques than controls. In this line, a study focusing on early atherosclerosis in liver disease (NAFLD, HCV and HBV) found that all three conditions were strongly associated with early atherosclerosis (OR 1.96, 1.61 and 1.40 respectively), regardless of the patients' classical risk factors, including insulin resistance and metabolic syndrome [20].

Table 4 Baseline characteristics and analyses of factors associated with the presence of subclinical atherosclerosis of patients with hepatitis B virus infection

	Subclinical atherosclerosis	No subclinical atherosclerosis	Univariate analysis	Multivariate analysis		Adjusted multivariate analysis	
	n = 49	*n* = 152	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age, yr	57 (53.5-62.0)	42 (33.0-52.0)	< 0.001	1.10 (1.06-1.16)	< 0.001	1.19 (1.12-1.25)	< 0.001
Age > 50 yr (%)	45 (91.8)	46 (30.3)	< 0.001	21.9 (6.7-71.8)	< 0.001		
Male sex (%)	31 (63.3)	84 (55.3)	0.207	-	-		
BMI, kg/m^2	70.0 (64-77)	69.5 (62-80)	0.261	-	-		
Central obesity (%)	13 (26.5)	24 (16.0)	0.079	-	0.298		0.356
Tobacco exposure (%)	22 (44.9)	38 (25.2)	0.008	-	0.208		0.920
Alcohol intake[1] (%)	14 (28.5)	20 (13.5)	0.016	-	0.876		0.092
Arterial hypertension (%)	18 (36.7)	20 (13.2)	0.001	-	0.789		0.419
Diabetes mellitus (%)	5 (10.2)	5 (3.3)	0.067	-	0.994		0.457
Dyslipidemia (%)	16 (32.6)	18 (11.9)	0.001	-	0.876		0.786
Chronic hepatitis B (%)	20 (40.8)	28 (18.4)	0.002	3.35 (1.20-9.10)	0.017	1.89 (1.75-2.04)	< 0.001
Liver cirrhosis (%)	5 (10.2)	7 (4.6)	0.138	-	-		
ALT, IU/mL	29 (22.0-43.5)	24 (17.0-34.0)	0.310	-	–		
ALT > ULN (%)	10 (20.4)	22 (14.5)	0.220	-	-		
GGT, IU/mL	31 (18.0-62.5)	20 (16.0-28.0)	< 0.001	-	0.120		
GGT > ULN (%)	16 (32.7)	8 (5.3)	< 0.001	5.90 (1.60-21.40)	0.007	1.27 (1.19-1.36)	< 0.001
HbA1c, %	5.5 (5.3-5.8)	5.4 (5.1-5.6)	0.004	-	0.78		0.551
HbA1c ≥ 6% (%)	7 (14.6)	6 (4.1)	0.018	-	-		
HOMA index	3.3 (2.2-6.0)	2.4 (1.7-3.6)	0.038	-			0.054
HOMA index > 3 (%)	22 (45.8)	51 (34.2)	0.102	-	-		
HBsAg, logIU/mL	3.2 (2.5-3.6)	3.3 (2.4-4.0)	0.321	-	-		
HBV DNA, logIU/mL	3.1 (2.4-3.8)	2.9 (2.3-3.5)	0.533	-	-		
Transient elastography, kPa	6.2(4.2-10.3)	5.2 (4.2-6.9)	0.059	–	0.327	1.01 (1.00-1.01)	< 0.001
CAP, dB/m	246 (210.0-289.0)	213 (185.0-261.5)	0.004	–	0.220	1.000 (1.000-1.001)	0.006
CAP > 227 dB/m (%)	29 (67.4)	51 (38.3)	0.001	–	0.172		

Data are given as mean ± SD or as n (%).

[1]Significant alcohol intake was defined as > 30 g per day for male and > 20 g per day for female.At the multivariate logistic regression model only patients with available data for all the variables were included (n = 250). The cut-off for inclusion was a *P* value < 0.10 in the univariate model. ALT: Alanine transaminase; BMI: Body mass index; HBV: Hepatitis B virus; CI: Confidence interval; CAP: control attenuation parameter; HbA1c: Hemoglobin A1c; GGT: Gamma glutamyltransferase; OR: Odds ratio; ULN: Upper limit of normality; HOMA: Homeostasis model assessment; HBsAg: Hepatitis B surface antigen.

The suggested mechanisms to explain HBV-related atherosclerosis is direct vascular damage by the virus and particularly accelerated oxidative damage and the pro-inflammatory state of chronic HBsAg carriers[21]. Knowledge about the immune response in HBV-infected patients has increased considerably in recent years[9]. The production of proinflammatory cytokines (*e.g.*, interleukin1b, tumor necrosis factoralpha) steadily increases during early life until it reaches the state of chronic low-

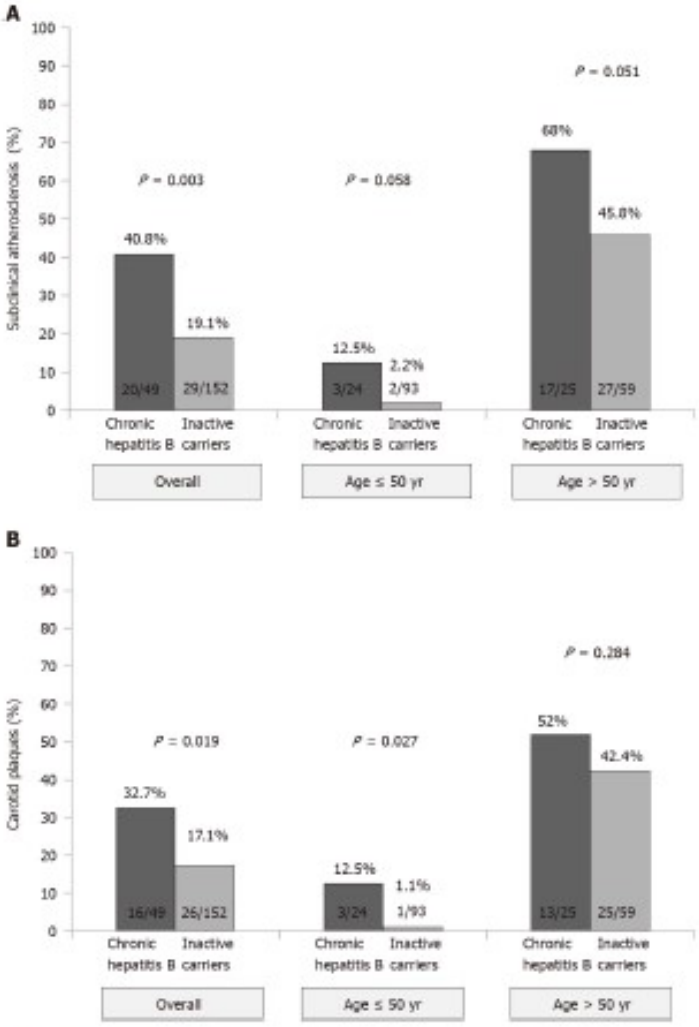

Figure 2 Rate and impact of age and hepatitis B e antigen negative phase of infection (chronic hepatitis *vs* inactive carriers) in subclinical atherosclerosis and carotid plaques in the cohort of patients chronically infected by hepatitis B virus. A: Subclinical atherosclerosis; B: Carotid plaques.

grade systemic inflammation that occurs in elderly persons[22]. HBeAg-negative CHB [3] has been linked with a propensity to mount proinflammatory immune reactions [9]. In this population, liver inflammation is triggered by HBV-specific CD8 T cells, and it is associated with increased levels of chemokines and natural killer cell activation[23]. This proinflammatory state is independent of ALT levels and even HBV DNA levels, which usually fluctuate in this stage of the disease[24]. However, it has been clearly associated with progression of liver disease[9].

In our study, neither ALT levels nor HBV DNA were associated with an increased prevalence of subclinical atherosclerosis. This fact may be explained by the inclusion of patients with CHB with normal ALT but increased values of HBV DNA and liver damage at liver biopsy. On the other hand, some of the patients with liver cirrhosis presented relatively low HBV DNA levels. Older age and CHB status were independent factors associated with increased carotid plaques and subclinical atherosclerosis, in line with the proinflammatory state induced by older age and progression of liver damage.

Serum paraoxonase-1 and arylesterase activities, plasma free sulfhydryl groups and total antioxidant capacity, all factors associated with increased susceptibility to atherogenesis[24,25], are lower in HBV patients than in non-infected controls[26]. This finding can also contribute to the development of atherosclerosis in patients with HBV infection. Moreover, the association between fibrosis progression and exacerbated immune responses in patients with CHB is well established[9,10,27], so this dysfunctional immunological response might also bring an increase in cardiovascular risk.

Accordingly, HCV infection has been linked with increased prevalence of carotid plaques in those patients with evidence of advanced liver fibrosis[4]. In that study, Petta *et al*[4] showed that 73 of 174 HCV patients (42%) had carotid plaques, with older age and liver fibrosis as independent factors associated with carotid atherosclerosis, results in line with our findings because age and CHB were the two variables independently linked with increased risk of both carotid plaques and subclinical atherosclerosis. The role of liver damage is especially relevant in view of the lack of statistical differences when HBV ICs were compared with controls, suggesting that HBV infection may predispose to cardiovascular risk only when it is associated with a proinflammatory state, as described in patients with CHB[9,27].

This study has some limitations. First, the fact that only naïve patients were included turned out in a relatively low number of patients with HBeAg negative CHB and inferior to the cohort of HBV ICs. However, these patients were well characterized, and all met the European Association for the Study of the Liver criteria for CHB, including 24% with liver cirrhosis. Second, there were some differences among the groups. In order to minimize this potential bias, a propensity score was carried out, confirming the role of CHB status as cardiovascular risk factor. Moreover, data presented herein derived from a prospective, collaborative cohort of well-characterized patients, including different ethnicity and therefore HBV genotypes.

Interestingly, since reversion of liver fibrosis in patients with CHB is possible due to nucleos(t)ide analog therapy[28], it would be appealing to assess the potential impact of oral antiviral therapy on early atherosclerosis related to HBV infection, especially to view the effect of antiviral treatment for HCV in the overall cardiovascular risk and specifically in the carotid plaques[7].

CONCLUSION

In conclusion, in this prospective, case-control collaborative study, presence of subclinical atherosclerosis and carotid plaques were more frequent in patients with HBV infection than controls. The presence of liver damage was an independent factor associated with subclinical atherosclerosis and carotid plaques, regardless of the classical cardiovascular factors.

ARTICLE HIGHLIGHTS

Research background

There is an increased risk of atherosclerosis in patients with chronic hepatitis C and also in individuals with human immunodeficiency virus infection.

Research motivation

There is scarce data on the potential role of hepatitis B virus infection as a cardiovascular risk factor.

Research objectives

To assess whether the stage of hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus infection impacts the presence of both carotid plaques and subclinical atherosclerosis and to evaluate if the risk of both carotid plaques and subclinical atherosclerosis in HBeAg-negative patients differ to those of healthy controls.

Research methods

Prospective case-control study with 402 subjects prospectively recruited at the outpatient clinic. Anthropomorphic and metabolic measures, liver stiffness and carotid Doppler ultrasound were performed.

Research results

Patients with HBeAg-negative chronic hepatitis B presented a higher rate of carotid plaques than healthy controls (32.7% *vs* 18.4%, $P = 0.002$), but no differences were observed between controls and hepatitis B inactive carriers. HBeAg-negative chronic hepatitis B was an independent risk factor for carotid plaques as well as age, dyslipidemia and central obesity.

Research conclusions

These results suggest that hepatitis B infection may have a role as a cardiovascular risk factor in patients with chronic hepatitis B.

Research perspectives

Further studies should assess the potential impact of oral antiviral therapy on early atherosclerosis related to hepatitis B virus infection.

ACKNOWLEDGEMENTS

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10.3 Comunicaciones en congresos nacionales e internacionales

10.3.1 Congresos nacionales

- M Riveiro-Barciela, F Martínez-Valle, **C Marcos-Fosch**, M Bes, I Sanz-Pérez, D Tabernero, F Rodríguez-Frias, S Sauleda, R Esteban, M Buti. Papel de la respuesta inmune específica T contra los antígenos del VHB en el aumento de aterosclerosis subclínica en hepatitis crónica B. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2017. Póster.

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Objetivos: La infección por el virus de la hepatitis E (VHE) puede ser causa de hepatitis aguda y crónica en pacientes trasplantados de órgano sólido (TOS) o hematopoyético (TPH). Sin embargo, los datos relativos a la prevalencia de la hepatitis E antes del trasplante son escasos. Se calcula que en nuestro medio un 11% de los donantes sanos ha tenido contacto con el VHE [Sauleda et al. Transfusion. 2015;55:972-9]. El objetivo de este estudio fue analizar la prevalencia y los factores de riesgo de infección por hepatitis E en receptores de órganos sólidos o hematopoyéticos previo al trasplante.

Métodos: Estudio prospectivo, unicéntrico que incluyó pacientes que posteriormente recibieron un TOS o TPH durante el año 2014. La infección por hepatitis E se evaluó mediante determinación de ARN del VHE (Cobas VHE®, Roche Diagnostics, 95% límite de detección 15,9 UI/ml) y serología (IgG anti-VHE, ensayo Mikrogen). Después de firmar el consentimiento informado, los pacientes completaron una encuesta epidemiológica de posibles factores de riesgo para la infección por VHE.

Resultados: Se incluyeron un total de 199 pacientes: 155 TOS (60 pulmón, 62 hígado y 33 de riñón- todos ellos en hemodiálisis) y 44 TPH (todos tratados previamente con quimioterapia). Características basales: 128 (64,3%) hombres, edad media 55 años y 84,3% de raza caucásica. El 60% presentaba uno o más factores de riesgo cardiovascular. Analíticamente, la mediana de AST fue 20 UI/L (rango 5-49), ALT 19 UI/L (rango 4-58), bilirrubina 0,53 mg/dl (0,19-1,79) y albúmina 3,9 g/dl (2,3-5). Todos los pacientes tenían RNA del VHE indetectable y IgG anti-VHE fue positiva en siete pacientes (5,6%). Estos 7 sujetos eran hombres, con edad media de 52 años, 3 (43%) de raza no caucásica, 5 de ellos en lista de trasplante renal y los otros dos en lista de pulmón y a destacar que 5 de ellos (71%) eran residentes en áreas rurales. No se asoció con la exposición al VHE los antecedentes profesionales, el consumo de carne cruda o de caza, vivienda habitual en zonas rurales o viajes a países dónde la infección es endémica.

Conclusiones: La prevalencia de infección por VHE en receptores de órgano sólido y hematopoyético es baja, siendo la IgG anti-VHE del 6%. A pesar de incluir pacientes con cierto grado de inmunodepresión (cirrosis, hemodiálisis, terapia con quimioterapia) no se observaron casos de infección activa, lo que sugiere que el riesgo de infección por VHE se debe asociar principalmente la propia inmunosupresión postrasplante.

110. PAPEL DE LA RESPUESTA INMUNE ESPECÍFICA T CONTRA LOS ANTÍGENOS DEL VHB EN EL AUMENTO DE ATEROSCLEROSIS SUBCLÍNICA EN HEPATITIS CRÓNICA B

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Introducción: Los pacientes con hepatitis crónica B (HCB) con lesión hepática leve presenta un aumento del grosor media-íntima (GMI) [Riveiro-Barciela et al. AEEH. 2016].

Objetivos: Valorar la asociación entre GMI y la respuesta inmune T contra diferentes antígenos del virus de la hepatitis B (VHB) en una serie más amplia de pacientes HCB, incluyendo sujetos con lesión hepática significativa.

Métodos: Estudio prospectivo con 173 pacientes sin tratamiento antiviral. El GMI fue estimado mediante Doppler carotídeo. La presencia de placas de ateroma o GMI ≥ 1,2 mm se consideró diagnóstico de aterosclerosis subclínica (AS) [Sinn et al. Gastroenterology. 2016]. El riesgo cardiovascular (CV) fue valorado mediante análisis de distintos factores asociados tanto del huésped (síndrome metabólico, edad, elastografía y controlled attenuation parameter-CAP) como de la infección por VHB. Los resultados de GMI fueron comparados con una cohorte española de sujetos sanos, estratificada por edad y sexo [Junyent et al. Med Clin (Barc). 2005]. La respuesta inmune específica T contra el VHB fue estudiada mediante ELISpot IFNγ contra 3 antígenos recombinantes (rHBsAg, rHBcAg, rHBeAg) en un subgrupo de 63 sujetos.

Resultados: 99 (57%) hombres, 67% caucásicos, edad media 46 ± 13 años, 20 (12%) con fibrosis hepática significativa (fibrosis ≥ 2 y/o necroinflamación ≥ 2 -índice de ISHAK). 76 (44%) presentaban al menos un factor de riesgo CV y 11 (6%) cumplían criterios de síndrome metabólico. En comparación con sujetos sin infección por VHB se observó un aumento significativo del GMI en los pacientes con HCB (0,8 vs 0,65, p < 0,001), tanto en portadores inactivos como con lesión hepática. El GMI fue mayor en los sujetos con lesión hepática que en portadores inactivos (0,86 vs 0,81) diferencia que no alcanzó significación estadística. La presencia de AS fue similar entre pacientes con lesión hepática y portadores inactivos. Los niveles de ALT, ADN VHB o HBsAg no se correlacionaron con el GMI. Sin embargo, sí se observó correlación positiva entre el GMI y el número de parámetros que componen el síndrome metabólico (r = 0,41, p < 0,001), el diámetro abdominal (r = 0,42, p < 0,001), CAP (r = 0,38, p < 0,001), niveles de triglicéridos (r = 0,21, p = 0,006) y colesterol total (r = 0,2, p = 0,008). La respuesta inmune específica T contra rHBsAg, rHBcAg y rHBeAg fue 18,6 ± 46,8, 19 ± 24 y 18 ± 22 SFC/106 PMNC. Existió una correlación positiva entre respuesta contra el rHBcAg y mayor GMI (r = 0,25, p = 0,046). En los pacientes con AS los niveles de IFNγ contra rHBcAg fueron superiores a aquellos sin AS (25 vs 16 SFC/106 PMNC), diferencia que no alcanzó significación estadística, si siendo significativas las diferencias en los niveles de GGT y CAP.

Conclusiones: Los sujetos con HCB presentan un mayor GMI que los sujetos sanos. La presencia de AS se relacionó con factores asociados a esteatosis hepática (GGT, CAP, diámetro abdominal) aunque también con mayor respuesta T contra el rHBcAg.

111. CAMBIO PROGRESIVO EN LA INDICACIÓN DE TRATAMIENTO DEL VHC CON AAD: AUMENTO DE LOS *NAÏVE* Y TRATAMIENTO DE LOS PACIENTES CON POCA FIBROSIS HEPÁTICA

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Introducción: A partir del año 2015, coincidiendo la puesta en marcha del Plan Estratégico para el VHC y la rápida aparición de

- Mar Riveiro-Barciela, **Cristina Marcos-Fosch**, Fernando Martínez-Valle, Fabrizio Bronte, Olimpia Orozco, Isidro Sanz-Pérez, Daniele Torres, María-Teresa Salcedo, Salvatore Petta, Rafael Esteban, María Buti. La presencia de hepatitis crónica B es un factor de riesgo independiente de aterosclerosis subclínica en pacientes HBeAg negativo. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2018. Comunicación oral.

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COMUNICACIONES ORALES

43.º Congreso Anual de la Asociación Española para el Estudio del Hígado

Madrid, 21-23 de febrero de 2018

Sesión oral n.º 2

Moderadores: Xavier Torras y Beatriz Mínguez

EL CRUCE DE BILIRRUBINA Y PROTROMBINA MEJORA LA CAPACIDAD PRONOSTICA DEL CLIF-C ACLF SCORE EN PACIENTES CON *ACUTE-ON-CHRONIC LIVER FAILURE*

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Introducción: El fracaso hepático agudo-sobre-crónico (ACLF) asocia una alta mortalidad y recientemente se ha propuesto un modelo pronóstico específico (CLIF-C ACLF). Algunos pacientes con ACLF presentan valores de bilirrubina (mg/dL) superiores al índice de protrombina (%), lo que se postula como marcador de pronóstico ominoso aunque nunca se ha comprobado. El estudio actual evalúa el papel pronóstico del cruce bilirrubina/protrombina en una cohorte contemporánea de pacientes con ACLF.

Métodos: Se recogieron retrospectivamente pacientes ingresados en UCI (2008-16) con criterios de ACLF y se analizó la supervivencia libre de trasplante a 28 y 90 días. Se identificaron los pacientes que en algún momento presentaron valores de bilirrubina (mg/dL) superiores al índice de protrombina (%). Se recogieron los días desde el ingreso al evento cruce, día de decisión de limitación terapéutica y muerte. Se evaluó la predicción del modelo CLIF-C ACLF al tercer día, solo y asociado a la variable cruce. Se estudió la discriminación y calibración de los modelos (ROC y test Hosmer-Lemeshow) y y la mejora del CLIF-C ACLF score al añadir la variable cruce mediante el test de Delong.

Resultados: Se incluyeron 366 pacientes con ACLF grados 1(25%), 2(41%) y 3(34%). Las etiologías de la cirrosis fueron alcohol (55%), VHC (29%), alcohol + virus (11%) y otros (5%) y las causas de ingreso fueron sepsis (35%), hemorragia (21%), encefalopatía (18%) y otros (26%). En 54 (15%) pacientes se observó el cruce de bilirrubina/protrombina, que asoció una alta mortalidad a los 28 y 90 días: 89% de (47 muertes, 1 trasplante) y 98% (51 muertes, 2 trasplantes). La mediana de tiempo desde el ingreso al cruce fueron 5,5 días (IQR 15), desde el cruce a la limitación terapéutica (en 33/54 pacientes) fueron 4 días (IQR 9,5) y desde el cruce a la muerte fueron 4,5 días (IQR 12). El score CLIF-C ACLF al tercer día pronosticó correctamente la mortalidad a 28 y 90 días: AUROC 0,831 (0,79-0,88) y 0,804 (0,76-0,85), respectivamente. El cruce de bilirrubina/protrombina se asoció a la mortalidad a los 28 y 90 días independientemente del CLIF-C ACLF score: OR 11,9 (4,5-31,5) y 35,6 (4,7-270), respectivamente. La adición de esta variable al CLIF-C ACLF mejoró significativamente sus predicciones a 28 y 90 días: AUROC 0,865 y 0,837 respectivamente (Delong test p < 0,05). La calibración del score CLIF-C ACLF con o sin variable cruce fue buena a los 28 y 90 días (test H-L p = ns). En pacientes que presentaron el evento cruce, el CLIF-C ACLF score calculado en ese momento no mejoró el rendimiento del modelo. El MELD y Child-Pugh scores mostraron subóptimas predicciones de mortalidad (AUROC < 0,7).

Conclusiones: En pacientes con ACLF ingresados en UCI el cruce de valores de bilirrubina y protrombina se asoció a una alta tasa de mortalidad. Esta variable mejoró las predicciones del CLIFC-ACLF score y podría ser una herramienta útil para decidir la limitación del tratamiento médico estándar.

LA PRESENCIA DE HEPATITIS B CRÓNICA ES UN FACTOR DE RIESGO INDEPENDIENTE DE ARTERIOSCLEROSIS SUBCLÍNICA EN PACIENTES HBEAG NEGATIVO

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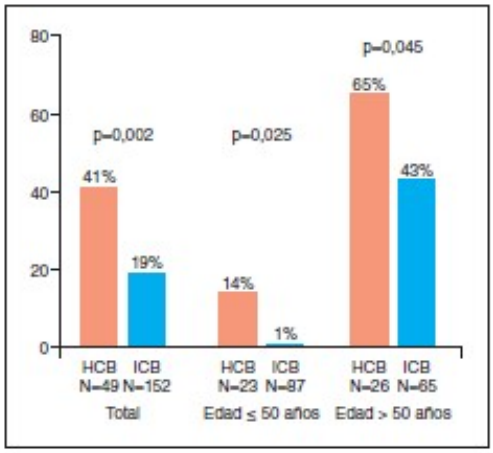
Introducción y objetivos: Algunas infecciones como el VHC se han asociado a un riesgo aumentado de arteriosclerosis, principalmente en sujetos con fibrosis avanzada. La infección crónica por

VHB se ha asociado a un mayor grosor íntima-media (GIM) que sujetos no infectados [Riveiro-Barciela M. EASL 2016]. El objetivo de este estudio fue evaluar la prevalencia de arteriosclerosis subclínica (AS) y factores asociados en una cohorte amplia de sujetos HBeAg negativo.

Métodos: Estudio prospectivo colaborativo (Di.Bi.M.I.S., Palermo y H. Vall d'Hebron) con 201 pacientes HBeAg negativo sin tratamiento antiviral ni antecedentes de enfermedad cardiovascular. Los pacientes se clasificaron de acuerdo a las guías de EASL (49 hepatitis crónica B -HCB- y 152 infección crónica B -ICB-). Se evaluaron parámetros analíticos, antropomórficos, elastografía hepática y ecodoppler carotídeo. La AS fue definida como un GIM incrementado (≥ 1,2 mm) y/o la presencia de placa de ateroma [Criterios de Manheim].

Resultados: Un total de 49 (24,4%) pacientes presentaban AS. La prevalencia de AS fue mayor en los sujetos con HCB que ICB (42% vs 19%, p = 0,002). El impacto de HCB en la AS se mantuvo cuando los pacientes se estratificaron por edad (≤ 50 años: 14% vs 1%, p = 0,025; > 50 años: 65% vs 43%, p = 0,045). El análisis univariante mostró asociación entre AS y la exposición tabáquica, consumo de alcohol, hipertensión arterial, dislipemia, el estado de HCB y valores aumentados de GGT, Hb A1c y CAP. El análisis multivariado evidenció que la edad avanzada (OR 1,11, p < 0,001) y el estado de HCB (OR 4,1, p = 0,004) eran los factores independientes asociados a AS.



Conclusiones: En los pacientes con infección crónica por VHB HBeAg negativo la presencia de lesión hepática es un factor de riesgo independiente de arteriosclerosis subclínica. Estos resultados sugieren que la infección crónica por VHB, especialmente en fase de HCB, puede tener un papel como factor de riesgo cardiovascular.

CARACTERIZACIÓN MOLECULAR DEL CARCINOMA HEPATOCELULAR ASOCIADO A ESTEATOHEPATITIS NO ALCOHÓLICA

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Introducción: La esteatohepatitis no alcohólica (NASH) es un factor de de riesgo emergente para el desarrollo del carcinoma hepatocelular (CHC). No obstante, la patogénesis molecular de los tumores NASH-CHC está poco definida. El objetivo del presente estudio es caracterizar el perfil molecular de NASH-CHC.

Métodos: Un total de 279 muestras de pacientes NASH-CHC resecados/trasplantados (n = 105) y de pacientes NASH (n = 174) fueron recogidas retrospectivamente en 6 centros. NASH fue diagnosticado histopatológicamente según el sistema de valoración establecido. La caracterización genómica se realizó en 158 muestras parafinadas con información clínica, incluyendo: análisis del transcriptoma (n = 52 NASH-CHC; n = 103 NASH), secuenciación de exomas (n = 31 NASH-CHC, incluyendo 17 casos previamente publicados) y SNP-array (n = 44 NASH-CHC).

Resultados: Los pacientes de la cohorte NASH-CHC presentaron una edad más avanzada que los de la cohorte NASH (media de edad 56 vs 65, p < 0,001) y una mayor prevalencia de género masculino (39% vs 76%, p < 0,001). Asimismo, los casos NASH-CHC presentaban mayor prevalencia de diabetes (49% vs 78%, p = 0,001), hipertensión (49% vs 81%, p < 0,001) y cirrosis (27% vs 75%, p < 0,001). El perfil de expresión de las muestras NASH mostró asociación con vías metabólicas en el grupo control (vs NASH-CHC, p < 0,01). Por el contrario, los tumores NASH-CHC mostraron activación de vías de señalización relacionadas con la transición epitelio-mesénquima (p < 0,05) y pro-inflamatorias (TNFA-NFKb, TGFB1 y IL1, p < 0,001). El análisis no supervisado de los tumores NASH-CHC reveló la presencia de CHC de la subclase "proliferación" y "no proliferación" (~50% en cada caso). A nivel mutacional, los tumores NASH-CHC presentaron alteraciones en oncogenes ya descritos en CHC siendo CTNNB1 (32%), TP53 (19%), KEAP1 (6,5%) and SETD2 (6,5%) los genes más prevalentes, seguidos por ARID1A, ARID2, ATM, NFE2L2, JAK3 (3% de las muestras). Estos análisis también mostraron mutaciones ACVR2A - receptor de la familia TGFb- en un 13% de los NASH-CHC. El análisis de firmas mutacionales identificó 27 de las firmas previamente descritas en COSMIC (mediana: 4 firmas/tumor, rango de 1-8). Concretamente, firmas mutacionales descritas en cáncer de hígado (#5, #16, #24) se identificaron en un 30-50% de los pacientes, y firmas que hasta el momento no relacionadas con CHC (#8, #29), en ~20% de las muestras.

Conclusiones: NASH-CHC se caracteriza por la activación de vías pro-inflamatorias cómo TNFa-NFKb, TGFb y IL-1, sugiriendo un papel de estas vías en la carcinogénesis de este cáncer. Asimismo, el receptor ACVR2A relacionado con TGFb se ha identificado como el oncogén más frecuentemente mutado después de CTNNB1 y TP53. Se han identificado firmas mutacionales no relacionadas con CHC en un ~20% de los NASH-CHC analizados.

- MR Brunetto, I Carey, B Maasoumy, **C Marcos-Fosch**, G van Halewijn, GP Caviglia, A Loglio, D Cavallone, C Scholtes, A Smedile, M Riveiro-Barciela, F van Bömmel, AA van der Eijk, F Zoulim, T Berg, M Cornberg, P Lampertico, K Agarwal, M Buti. El antígeno relacionado con el core de la Hepatitis B (HBcrAg) es mejor marcador que el HBsAg para discriminar entre infección crónica B y hepatitis crónica B en una cohorte europea HBeAg negativa. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2019. Comunicación oral.

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COMUNICACIONES ORALES

44.° Congreso Anual de la Asociación Española para el Estudio del Hígado

Madrid, 20-22 de febrero de 2019

Sesión oral n.° 1

Moderadores: Enric Reverter y Rita García

EL ANTÍGENO RELACIONADO CON EL CORE DE LA HEPATITIS B (HBCRAG) ES MEJOR MARCADOR QUE EL HBSAG PARA DISCRIMINAR ENTRE INFECCION CRONICA B Y HEPATITIS CRONICA B EN UNA COHORTE EUROPEA HBEAG NEGATIVA

M.R. Brunetto[1], I. Carey[2], B. Maasoumy[3], C. Marcos-Fosch[4], G. van Halewijn[5], G.P. Caviglia[6], A. Loglio[7], D. Cavallone[1], C. Scholtes[8], A. Smedile[6], M. Riveiro-Barciela[4], F. van Bömmel[9], A.A. van der Eijk[5], F. Zoulim[8], T. Berg[9], M. Cornberg[3], P. Lampertico[7], K. Agarwal[2] y M. Buti[4]

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Introducción: La historia natural de la infección crónica por VHB está caracterizada por diferentes fases relacionadas con la interacción entre el virus y el huésped. Las guías internacionales señalan que una determinación aislada de ALT y de ADN VHB es insuficiente para catalogar a los sujetos en una fase concreta de la infección crónica por VHB y por lo tanto es necesario un seguimiento con múltiples determinaciones. El antígeno relacionado con el core de la hepatitis B (HBcrAg) es un nuevo marcador serológico con un potencial valor clínico para clasificar a los sujetos HBeAg negativo entre infección crónica y hepatitis crónica B.

Métodos: Estudio multicéntrico europeo que incluye 1.584 muestras de individuos HBeAg negativos de nueve centros. Se determinó el ADN VHB, HBsAg, HBcrAg y ALT. Siguiendo las guías de la EASL los pacientes fueron clasificados en tres grupos: hepatitis crónica B (HCB, N = 552), infección crónica B (IC-B, N = 720), infección crónica con viremia baja fluctuante (IC-viremia baja, DNA VHB < 20.000 IU/mL, N = 322). Los datos se recogieron de forma anónima a través de un archivo compartido y protegido de eCloud y se analizaron con el software R v3.4.3 por un estadístico independiente (IDDI). La concentración de HBcrAg se determinó por ELISA y se expresa en una unidad arbitraria (Fujirebio, Lumipulse G HBcrAg, RUO).

Resultados: La mayoría de los pacientes eran hombres (59%), caucásicos (57%), con una edad media de 44 años (rango 9-79). Genotipo del VHB: 15% A, 2% B, 2% C, 45% D, 9% E, 1% F y 26% desconocido. Los valores medios (DS) para el ADN VHB fueron 3,6 (1,80) logIU/mL, HBcrAg 3,3 (1,47) logU/mL y HBsAg 3,2 (1,02) logIU/mL. La curva ROC para HBsAg tenía un área bajo la curva (AUC) de 0,73 (IC95% [0,70, 0,76]), con un punto de corte óptimo para HBsAg de 2,99 LogIU/mL (IC95% [2,84, 3,44]), sensibilidad de 0,52 y especificidadde 0,88, respectivamente. La curva ROC para HBcrAg tuvo un AUC de 0,97 (IC95% [0,96, 0,98]), lo que sugiere un alto valor diagnóstico para discriminar entre HCB y IC-B independientemente del genotipo del VHB. El punto de corte óptimo para HBcrAg fue 3,14 LogU/mL (IC95% [3,02, 3,27]), sensibilidad de 0,93, especificidad de 0,92, VPN de 0,91 y VPP de 0,94, respectivamente. La combinación de HBcrAg y HBsAg no obtuvo un mejor rendimiento diagnóstico que el HBcrAg solo. Al clasificar los pacientes con IC-viremia baja según el punto de corte del HBcrAg se obtuvieron un 19% de HCB y 81% de IC-B.

Conclusiones: Los valores de HBcrAg sérico junto con los niveles de ADN VHB y ALT permiten diferenciar en una única determinación entre IC-B y HCB. Los valores de HBcrAg son independientes del genotipo del VHB. Su combinación con el HBsAg no mejoró el rendimiento diagnóstico.

NEW SYNTHETIC CONJUGATES OF URSODEOXYCHOLIC ACID INHIBIT HEPATORENAL CYSTOGENESIS IN EXPERIMENTAL MODELS OF POLYCYSTIC LIVER DISEASE

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- **Cristina Marcos-Fosch**, Felipe Palma-Alvarez, Ariadna Rando-Segura, Constanza Daigre, Mar Riveiro-Barciela, Jordi Llaneras, Marta Perea, Francisco Rodriguez-Frias, Rafael Esteban, Lara Grau-López, María Buti. Dificultad en el cribado y tratamiento del VHC en pacientes con trastorno por uso de sustancias o patología dual, a pesar del manejo centralizado en el Centro de Atención y Seguimiento. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2020. Póster.

Conclusiones: El tratamiento *in-vitro* con IL-15 aumenta el número de células memory-like periféricas y modifica su metabolismo hacia uno menos glicolítico lo que permite generar una progenie más abundante y con mejor capacidad efectora.

144. DIFICULTAD EN EL CRIBADO Y TRATAMIENTO DEL VHC EN PACIENTES CON TRASTORNO POR USO DE SUSTANCIAS O PATOLOGÍA DUAL, A PESAR DEL MANEJO CENTRALIZADO EN EL CENTRO DE ATENCIÓN Y SEGUIMIENTO

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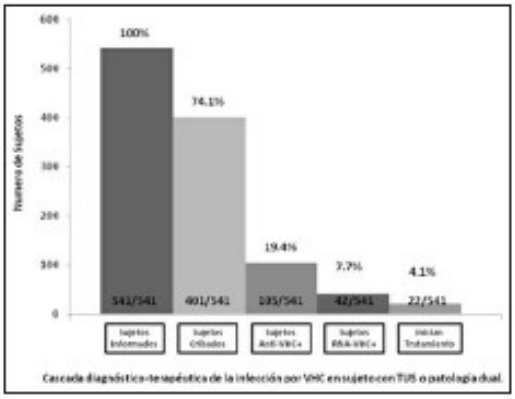
Introducción: La eliminación de la hepatitis C es un objetivo de la OMS para el 2030. Para ello, son necesarias estrategias de cribado y tratamiento de poblaciones de riesgo con menor acceso al sistema sanitario. El objetivo del estudio fue establecer un programa de cribado y tratamiento de VHC en sujetos con trastorno por uso de sustancias (TUS) o patología dual (psiquiátrica + TUS) atendidos en un Centro de Atención y Seguimiento (CAS).

Métodos: Estudio prospectivo de cribado y tratamiento de VHC en sujetos con TUS o patología dual seguidos en un CAS desde noviembre/ 2018 a junio/ 2019. Se determinó en el suero los anticuerpos anti- VHC y de forma refleja el RNA-VHC. En los casos RNA-VHC+ se evaluó la lesión hepática y se inició el tratamiento en el propio CAS.

Resultados: Se propuso participar a 541 sujetos y 401 (74%) aceptaron. El 75% eran varones, la edad media 45 años y el 61% tenían patología dual. 105 (26,2%) fueron anti-VHC+ y 42 (10,5%) RNA-VHC+. Solo se inició tratamiento a 22 casos dada la alta pérdida de seguimiento. Aquellos anti-VHC+ tenían mayor frecuencia de politoxicomanía ($p < 0,001$), ingresos en comunidades terapéuticas ($p < 0,001$), TUS a sustancias ilegales ($p < 0,001$), uso de vía inyectada ($p < 0,001$), número de episodios de sobredosis ($p < 0,001$), uso de terapia de sustitución de opioides ($p < 0,001$), trastornos de personalidad ($p = 0,02$) y síntomas psicóticos por sustancias ($p < 0,001$). Los sujetos RNA-VHC+ eran en mayor proporción mujeres ($p = 0,02$), más jóvenes ($p = 0,003$), con más consumo de cocaína en los últimos 6 meses ($p = 0,02$) y mayor deterioro de la calidad de vida mental ($p = 0,04$) que los RNA-VHC negativo.

Conclusiones: Existe una dificultad importante para el acceso al cribado y tratamiento de la hepatitis C en sujetos con TUS o patología dual probablemente relacionado con su patología de base. Los sujetos virémicos son a menudo mujeres jóvenes, con mayor consumo de cocaína y más deterioro de la calidad de vida mental.



Cascada diagnóstico-terapéutica de la infección por VHC en sujetos con TUS o patología dual.

Miscelánea

145. ENVISION, A PHASE 3 STUDY OF SAFETY AND EFFICACY OF GIVOSIRAN, AN INVESTIGATIONAL RNAI THERAPEUTIC, IN ACUTE HEPATIC PORPHYRIA PATIENTS

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Objectives: Acute Hepatic Porphyria (AHP) is a family of rare genetic diseases due to enzyme defects in heme synthesis involving acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and ALAD-deficiency porphyria. Induction of 5-aminolevulate acid synthase 1 can lead to accumulation of neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), resulting in neurovisceral attacks and chronic manifestations. Givosiran, an investigational RNAi therapeutic, targets liver ALAS1 to reduce ALA/ PBG and is being evaluated for its ability to reduce attacks and disease manifestations.

Methods: ENVISION (NCT03338816), a Phase 3 global, multicenter, randomized, double-blind, placebo-controlled trial with an open label extension (OLE), evaluated the efficacy and safety of subcutaneous givosiran in AHP. The primary endpoint was composite annualized attack rate in AIP over six months. Secondary end-

- **Cristina Marcos-Fosch**, Lara Grau-López, Raúl-Felipe Palma-Alvarez, Constanza Daigre, Ariadna Rando-Segura, Jordi Llaneras, Mar Riveiro-Barciela, Francisco Rodriguez-Frias, Joan Colom, Rafael Esteban, Maria Buti. La adherencia a los centros de adicción durante la pandemia por COVID19 de los individuos con trastornos por uso de sustancias es baja, lo que dificulta el cribado y tratamiento de la hepatitis C. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2021. Póster.

instituciones que habitualmente se encargan del cuidado de estos pacientes, como es Cruz Roja en nuestro caso, es crucial para la puesta en marcha de programas de microeliminación en dicha población.

93. LA ADHERENCIA A LOS CENTROS DE ADICCIÓN DURANTE LA PANDEMIA POR COVID-19 DE LOS INDIVIDUOS CON TRASTORNOS POR USO DE SUSTANCIAS ES BAJA, LO QUE DIFICULTA EL CRIBADO Y TRATAMIENTO DE LA HEPATITIS C

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Introducción: El control de la infección por virus de la hepatitis C (VHC) en individuos con trastornos por uso de sustancias (TUS) y usuarios de drogas por vía parenteral es clave para alcanzar el objetivo de la OMS de eliminación de la hepatitis C. A pesar de los esfuerzos volcados para llegar a esta población, el cribado y tratamiento sigue suponiendo un reto. El objetivo del estudio fue analizar la incidencia de infección de VHC en una cohorte de sujetos con TUS que previamente habían sido cribados y tratados y conocer el grado de adherencia a los centros de adicción especialmente durante la pandemia por COVID-19.

Métodos: Estudio prospectivo realizado en un centro de adicciones vinculado a un hospital universitario que incluyó sujetos con TUS, a los que previamente (2018-2019) se les realizó cribado de VHC y se les ofreció tratamiento por un equipo multidisciplinar en la unidad de adicciones. Durante la pandemia de COVID 19 se les ofreció nuevamente cribado del VHC para valorar el grado de adherencia al centro de adicción y la incidencia de nuevas infecciones y reinfecciones.

Resultados: En el primer estudio se reclutaron 401 individuos con TUS de los cuales 112 (30%) eran anti-VHC positivos y 42 (10%) RNA-VHC positivo. Se logró iniciar tratamiento y verificar RVS12 en 15 de ellos, siendo el resto pérdidas de seguimiento. Dieciocho meses más tarde solo 242 pacientes (60,3%) seguían adheridos al centro de adicciones y de ellos, 176 (72%) aceptaron ser cribados. Se detectaron 58 (33%) casos anti-VHC positivos (dos previamente negativos) y el RNA-VHC se detectó en 6 (3,4%) de los anti-VHC positivos. Cuatro eran previamente conocidos y no habían aceptado tratarse y 2 (1,1%) eran nuevas infecciones. Entre los pacientes previamente tratados y curados no hubo ninguna reinfección. La adherencia al centro de adicción fue significativamente más alta en los sujetos de mayor edad (47 ± 11 vs 44 ± 12, p < 0,02) y en aquellos con consumo previo o activo de opiáceos (70% vs 30%, p < 0,008). Por el contrario, los pacientes con consumo de cocaína fueron menos adherentes al seguimiento (45% vs 55%, p < 0,049). La presencia de antecedentes psiquiátricos, como trastornos psicóticos y afectivos, mejoró la adherencia al seguimiento (66% vs 34%, p < 0,003; 72% vs 28%, p < 0,043; 70% vs 30%, p < 0,007; respectivamente).

Conclusiones: Los pacientes con TUS a pesar del cribado y tratamiento mantienen una prevalencia y incidencia de infección por VHC alta. La adherencia a los centros de adicción es baja, siendo la tasa de abandono del seguimiento del 40%. Se evidencian diferencias significativas demográficas, clínicas y en el patrón de consumo de sustancias entre los pacientes adherentes y los que abandonan el seguimiento.

94. LA BÚSQUEDA DEL DAÑO HEPÁTICO Y SEROLOGÍA HEPATITIS B EN PACIENTES CON INFECCION POR COVID-19 ES SUBOPTIMA: RESULTADOS DE UNA ENCUESTA A FACULTATIVOS

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Introducción: El daño hepático (DH) definido por elevación de los enzimas hepáticos se ha asociado con mayor gravedad y peor evolución clínica, pero no está estipulado como factor pronóstico en las guías de práctica clínica. Estos pacientes son atendidos por equipos médicos multidisciplinares y habitualmente tratados con fármacos con capacidad para reactivar una hepatitis B. Nuestro objetivo es determinar si se realiza una búsqueda sistemática de DH y hepatitis B por parte de los facultativos.

Métodos: Se distribuyó una encuesta de 13 preguntas de elaboración propia a facultativos que tratan pacientes con COVID-19 en distintos hospitales nacionales. Se indagó sobre la búsqueda y seguimiento del DH, la determinación de serologías de hepatitis B y la opinión de los encuestados sobre la asociación del DH con la gravedad y pronóstico de la COVID-19.

Resultados: Se obtuvieron 173 respuestas de 13 centros hospitalarios, con heterogeneidad respecto a especialidad médica, experiencia laboral y lugar de atención a pacientes con COVID-19. La búsqueda sistemática del DH en la valoración inicial de estos pacientes se realizó por el 50,9% de los encuestados, siendo el motivo principal (72,3%) por estar protocolizado en su centro. Los porcentajes no superaron el 45% para la búsqueda sistemática o esporádica del daño hepático durante la hospitalización o seguimiento ambulatorio, incluso si presentaban hepatopatía conocida. La determinación sistemática de serología de virus B se realizó en el 36,4%, y el 19,7% únicamente la determinaban si planeaban iniciar un tratamiento inmunomodulador. El 54,7% consideró que existe asociación no relevante entre DH y gravedad/evolución desfavorable, pero solo el 9,8% consideró que esta asociación es relevante.

Conclusiones: El grado de búsqueda de DH y hepatitis B en pacientes con COVID-19 por parte de los facultativos encuestados es subóptimo. Consideramos necesario concienciar sobre las implicaciones pronósticas del DH en estos pacientes.

95. MEJORA DEL CONTROL GLUCÉMICO DE LA DIABETES MELLITUS TIPO 2 TRAS LA CURACION DE LA INFECCION DEL VIRUS HEPATITIS C CON LOS NUEVOS ANTIVIRALES DE ACCION DIRECTA

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La infección por el virus de la hepatitis C (VHC) está asociada con la diabetes mellitus tipo 2 (DM2) y puede empeorar el control glucémico de estos pacientes. Nuestro objetivo fue investigar si la erradicación de la infección por VHC con agentes antivirales de acción directa (AAD) se asocia con un mejor control glucémico en pacientes con DM2. Se realizó un estudio descriptivo evaluativo antes-después, que incluyó 59 pacientes con DM2 e infección por VHC que lograron una respuesta viral sostenida con los AAD desde abril de 2015 hasta diciembre 2016 en el Hospital San Pedro de

- Beatriz Mateos Muñoz, María Buti, Inmaculada Fernández Vázquez, Marta Hernández Conde, Vanesa Bernal Monterde, Fernando Díaz Fontenla, Rosa María Morillas Cunill, María Luisa Gar-cía Buey, Ester Badía, Mireia Miquel Planas, Alberto Amador Navarrete, Sergio Rodríguez Tajes, Lucía Ramos Merino, Antonio Madejón, Montserrat García Retortillo, Juan Ignacio Arenas Ruiz Tapiador, Joaquín Cabezas, Jesús González Santiago, Conrado Fernández Rodríguez, Patricia Cordero, Moisés Diago, Antonio Mancebo Martínez, Alberto Pardo Balteiro, Manuel Rodríguez, Elena Hoyas Pablos, Javier Moreno Palomares, Juan Turnes Vázquez, Miguel Ángel Simón Marco, **Cristina Marcos**, José Luis Calleja, Rafael Bañares, Sabela Lens, Javier Crespo, Manuel Romero Gómez, Enrique Rodríguez de Santiago, Santiago Moreno, Agustín Albillos Martínez. El tratamiento con tenofovir reduce la gravedad de la enfermedad covid-19 en pacientes con hepatitis crónica B. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2021. Comunicación oral.

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46.º Congreso Anual de la Asociación Española para el Estudio del Hígado

Madrid, 14-16 de junio de 2021

Sesión General 2

Moderadoras:
Zoe Mariño (Barcelona)
Maite García (Pamplona)

Hepatitis virales "Clínica"

EL TRATAMIENTO CON TENOFOVIR REDUCE LA GRAVEDAD DE LA ENFERMEDAD COVID-19 EN PACIENTES CON HEPATITIS CRONICA B

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Introducción: Los análogos de nucleótidos como el tenofovir (TDF) han demostrado *in vitro* actividad frente a la polimerasa del SARS CoV2. Un estudio previo español objetivó que los pacientes VIH positivos tratados con regímenes que incluyeran TDF presentaban menor riesgo y gravedad de la COVID-19. Desconocemos si el tratamiento con TDF o entecavir (ETV) modifica el riesgo y la gravedad de la COVID-19 en pacientes con hepatitis B crónica (HBC).

Métodos: Se recogieron los casos de COVID-19, definida por una reacción en cadena de la polimerasa positiva, diagnosticados entre el 1 de febrero y el 30 de noviembre de 2020 en pacientes adultos con HBC en tratamiento con TDF o ETV de 28 hospitales españoles. Se realizó un análisis bivariado de la mortalidad, la necesidad de ingreso en unidad de cuidados intensivos (UCI) y de soporte ventilatorio (intubación orotraqueal o ventilación mecánica no invasiva). Se definió COVID-19 grave por la presencia de neumonía bila-

teral, síndrome de distrés respiratorio agudo, sepsis o shock séptico, según los criterios de la OMS. Se estimó el efecto del tratamiento antiviral en el riesgo de padecer COVID-19 grave mediante un estudio de probabilidad inversa de ponderación del tratamiento (IPTW).

Resultados: Se identificaron 117 casos de COVID-19 entre 4.736 pacientes con HBC en tratamiento activo (2,5%, IC95% 2,1-2,9%), 67 en TDF y 50 ETV. De estos 117 pacientes, 41 (35%) fueron hospitalizados, 5 (4,3%) requirieron ingreso en UCI y 6 (5,1%) murieron. Los pacientes en tratamiento con TDF presentaban significativamente (p < 0,05) mayores tasas de obesidad (22 vs 9%), diabetes (32 vs 12%), cardiopatía isquémica (14 vs 3%) e hipertensión arterial (44 vs 18%) que los tratados con ETV. La presencia de fibrosis hepática avanzada (F3-F4) fue más frecuente en el grupo de ETV (35 vs 18%, p = 0,06). No se encontraron diferencias en la incidencia de COVID-19 en pacientes tratados con TDF o ETV (0,023 vs 0,026, p = 0,44). En comparación con TDF, los pacientes con ETV presentaron mayor frecuencia de COVID-19 grave (36% vs 6%, p <0,01) y mayores necesidades de ingreso en UCI (10% vs 0, p = 0,01), soporte ventilatorio (20% vs 3%, p < 0,01), estancia hospitalaria (10,8 ± 19 vs 3,1 ± 7, p <0,01) y muerte (10% vs 1,5%, p = 0,08). En el estudio de regresión logística ajustado a edad, sexo, obesidad, comorbilidades y fibrosis hepática, el tratamiento con TDF redujo en 6 veces el riesgo de padecer COVID-19 grave (IPTW ajustado-OR 0,17, IC95% 0,04-0,67, p = 0,01).

Conclusiones: Los pacientes con HBC en tratamiento con TDF presentan un menor riesgo de COVID-19 grave que los tratados con ETV. TDF podría tener un papel protector a padecer COVID-19 grave en pacientes con HBC.

Hepatopatía alcohólica y enfermedad hepática metabólica "Básica"

MICROBIOTA ASOCIADA A UNA HIPERACTIVIDAD MITOCONDRIAL REVIERTE LA ENFERMEDAD HEPÁTICA POR DEPOSITO DE GRASA

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Introducción: La disfunción mitocondrial es una de las múltiples causas que participan en el desarrollo de la enfermedad de hígado graso no alcohólico (NAFLD). La deleción de la proteína MCJ, un regulador negativo del complejo mitocondrial I, potencia la actividad mitocondrial y disminuye el daño hepático y la acumulación lipídica inducida por dieta o por fármacos.

Objetivos: Determinar la contribución de la microbiota intestinal en el efecto protector frente al desarrollo de esteatohepatitis no alcohólica (NASH) asociado a la deficiencia de MCJ y su capacidad para determinar la susceptibilidad a la enfermedad en ratones libres de gérmenes (GFm).

Métodos: Ratones C57BL/6 *wild-type* (WT) y MCJ *knock-out* (MCJ-KO) fueron alimentados con dieta control o dieta rica en grasa y deficiente en colina (CDAHFD) durante 6 semanas. Se seleccionaron ratones donantes de cada grupo en base a parámetros asociados al desarrollo de NASH. Los GFm fueron colonizados con la microbiota cecal de los donantes y se sometieron a la misma intervención dietética durante 3 semanas. En ambos modelos, se analizó el desarrollo de enfermedad hepática, la composición de la microbiota intestinal y el metaboloma fecal.

Resultados: Tras 6 semanas de dieta CDAHFD, los ratones MCJ-KO mostraron una menor expresión de marcadores inflamatorios y menor grado de daño fibrótico por depósito de colágeno en el tejido hepático. Los GFm colonizados con la microbiota de donantes con genotipo MCJ-KO y alimentados con dieta CDAHFD mostraron una menor expresión de marcadores de fibrosis y citoquinas proinflamatorias en comparación con los colonizados con microbiota WT. El análisis metagenómico y metabolómico en ratones convencionales mostró la presencia de disbiosis intestinal asociada a la dieta CDAHFD, con un perfil microbiano y metabolómico fuertemente relacionado con el desarrollo de la enfermedad. Además, se observaron cambios específicos asociados al genotipo MCJ-KO, incluyendo un incremento de la abundancia de los géneros *Dorea* y *Oscillospira* y una disminución de *Ruminococcus y AF-12*. El análisis metagenómico en GFm reveló cambios en estos géneros con una tendencia similar a la observada en ratones convencionales, destacando un incremento de la abundancia del género *Dorea* en todos los grupos colonizados con microbiota de ratones MCJ-KO, independientemente de la dieta. Tras el análisis de una cohorte pública de pacientes con diferentes grados de NAFLD, se identificó una menor abundancia de *Dorea* en pacientes no obesos con NASH, señalando este género como posible biomarcador de dicha enfermedad y posible mediador del efecto protector del genotipo MCJ-KO en nuestro estudio.

Conclusiones: La deficiencia de la proteína MCJ confiere protección frente a la progresión de NAFLD, limitando los procesos inflamatorios y fibróticos en el hígado, mediante un mecanismo que involucra la modulación de la microbiota intestinal.

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Hepatopatía alcohólica y enfermedad hepática metabólica "Clínica"

HIPERTENSIÓN PORTAL EN LA ENFERMEDAD HEPÁTICA GRASA NO ALCOHOLICA EN AUSENCIA DE CIRROSIS: PREVALENCIA, MECANISMOS IMPLICADOS E IMPACTO CLINICO

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Introducción: Existe una escasa evidencia que apoya que los pacientes con enfermedad hepática graso no alcohólica (EHGNA) pue-

- Joan Martínez-Campreciós, Raquel Domínguez-Hernández, **Cristina Marcos-Fosch**, Ariadna Rando Segura, Mar Riveiro-Barciela, Francisco Rodríguez-Frías, Miguel Ángel Casado, Rafael Esteban, Maria Buti. Búsqueda y recuperación de pacientes con VHC perdidos en el sistema (estrategia relink-c): valor sanitario y económico. Asociación Española para el Estudio del Hígado (AEEH). Madrid, 2021. Póster.

dos GPs o entre GP y siRNA aumentó la eficiencia de inhibición del ARNpg (69,1 ± 16,5%; 66,7 ± 12,2%; 63,8 ± 21% para GP1+GP4; GP1+siRNA; GP4+siRNA, respectivamente) y solo interfirió parcialmente con la expresión de las proteínas virales.

Conclusiones: Los Gapmers son unas valiosas moléculas capaces de inhibir la expresión del VHB *in vitro*. La combinación entre GPs o entre GP y siRNA podría mejorar su capacidad inhibitoria cuando el tratamiento ocurre tras establecerse la infección (5pi). Ulteriores experimentos y otros sistemas de vehiculación son necesarios para mejorar la eficiencia de inhibición y crear una estrategia terapéutica efectiva en sistemas de infección *in vivo*.

Financiación: Instituto de Salud Carlos III (grant PI18/01436), cofinanciado por el European Regional Development Fund (ERDF).

55. UNA PROBABILIDAD ELEVADA DE PRESENCIA DE CELULAS CD8 REACTIVAS VHB-ESPECIFICAS TRAS SUSPENSION DEL TRATAMIENTO CON AN PRONOSTICA UNA RAPIDA DISMINUCION DEL AGHBS EN LA HEPATITIS CRONICA B EAG(-)

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Introducción y objetivos: El restablecimiento de una respuesta celular T citotóxica reactiva (RCTCR) durante el tratamiento de la hepatitis crónica B eAg(-)(HCBeAg(-)) con análogos de nucleós(t)idos (AN) podría conducir a la cura funcional. Desarrollamos un modelo para predecir la RCTCR con variables implicadas en el agotamiento celular y lo evaluamos como regla de parada del tratamiento.

Métodos: En pacientes HCBeAg(-) tratados con AN, analizamos la presencia de RCTCR VHB-específica. Realizamos un modelo de regresión logística (MRL) para predecir la probabilidad de detectar la RCTCR, basado en la edad de los pacientes (duración de la infección), duración del tratamiento con AN y nivel de AgHBs (presión antigénica). Se interrumpió el tratamiento (subgrupo fibrosis hepática < F3) y se evaluó si hubo un descenso superior al 50% del AgHBs durante el seguimiento (mediana 24 meses), según la probabilidad de detección de RCTCR.

Resultados: En los casos tratados por un periodo largo (> 78 meses) el nivel de AgHBs fue menor, y la detección de la RCTCR frente a VHB-core$_{18-27}$ y VHB-pol$_{455-63}$ y de células secretoras de IFN-γ fueron más frecuentes. No se detectaron células VHB-env$_{183-91}$. La correlación entre la edad y el nivel de AgHBs fue también negativa. El MRL predijo significativamente la presencia de RCTCR de células VHB-core$_{18-27}$, correlacionándose positivamente con la duración del tratamiento y negativamente con la edad, pero no con el nivel de AgHBs. El MRL explicó el 55% de la variabilidad observada. El descenso del AgHBs fue más rápido en los pacientes con probabilidad de RCTCR > 90%, independientemente del nivel basal de AgHBs, aunque la pérdida de AgHBs fue mayor en los casos con AgHBs < 1.000 UI/ml.

Conclusiones: Un tratamiento de larga duración con AN, y un tiempo reducido de exposición al AgHBs más que su nivel, influyen en la presencia de una RCTCR VHB-específica. La alta probabilidad de detección de células tras la retirada de ANs se asocia a una rápida reducción del AgHBs.

56. BÚSQUEDA Y RECUPERACIÓN DE PACIENTES CON VHC PERDIDOS EN EL SISTEMA (ESTRATEGIA RELINK-C): VALOR SANITARIO Y ECONÓMICO

J. Martínez-Camprecios[1,2], R. Domínguez-Hernández[3], C. Maroos-Fosch[1], A. Rando-Segura[4,5], M. Riveiro-Barciela[1,6], F. Rodríguez-Frías[4,7,8], M. Ángel Casado[3], R. Esteban[1,6] y M. Buti[1,6]

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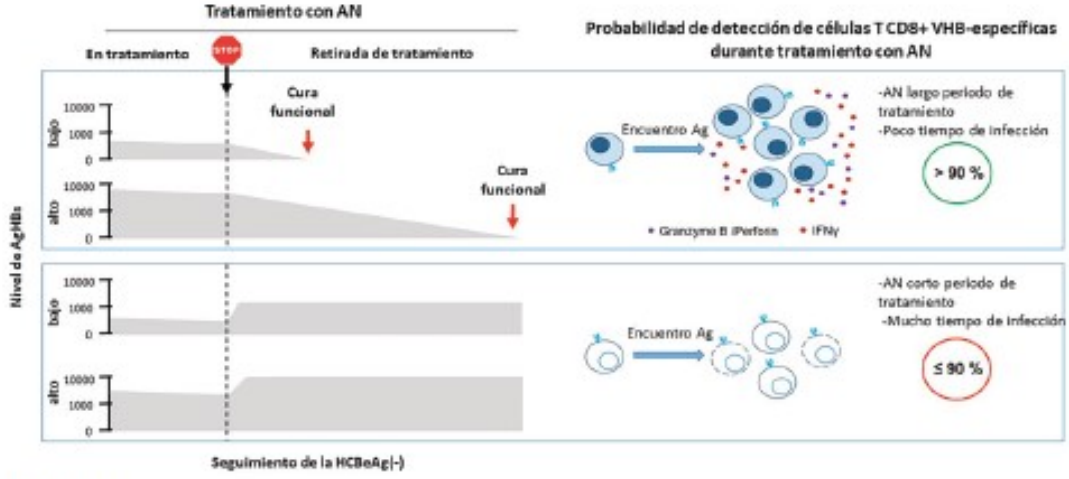


Figura P-55

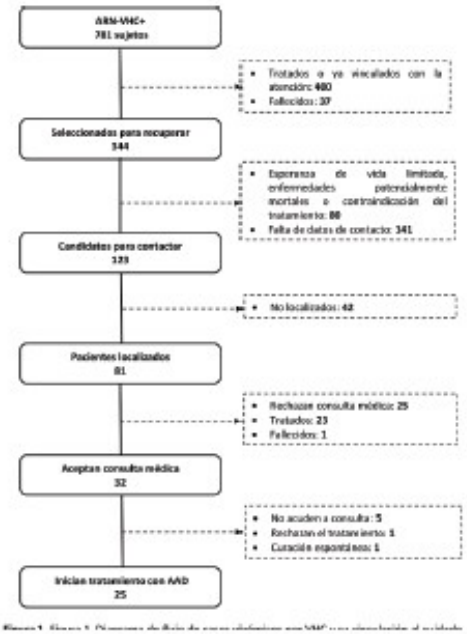
[1]Unidad de Patología Hepática, Departamento de Bioquímica y Microbiología, Hospital Universitario Vall d'Hebron, Barcelona, España.

Introducción: La eliminación del virus de la hepatitis C (VHC) requiere un incremento en el diagnóstico y vinculación al cuidado de los sujetos infectados.

Objetivos: Identificar y recuperar pacientes con VHC perdidos en el sistema (estrategia RELINK-C), y realizar una evaluación económica.

Métodos: Se revisaron datos del laboratorio del área de salud norte de Barcelona (450.000 habitantes) para identificar casos ARN-VHC+ en 2019 y se realizó una revisión de historias clínicas para recuperar pacientes no remitidos, perdidos o con infección activa. Se contactó con los pacientes por teléfono para vincularlos al cuidado. En la evaluación económica, se valoró el coste/estrategia y, mediante un modelo Markov, se estimaron los resultados en salud y económicos de por vida de los pacientes candidatos a contactar susceptibles de tratamiento de la estrategia RELINK-C vs no intervención.

Resultados: Sobre un total de 781 casos ARN-VHC+, se identificaron 344 pérdidas en el sistema o casos recuperables, de los cuales 123 eran candidatos a contacto. Los motivos de no contacto fueron: esperanza de vida limitada, enfermedades potencialmente mortales o contraindicación del tratamiento en 80 casos y falta de datos de contacto en 141. Se localizaron 81 pacientes de los 123 candidatos a contactar, 32 de ellos acudieron a consulta médica (25 rechazan visita, 23 ya tratados y 1 fallecido). De estos, 27 pacientes acudieron a visita y 25 iniciaron tratamiento (fig.). La inversión asociada a la estrategia RELINK-C fue 13.877 € (búsqueda y diagnóstico). El modelo basado en 123 pacientes (excluyendo 23 ya tratados, 1 fallecido y 1 curación espontánea) mostró que tratar a 25 pacientes en la estrategia RELINK-C vs no intervención reduce las complicaciones hepáticas entre 22-27% y su coste en 278.534 €, y la mortalidad (-23%).



Conclusiones: La estrategia RELINK-C permite recuperar y tratar pacientes VHC perdidos en el sistema de manera eficiente contribuyendo a la eliminación de la hepatitis C.

57. IMPACTO EN SALUD PÚBLICA DE PRIMEROS 1.000 PACIENTES CON TEST DESCENTRALIZADO DE HEPATITIS C EN CENTROS DE ATENCIÓN A LAS DROGODEPENDENCIAS COMPARADO CON DIAGNÓSTICO CENTRALIZADO EN POBLACIÓN GENERAL

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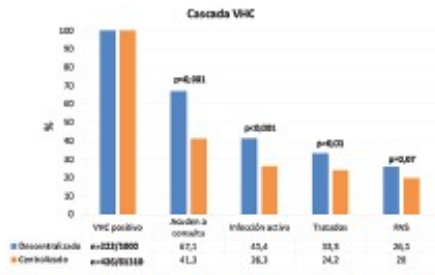
Introducción: Para lograr los objetivos de la OMS de eliminación del virus de la hepatitis C (VHC) se precisa de estrategias en poblaciones de alta prevalencia, como son los pacientes atendidos en los Centros de Atención a las Drogodependencias (CAD). Se han propuesto circuitos asistenciales con diagnóstico descentralizado mediante el test de gota de sangre seca (TGSS). Nuestro objetivo fue evaluar el impacto en salud pública de un circuito asistencial entre CAD y atención especializada basado en TGSS, y compararlo con el diagnóstico centralizado en población general.

Métodos: Se incluyeron entre 2017-2020 a todos los pacientes que voluntariamente participaron en un circuito asistencial diagnóstico con TGSS y de derivación entre 10 CAD y atención especializada. Se registraron variables epidemiológicas y clínicas. Se comparó la cascada de manejo de VHC con la de pacientes con diagnóstico serológico centralizado en el mismo periodo de tiempo.

Resultados: Durante 2017-2020 se realizó TGSS a un total de 1.000 pacientes (82% hombres, 43 ± 10 años) en los CAD y 61310 serologías en población general (50,2% hombres, 44 ± 18 años). La figura muestra la cascada de manejo de VHC en los positivos (222/1.000 y 426/61.310) de ambos grupos. El 79,3% de los pacientes virémicos de CAD tenían una solicitud positiva de VHC previa a participar en el circuito (media 7,2 ± 4,7 años) y 25% eran cirróticos. Los pacientes de los CAD estaban inactivos laboralmente un 89,1%, con historia de uso de drogas por vía parenteral el 92,4%, consumo de alcohol 50% y en tratamiento con metadona un 41,3%.



Conclusiones: Un circuito asistencial entre CAD y especializada basado en TGSS descentralizado, es eficaz al rescatar más del 75% de pacientes infectados diagnosticados previamente sin asistencia.

10.3.2 Congresos internacionales

- Mar Riveiro-Barciela, **Cristina Marcos-Fosch**, Fernando Martínez-Valle, Fabrizio Bronte, Olimpia Orozco, Isidro Sanz-Pérez, María-Teresa Salcedo, Antonio Craxi, Rafael Esteban, María Buti. Liver fibrosis is associated with subclinical atherosclerosis in patients with chronic hepatitis B: Resultas from a prospective multicentre study. American Association for the Study of Liver Diseases (AASLD). Washington, 2017. Póster.

12 IU/mL) at all time-points in the 5 NUC treated pts and in 2 IC. Among the remaining 4 IC, HBV-DNA levels peaked at T4 in 3 pts (median Log T4: 3.24 vs BL: 1.62) and remained undetectable in the other one, whose viremia became detectable at the end of therapy (1.64 Log). HBsAg and IP-10 levels significantly (T test for paired data) decreased during DAAs therapy as shown in the Table. ALT decline was not influenced by the HBV-DNA fluctuations. At FU12 there was a trend for a greater HBsAg decline in IC than in NUC treated pts (Delta Log: -0.42 ± 0.45 vs -0.03 ± 0.13; P=0.09 by ANOVA). **Conclusions** A temporary, mild increase of HBV replication may occur in HBV-HCV co-infected individuals early during DAAs in association with a progressive decline of serum HBsAg and a rapid decrease of IP-10 levels. HBV-DNA fluctuations did not lead to any clinical event in IC. The asymmetry of HBV markers kinetics needs further investigation.

Parameter		Pre-T	BL	T4	T12	FU12
HBsAg	Mean (SD)	2.12 (1.47)	2.09 (1.56)	1.82 (1.54)	1.76 (1.78)	1.84 (1.68)
P Value	BL vs Time	0.739	ns	<0.001	0.002	0.002
IP-10	Mean (SD)	-	2.35 (0.30)	1.66 (0.57)	1.75 (0.49)	1.69 (0.55)
P Value	BL vs Time	-	ns	<0.001	<0.001	0.003

Disclosures:

Ferruccio Bonino - Advisory Committees or Review Panels: Roche, MSD: Speaking and Teaching: Gilead, Novartis, BMS

Maurizia R. Brunetto - Board Membership: MSD, AbbVie, Gilead, Janssen: Speaking and Teaching: AbbVie, MSD, Gilead, BMS, Janssen, Roche

The following people have nothing to disclose: Piero Colombatto, Riccardo Gattal, Daniela Cavallone, Gabriele Ricco, Barbara Coco, Pierpaola Tannorella

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Liver fibrosis is associated with subclinical atherosclerosis in patients with chronic hepatitis B: Results from a prospective multicentre study.

Cristina Marcos-Fosch[1], Fernando Martinez-Valle[4], Fabrizio Bronte[3], Mar Riveiro-Barciela[1,2], Olimpia Orozco[4], Antonio Craxi[3], Rafael Esteban[1,2], Maria Buti[1,2]; [1]Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [3]Sezione di Gastroenterologia, DIBIMIS, University of Palermo, Palermo, Italy; [4]Systemic Diseases Unit, Internal Medicine Department, Vall d'Hebron Hospital, Barcelona, Barcelona, Spain

Background: HCV and HIV are associated with cardiovascular events. In chronic Hepatitis B (CHB) subjects, a pro-inflammatory state with high risk of carotid plaque [Ishizaka N. *Circulation* 2002] and worse outcome after acute myocardial infarction [Kuo PL. *Medicine* 2016] have been reported. We have previously shown that subjects chronically infected by HBV presented increased intima-media thickness (IMT) compared with healthy controls [Riveiro-Barciela, EASL 2016]. The aim of the study was to assess the presence of subclinical atherosclerosis in patients chronically infected by HBV and its relation to the severity of the disease. **Methods:** Multicenter prospective study including 201 untreated patients of whom 58 (24%) had CHB (HBV DNA >20.000 + ALT >2xULN or HBV DNA >2.000 IU/mL plus liver biopsy with at least moderate fibrosis (ISHAK score >2) and 143 were HBV carriers (no evidence of liver damage). The cardiovascular risk was evaluated by the presence of metabolic syndrome, NAFLD score, transient elastography with controlled attenuation parameter (CAP) and carotid Doppler study. Subclinical atherosclerosis was defined by an increased IMT (≥1.2mm) and/or presence of atheroma plaques. **Results:** 115 (57%) were male, mean age 47±13 years. Cardiovascular risk factors: 19% arterial hypertension, 17% dyslipidemia, 10% BMI > 30, 5% diabetes. 7.5% met criteria of metabolic syndrome. 58 (24%) presented CHB: 44 (76%) moderate fibrosis and 14 (24%) liver cirrhosis. Distribution of risk factors was similar, except for dyslipidemia, higher in chronic HBV carriers (20% vs 6%, p=0.015). Subclinical atherosclerosis was found in 49 (24%), finding more frequent among those with CHB than chronic HBV infection (40% vs 20%, *p*=0.005). This difference was even higher in patients with liver cirrhosis (50% vs 23%, p=0.029). Patients with subclinical atherosclerosis presented higher tobacco exposure, alcohol intake, older age, arterial hypertension, dyslipemia, CHB state and increased GGT, HbA1c and CAP. Factors independently associated with the presence of subclinical atherosclerosis in the multivariate analysis were older age (<50 vs >50 years, OR: 25, p<0.001), GGT levels (<35 vs >35 IU/mL, OR: 2.99, p=0.015), and CHB (OR: 2.91, p= 0.02). NAFLD score was >0.676 in 4 cirrhotics patients, 2 with subclinical atherosclerosis but no cardiovascular risk factors for NAFLD. **Conclusions:** Subclinical atherosclerosis was more frequent in patients with CHB than HBV carriers. Independent factors associated with subclinical atherosclerosis were age, GGT levels and CHB. These data suggest that HBV infection is a cardiovascular risk factor, especially in presence of liver fibrosis.

Disclosures:

Rafael Esteban - Speaking and Teaching: MSD, BMS, Novartis, Gilead, Glaxo, Janssen

Maria Buti - Advisory Committees or Review Panels: Gilead, Janssen, MSD: Board Membership: Abbvie: Grant/Research Support: Gilead, Janssen: Speaking and Teaching: Gilead, Janssen, BMS

The following people have nothing to disclose: Cristina Marcos-Fosch, Fabrizio Bronte, Mar Riveiro-Barciela, Olimpia Orozco, Antonio Craxi

1501

Hepatitis B virus up-regulates IL8 expression via endoplasmic reticulum stress and leads to suppress interferon responsiveness

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Background & Aims: Since next-generation sequencing (NGS) has been developed, more sensitive and more informative gene expression profiles could be obtained. In this study, we used human hepatocyte chimeric mice, in which T cells and B cells were depleted and whose liver highly replaced human hepatocytes, and analyzed direct influences on human hepatocytes by hepatitis B virus (HBV) infection under immunodeficient conditions. Methods: Twelve chimeric mice were prepared and divided into three groups (Group A; without HBV infection, Group B; 10 days of HBV infection, Group C; 8 weeks of HBV infec-

★ Denotes AASLD Presidential Poster of Distinction

- Maurizia R. Brunetto, Ivana Carey, Benjamin Maasoumy, **Cristina Marcos**, Gijs Van Halewijn, Gian Paolo Caviglia, Alessandro Loglio, Daniela Cavallone, Caroline Scholtes, Antonina Smedile, Mar Riveiro-Barciela, Florian van Bömmel, Annemiek Van Der Eijk, Fabien Zoulim, Thomas Berg, Markus Cornberg, Pietro Lampertico, Kosh Agarwal, Maria Buti. Hepatitis B Core-Related Antigen Is a Better Marker Than HBsAg for Discriminating between Chronic HBV Infection and Chronic Hepatitis B in a HBeAg-negative European Cohort. American Association for the Study of Liver Diseases (AASLD). San Francisco, 2018. Póster.

★ 2076

Epidemiological Trends of HBV and HDV Coinfection Among HIV+ Patients

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Background: Despite vaccination recommendations for HIV+ individuals hepatitis B (HBV) and D (HDV) coinfections are common in HIV-patients. Recent immigration trends and high-risk behaviour among MSMs might have changed the epidemiology of HBV/HDV coinfection among HIV+ in Europe. Thus, we retrospectively evaluated HBV/HDV epidemiology in the current HIV+ population in Vienna. **Methods:** N=1874 HIV+ patients attending our clinic between 2014-2016 were assessed for their HBV/HDV-serology at HIV-diagnosis (first visit) and at last contact. We assessed immunization status as well as HBV (HBsAg(+)/HBVDNA(+)) and HDV (anti-HDV(+)) coinfection rates at first and at last visit. Case numbers and frequency rates were analyzed. **Results:** The median latency period between HIV diagnosis and first available HBV-testing was 12.7 months, while n=68 (3.6%) were never tested for HBV coinfection. At first visit n=89/1793 (5.0%) patients showed HBsAg(+) and/or HBVDNA viremia. Another n=417 (23.3%) showed virological HBV clearance (HBsAg(-)/anti-HBc(+)/anti-HBs(+)). N=1081 (60.3%) were HBV-negative (HBsAg(-)/anti-HBc(-)). However, only n=377 (34.9%) of the HBV-negative individuals had received vaccinations and showed anti-HBs(+). Among the n=89 HBV/HIV coinfected patients, only n=53 (60.0%) were tested for HDV: n=11/53 (20.8%) had anti-HDV(+), of which n=3/7 (42.9%) showed HDVRNA viremia. Among the 1081 initially HBV-negative patients, n=939 (86.9%) received a follow-up HBV-test (median follow-up: 5.8 years): n=7 (0.7%) acquired new HBV infection (including one initially vaccinated patient) – resulting in a total number of n=59/1607 (3.7%) HBV/HIV-patients with n=21/32 (65.6%) HBeAg(+) and n=11/32 (34.4%) HBeAg(-) patients at last visit. Another n=36/939 (3.8%) showed new anti-HBc(+)/HBsAg(-) at last examination. N=136/649 (21.0%) received HBsAg-vaccinations. Among the n=89 initially HBV/HIV coinfected patients, n=50 (56.2%) underwent HBVDNA PCR testing at last visit (median follow-up: 6.4 years) and n=40 (80%) showed HBVDNA suppression. HDV-testing by HDV-serology/HDVRNA PCR was performed in n=22/59 (37.3%) of HBV-patients at last visit, and HBV/HDV coinfection was present in n=7/22 (31.8%) of HBV/HIV-patients. In a preliminary data analysis, 62/66 (93.9%) had ALT levels <2xULN, while 4/66 (6.1%) showed ALT levels >2xULN, including n=1 with a positive HBVDNA PCR and n=1 with HDV coinfection. **Conclusion:** While HBV-testing is regularly performed among HIV+ patients, HBV vaccinations were not sufficiently implemented with only 45.3% of eligible HIV+ patients showing protective anti-HBs titers. Importantly, HDV-testing is not systematically performed, while up to one third of HBV/HIV-patients may have HDV coinfection.

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Hepatitis B Core-Related Antigen Is a Better Marker Than HBsAg for Discriminating between Chronic HBV Infection and Chronic Hepatitis B in a HBeAg-negative European Cohort.

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Background: The natural history of chronic hepatitis B infection is characterized by multiple phases of host-virus interplay and the knowledge on the phase is necessary for making treatment decisions. The international guidelines underline that single ALT and HBV DNA levels are insufficient to assign the phase of infection or hepatitis. Hence, a longitudinal follow-up with multiple measurements is required. Hepatitis B core-related antigen (HBcrAg) is a novel serological marker with promising clinical value but an evaluation on a large European cohort has yet to be performed. **Methods:** Multicenter study including 1584 samples from individuals in HBeAg negative phase from 9 centers. HBV DNA, HBsAg, HBcrAg and ALT were collected. The patients are categorized in three groups according to EASL guidelines as chronic hepatitis B (CHB, N=552), chronic infection B (CI-B, N=720),

chronic infection with fluctuating low viremia (CI-low viremia, HBV DNA<20,000IU/mL, N=322). Data were collected anonymized through a protected eCloud sharefile and analyzed with software R v3.4.3 by an independent statistician (IDDI). The concentration of HBcrAg is expressed in arbitrary unit (Fujirebio, Lumipulse G HBcrAg, RUO). **Results:** Patients were primarily male (59%) and Caucasian (57%), mean age 44 (range 9-79). HBV genotypes were 15% A, 2% B, 2% C, 45% D, 9% E, 1% F and 26 % unknown. Mean values (SD) for HBV DNA were 3.6 (1.80) logIU/mL, HBcrAg 3.3 (1.47) logU/mL and HBsAg 3.2 (1.02) logIU/mL. The ROC-curve for HBsAg had an area under the curve (AUC) of 0.73 (95%CI [0.70, 0.76]), with optimal cut-off for HBsAg of 2.99 LogIU/mL (95%CI [2.84, 3.44]), sensitivity of 0.52 and specificity of 0.88, respectively. The ROC-curve for HBcrAg had an AUC of 0.97 (95%CI [0.96, 0.98]), suggesting a high diagnostic value to discriminate between CHB and CI-B regardless of HBV genotype. The optimal cut-off for HBcrAg was 3.14 LogU/mL (95% CI [3.02, 3.27]), sensitivity of 0.93, specificity of 0.92, NPV of 0.91 and PPV of 0.94, respectively. Combining HBcrAg and HBsAg did not further improve the diagnostic performance of HBcrAg only. Classification of CI-low viremia patients according to the HBcrAg cut-off was 19 % CHB and 81% CI-B. **Conclusion:** Along with HBV DNA and ALT, serum HBcrAg may be a useful biomarker for a faster identification of inactive chronic HBV-infection from CHB, independently of HBV genotype. Combination with serum HBsAg did not improve its diagnostic performance.

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★ 2078

Risk Factors for Progression to Chronic Hepatitis in Patients with Acute Hepatitis B: Results from the Acute Hepatitis B Global Study

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Background: There are no recognized risk factors for progression to chronic hepatitis in adults with acute hepatitis B virus (HBV) infection. We aimed to identify risk factors of progression to chronic hepatitis in adults with acute hepatitis B. **Methods:** From August/2015 to September/2017 patients aged >17 years with acute hepatitis B were prospectively included. Patient who received immunosuppression over the 24 week-period prior to enrolment or who were unwilling to consent were excluded. Acute hepatitis B was considered in symptomatic patients with positive anti-HBc IgM and ALT > 250 IU/L. Patients were followed for 6 months and divided into two groups according to the evolution of the acute infection: patients who resolved the infection (HBsAg clearance during follow up) and patients who evolved to chronic hepatitis (HBsAg persistence during follow up). We evaluated the effect of different factors on evolution to chronic hepatitis, including ALT<1700 IU/L at diagnosis. We chose this cutoff based on ROC curve analysis [negative predictive value of evolving to chronic hepatitis 97.7% (95%CI 93.3%-99.5%)]. **Results:** Two hundred patients were included. Median age was 44 (35-56) years and 163 (81%) were male. Sexual transmission was declared in 169 (84%) patients. HBV genotype was available in 145 patients: F: 111 (77%), A: 29 (20%) and D: 5 (3%). At diagnosis 171 (89%) were HBeAg-positive. A total of 23 patients (11.5%, 95% CI: 7.7%- 17.0%) evolved to chronic hepatitis. Bivariate analysis is shown in table 1. After adjusting for age, basal bilirubin and prothrombin time, for every increase in 100 IU/L in ALT at the moment of the diagnosis, the odds of evolving to chronic hepatitis was 0.85 (95%CI 0.78 - 0.92, p < 0.001). Adjusting for the same variables, the odds of evolving to chronic hepatitis in patients with ALT<1700 IU/L at diagnosis was 8.32 (95%CI 2.20 - 31.40, p 0.002) **Conclusion:** Patients with acute HBV infection with lower ALT levels at diagnosis are at higher risk of evolving to chronic hepatitis. Closer follow up of these patients is recommended.

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- **Cristina Marcos Fosch**, Lara Grau-López, Constanza Daigre, Raul Felipe Palma-Alvarez, Ariadna Rando-Segura, Jordi Llaneras, Marta Perea-Ortueta, Francisco Rodríguez-Frías, Nieves Martinez-Luna, Mar Riveiro Barciela, Jose Antoni Ramos-Quiroga, Rafael Esteban-Mur, Maria Asuncion Buti Ferret. Screening and treatment difficulties in hepatitis C virus-infected patients with substance use disorders or dual diagnoses, despite centralized management in an addiction and dual diagnosis center. American Association for the Study of Liver Diseases (AASLD). Virtual meeting, 2020. Póster.

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REGRESSION OF LIVER STIFFNESS MEASUREMENT AFTER SUSTAINED VIROLOGICAL RESPONSE BY DIRECT-ACTING ANTIVIRALS DECREASES THE RISK OF CLINICAL OUTCOMES

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Background: The role of liver stiffness measurement (LSM) after sustained virological response (SVR) in HCV patients treated by direct-acting antivirals (DAAs) remains unclear. We aimed to evaluate the prognostic value of LSM regression after SVR and to identify risk factors associated with clinical outcomes. **Methods:** This retrospective study analyzed data of patients treated by DAAs with LSM by transient elastography before treatment and post-SVR. Patients with previous decompensation of cirrhosis were excluded. Medical records were reviewed to identify clinical outcomes [liver-related complications or death]. Kaplan-Meier curves and time-to-event Cox proportional-hazard models were used to identify factors associated with clinical outcomes post-SVR. **Results:** 757 patients [64.7% female, median age 62 years (IQR,55-68), 7.4% HIV-coinfected, 41% with cirrhosis] were included. During a median follow-up of 2.0 years (IQR,1.1-2.6), 56 SVR-patients developed 68 outcomes [40.3 (95%CI 31.0-52.4) per 1,000-persons-years]. The cumulative incidence of clinical outcomes at 2-year of follow-up was significantly lower in patients who regressed LSM ≥ 20% after SVR [5.5% (95%CI, 3.3–9.0) vs. 10.7% (7.7–15.0), log-rank-p=0.01]. The following factors were independently associated with clinical outcomes [Hazard-Ratio (95%CI)]: male-gender [1.95 (1.07-3.55)], HCV-genotype-1 [0.43 (0.21-0.88)], baseline serum albumin < 3.5 mg/dL [3.97 (2.15-7.34)], baseline positive Baveno-VI criteria (LSM≥20 kPa or platelet count<150 x 10^9/mm^3) [1.94 (1.01-3.73)] and LSM regression ≥ 20% after SVR [0.42 (0.23-0.78)]. **Conclusion:** Regression of LSM after SVR significantly decreased the risk, as well as low baseline serum albumin and positive Baveno-VI criteria before HCV treatment were associated with a higher risk for clinical outcomes adjusted for confounding factors.

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SCREENING AND TREATMENT DIFFICULTIES IN HEPATITIS C VIRUS-INFECTED PATIENTS WITH SUBSTANCE USE DISORDERS OR DUAL DIAGNOSES, DESPITE CENTRALIZED MANAGEMENT IN AN ADDICTION AND DUAL DIAGNOSIS CENTER

Cristina Marcos Fosch[1], Lara Grau-López[2], Constanza Daigre[2], Raul Felipe Palma-Alvarez[2], Ariadna Rando-Segura[3], Jordi Llaneras[1], Marta Perea-Ortueta[2], Francisco Rodriguez-Frías[3], Nieves Martinez-Luna[2], Mar Riveiro Barciela[4], Jose Antoni Ramos-Quiroga[2], Rafael Esteban-Mur[1] and Maria Asuncion Buti Ferret[4], (1)Liver Unit, Hospital Vall D'hebron, (2) Department of Psychiatry, Hospital Vall D'hebron, (3)Virology Unit, Microbiology Department, Hospital Vall D'hebron, (4) Liver Unit, Internal Medicine Department. Hospital Universitari Vall d'Hebron, Barcelona, Spain, University Hospital Vall D'hebron

Background: Hepatitis C virus (HCV) elimination is difficult in people with substance use disorder (SUD). Screening and treatment are challenging and depend on the individual's characteristics and associated psychiatric disorders. This study aimed to set up a program of HCV screening and linkage to care in patients attending an addiction and dual diagnosis center (ADDC) and analyze the demographics, SUD rates, and presence of a dual diagnosis (DD) (psychiatric plus SUD) in HCV-RNA positive vs HCV-RNA negative individuals. **Methods:** Prospective non-interventional study designed to integrate HCV care in the management of individuals with SUD or DD, including screening, diagnosis, and HCV therapy with DAAs within the first 6 months after HCV diagnosis. HCV screening was offered to all patients attending an ADDC from November 2018 to June 2019, and in those testing positive therapy was offered. Screening was incorporated in the standard of care provided by the center's staff, and treatment was prescribed by hepatologists at the same ADDC. **Results:** The study was proposed to 528 individuals and 401 (76%) accepted and were screened. The mean age was 45 years, 75% were men and 63% had DD. 112 (28%) were anti-HCV positive and 42 (10%) had detectable HCV RNA. Only 20 of the 42 started DAA therapy due to the high loss of follow-up, and 15 achieved SVR. There were no significant differences in the prevalence of HCV infection (p=0.282) or the presence of liver injury (p=0.367) between those with DD and those with only SUD, although HIV prevalence was higher in the DD group (p=0.007). Injecting drug use disorder (p<0.0001) and opioid (p<0.0001) and benzodiazepine (p<0.0001) use disorders were independently associated with the presence of anti-HCV. Patients testing HCV-RNA positive were younger (p=0.001) and had received fewer previous SUD medical treatments (p=0.007) than those testing negative. Patients who rejected DAA treatment reported use of a larger amount of cocaine during the last month (p=0.014), had lower academic level (p=0.047), and were less frequently employed (p=0.049) than those who started treatment. **Conclusion:** The presence of DD does not seem to increase the risk of HCV infection in comparison with SUD alone and does not hinder access to treatment. Centralized management with multidisciplinary teams is required, but does not suffice to ensure linkage-to-care in the SUD population.

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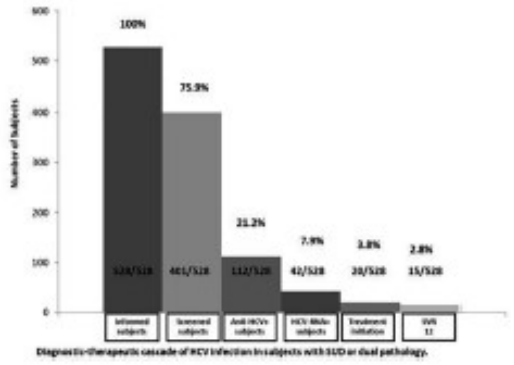

Diagnostic-therapeutic cascade of HCV infection in subjects with SUD or dual pathology.

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SEQUENTIAL TRANSIENT ELASTOGRAPHY AND ITS CONCORDANCE WITH NON-INVASIVE SERUM BASED TESTS FOR HEPATIC FIBROSIS IN A VETERANS ADMINISTRATION (VA) POPULATION

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Background: Non-invasive tests such as transient elastography (TE) are frequently used to assess hepatic fibrosis in patients with liver disease. The aims of our study were (a) to evaluate changes in fibrosis scores by sequential TE in Veterans with liver disease and (b) to compare sequential serum tests (STs) for fibrosis with sequential TE. **Methods:** We retrospectively reviewed the records of all patients undergoing TE (Fibroscan®Touch 502) at an urban VA. Fibrosis scoring (F0/1-F4) was based on Castera TE definitions. Variables collected included demographics, co-morbidities, and etiology of liver disease. Laboratory values were obtained to calculate the fibrosis-4 score (FIB4) and AST to Platelet Ratio Index (APRI) within 6 months of each TE date. **Results:** Of 1541 veterans undergoing TE, 34 (1.6%) had sequential TE measurements (median of 2 studies/patient and median time of 20.4 months between TEs). Patient characteristics are summarized in table 1. Fifteen patients (44%) showed regression and 6 patients (18%) showed progression in ≥ 1 fibrosis stage between each TE. Thirteen patients (38%) remained stable in fibrosis stage between each TE. Using sequential STs, 10 patients (29%) showed regression from F3-4 to F0-2, 1 patient (3%) showed progression from F0-2 to F3-4, and 23 patients (68%) remained stable either in F0-2 or F3-4. Changes in non-advanced fibrosis (F0-2) were most likely to be consistent between sequential TE and STs; APRI, in particular, showed high concordance with TE in F0/1 (87%) and F2 (82.6%) disease. The positive predictive value for advanced fibrosis detected by TE for both FIB4 and APRI was 50-53% and the negative predictive value was 73.6-75% (table 1). **Conclusion:** This longitudinal cohort of veterans with various etiologies of chronic liver disease provide important insights into the utility of sequential assessment of hepatic fibrosis using both TE and STs. Of note, 38% demonstrated no change in fibrosis via TE and 68% remained stable via sequential STs over a median period of 20.4 months, suggesting that repeat testing in most individuals within a short time period may not be helpful. Concordance between sequential TE and STs was most accurate in non-advanced fibrosis (F0-2). While STs were able to exclude advanced fibrosis with an accuracy of 73.6-75%, they were less reliable in detecting F3/F4 disease than TE. Thus, TE has an important role in detecting those at greater risk of developing complications of liver disease and cannot be replaced by the routine use of STs, which may be impacted by comorbid conditions and the limited specificity of available markers.

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STATE POLICIES LIMITING PROGRESS TOWARDS ELIMINATION IN THE U.S.

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Background: Despite commitment by the U.S. to eliminate hepatitis C virus by 2030, hepatitis C virus infections in the U.S. are increasing and contribute to the death of tens of thousands of Americans every year. Understanding policies that impede prevention and access to care is imperative for advancing elimination. This analysis examines state policies that impact the epidemiology of the disease. **Methods:** This study assesses hepatitis C treatment access policies under Medicaid, state laws impacting access to harm reduction and prevention services, viral hepatitis criminalization laws, and state department of corrections policies around testing and treatment, all from publicly available sources (StateofHepC.org, LawAtlas, HepCorrections). **Results:** State laws and policies impacting viral hepatitis prevention, testing, and treatment are highly variable by state. More than half (28) state Medicaid programs implement prior authorization criteria that restricts access to curative HCV therapy. Thirty two

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- Luisa Roade, Mar Riveiro Barciela, Elena Vargas-Accarino, Adriana Palom, Ana Barreira-Diaz, **Cristina Marcos Fosch**, Maria Asuncion Buti Ferret, Rafael Esteban-Mur. Viral load and liver stiffness are related to significant fibrosis and disease progression in HBeAg negative patients. A real-life cohort study. American Association for the Study of Liver Diseases (AASLD). Virtual meeting, 2020. Póster.

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VIRAL LOAD AND LIVER STIFFNESS ARE RELATED TO SIGNIFICANT FIBROSIS AND DISEASE PROGRESSION IN HBEAG NEGATIVE PATIENTS. A REAL-LIFE COHORT STUDY.

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Background: management of chronic hepatitis B virus infection is challenging due to its dynamic nature and the prognosis of different stages of HBV infection. Despite non-invasive markers, liver biopsy is still needed in majority of cases to characterize these patients. Aim: to assess the usefulness of non-invasive markers in HBeAg-negative individuals for the prediction of significant fibrosis and treatment eligibility criteria. **Methods:** observational study of HBeAg negative subjects chronically infected by HBV. Clinical, serological and virological data were collected annually. Liver fibrosis was estimated through liver stiffness measurement (LSM) and non-invasive biomarkers (APRI and FIB-4). Subjects were classified at baseline in HBV chronic carriers, HBeAg negative chronic hepatitis B (CHB) and grey zone (normal ALT+HBV-DNA >2000 IU/mL) and reclassified at the end of follow-up. A liver biopsy was performed in patients with persistent HBV-DNA>2, 000 IU/mL +normal ALT). **Results:** 372 subjects were included; baseline characteristics are summarized in table1. At baseline 244 (66%) were classified as chronic carriers, 22(6%) as HBeAg negative CHB and 106(29%) as grey zone. Liver biopsy was performed in 92 individuals (25%) with significant fibrosis (F≥2 Ishak) in 21(23%). Those undergoing liver biopsy presented baseline higher ALT (26 *vs* 50IU/ml, p<0.0001), qHBsAg (3 *vs* 3.6 log IU/ml, p<0.001), HBV DNA(2.4 *vs* 3.8log IU/ml, p<0.001) and LSM (5.4kPa vs 6.3kPa, p=0.012). Baseline factors independently associated with significant fibrosis were higher HBV-DNA (reference <2000IU/ml vs 2000-20000IU/ml vs 20000IU/ml, OR=6.6) and LSM (LSM>6.5kPa, OR=2.9). Baseline LSM showed an AUROC of 0.8 for identification of significant fibrosis. Out of 335 individuals with ≥1follow-up, 285(85%) were finally considered chronic carriers and 43(13%) CHB. Among 106 patients classified as grey zone, HBV-DNA (OR=3.1), and LSM (OR=6.1) were associated with later classification as CHB. 7 subjects remained unclassifiable due to high viral loads with mild/absent fibrosis in liver sample. 47 subjects initiated HBV therapy during follow-up, HBsAg was lost in 24(6.5%) and one decompensation and one liver-related death were registered. **Conclusion:** baseline viral load and liver stiffness are the only predictors for significant fibrosis and evolution to CHB in a real-life cohort of HBeAg negative subjects. An invasive approach is needed in up to 25% of subjects for proper classification.

Baseline characteristics and clinical outcomes (n=372)

HOST	Male	228 (61%)
	Age[a]	44 (±15)
	Coinfection	5 (1.3%)
	Race	
	Caucasian	228 (61%)
	African	91 (25%)
	Hispanic	28 (7%)
	Asian	25 (8%)
	Toxic habits:	
	Active smoker	71 (19%)
	Alcohol consumption	87 (21%)
	Comorbidities:	
	Arterial hypertension	54 (15%)
	Diabetes mellitus	15 (4%)
	Dyslipidemia	53 (14%)
	Obesity	63 (17%)
	ALT (IU/ml)[a]	32 (±78)
	Platelets (E109/ml)[a]	225 (±57)
VIRUS	Transmission	
	Sexual	49 (13%)
	Vertical	44 (12%)
	Blood transfusion	11 (3%)
	IDU	2 (0.5%)
	Genotype [b]	
	A	54 (29%)
	D	73 (39%)
	E	30 (16%)
	F	13 (7%)
	DNA-HBV (IU/ml log)[a]	2.8 (±1.2)
	qHBsAg (log)[a]	3.2 (±1.1)
	HBsAg>1000IU/ml[c]	209(56%)
	HBcrAg [a,e]	2.4 (±0.7)
LIVER	Liver cirrhosis[f]	9 (2.4%)
	Transient elastography (kPa)[a]	5.6 (±2.4)
	APRI[a]	0.5 (±0.7)
	FIB 4[a]	0.5 (±0.5)

ALT alanine aminotransferase; *APRI* aspartate aminotransferase to platelet ratio index; *CHB* chronic hepatitis B; *FIB-4* fibrosis index based on four factors; *HBcrAg* hepatitis B core-related antigen; *HBsAg* hepatitis B surface antigen; *kPa* kilopascal; [a]median (standard deviation); [b] out of 187 available; [c] out of 348 available. [e]Out of 241 available; [f] diagnosed by F5-6 in liver histological sample; signs of portal hypertension by image technique or clinical signs of cirrhosis.

Disclosures:

Mar Riveiro Barciela – AbbVie and Gilead: Speaking and Teaching

Ana Barreira-Diaz – Gilead: Employment

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- **Cristina Marcos Fosch**, Felipe Palma-Alvarez, Ariadna Rando, Constanza Daigre, Mar Riveiro Barciela, Jordi Llaneras, Marta Perea, Francisco Rodriguez Frias, Rafael Esteban, Lara Grau-López, Maria Buti. Screening and treatment difficulties of hepatitis C virus infected patients with substance use disorders or dual pathology, despite centralized management in an addiction and dual diagnosis center. The International Liver Congress (EASL). Virtual meeting, 2020. Póster.

Epclusa® or Maviret® within the charity premises after checking for drug drug interactions with their prescribed and non-prescribed medication.

Results: 46 FSSWs were tested during the 12 week period. 22/46 (47.8%) of those FSSWs tested were HCV antibody positive and 18/46 (39.1%) were HCV PCR positive indicating very high prevalence rates in line with their known high risk behaviour. Of those 18 PCR positive patients 13 commenced HCV treatment, three patients declined treatment and two are continuing to consider whether to be treated or not.

Outcomes - RNA Positive	No of FSSW	Outcomes - RNA Positive	No of FSSW
Started Treatment	13	Declined Assessment	0
Declined Treatment	3	Considering Treatment	2

Figure: Treatment Commencement for FSSW testing HCV PCR positive.

Conclusion: FSSWs have a very high prevalence of HCV PCR positivity but are willing to be treated for HCV if this service is provided outside of a healthcare centre and does not involve venepuncture. Following up this group post treatment to ensure cure and reduce risks of reinfection is also likely to be a challenging despite ongoing support and education in the charity sector.

THU344

Screening and treatment difficulties of hepatitis C virus infected patients with substance use disorders or dual pathology, despite centralized management in an addiction and dual diagnosis center

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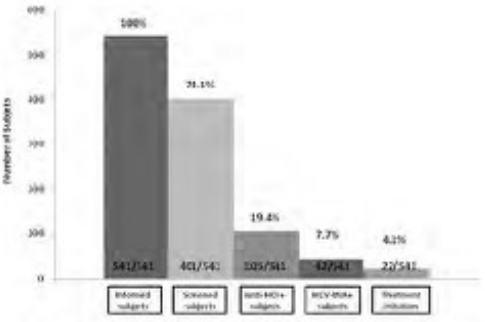
Background and Aims: WHO goal is to eliminate hepatitis C virus (HCV) infection as a public health threat by 2030. In order to achieve this target, screening and treatment strategies for risk populations with poor access to the health system are necessary. The objective of the study was to establish an HCV screening and treatment program for subjects with substance use disorders (SUD) or dual pathology (psychiatric plus SUD) treated in an Addiction and Dual Diagnosis Center (ADDC).

Method: Prospective study for screening and treatment of HCV in subjects with SUD or dual pathology followed in an ADDC from November 2018 to June 2019. Anti-HCV antibodies were determined with reflected HCV-RNA determination. In those HCV-RNA positive cases the liver lesion was evaluated and the treatment started at the ADDC.

Results: The study was proposed to 541 subjects and 401 (74%) accepted. 75% were male, the average age was 45 years and 61% had dual pathology. 105 (26.2%) were anti-HCV positive and 42 (10.5%) HCV-RNA positive. Treatment was only initiated to 22 subjects due to the high loss of follow-up. Those anti-HCV positive had higher frequency of poly-drug abuse ($p < 0.001$), need for internalization in therapeutic communities ($p < 0.001$), SUD to illegal substances ($p < 0.001$), use of injected drugs ($p < 0.001$), number of overdose episodes ($p < 0.001$), use of opioid substitution therapy ($p < 0.001$), personality disorders ($p = 0.02$) and psychotic symptoms due to substance abuse ($p < 0.001$).

Those HCV-RNA positive subjects were in larger proportion women ($p = 0.02$), younger ($p = 0.003$), with more cocaine consumption in the last 6 months ($p = 0.02$) and greater deterioration in mental quality of life ($p = 0.04$) than HCV-RNA negative.



Diagnostic-therapeutic cascade of HCV infection in subjects with SUD or dual pathology.

Conclusion: There is a significant difficulty in the screening and treatment of HCV in subjects with SUD or dual pathology probably related to their underlying pathology. The HCV-RNA positive are often young women with greater cocaine consumption and more deterioration of the mental quality of life.

THU345

Integrating hepatitis C virus screening by dry blood spot test into colorectal cancer screening: a randomized controlled trial

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Background and Aims: To achieve WHO goals for the elimination of hepatitis C virus (HCV) infection by 2030 screening is mandatory, and targeting high prevalence groups such as birth cohorts adults is a good option. Currently, in our health care setting this population is being invited for colorectal cancer (CRC) screening with biennial fecal immunochemical testing (FIT). Integrating a simplified diagnostic tool such as the dry blood spot test (DBS) to FIT screening could be of great help for HCV microelimination. However, it is unknown if both screening strategies interfere regarding participation. This study was aimed to study whether adding DBS to FIT CRC screening may improve HCV screening adherence.

Method: A randomized controlled trial (NCT04037046) was conducted in asymptomatic individuals aged 50–70 years, attended by four general practitioners (GPs) in our area. Participants ($n = 609$) were stratified by age, sex and address and randomized to one of three groups: 1) HCV (DBS kit) screening at the healthcare center, following invitation letter and appointment with their GP; 2) Combined screening for HCV and CRC (FIT kit); and 3) Self-testing screening for HVC and CRC with pre-sealed envelope for sending kit samples to the central laboratory. DBS were positive if >15 UI (Cobas 6800®) and FIT ≥ 20ug/g feces (OC-Sensor kit®).

Results: Among randomized patients (mean 59.4 ± 5.4 years, 51.2% male), and excluding 7.3% after not receiving postal mail, 132 (23.3%) subjects participated with test delivery in a median of 30.5 days (IQR 13.8–46.2); 30% in DBS, 28.4% in DBS+FIT and 13.5% in the self-testing strategy ($p < 0.01$). In the first two strategies, 38.7% and 25.2% had previous opportunistic screening with FIT or colonoscopy respectively, and 9% had performed a serology for HCV. No differences

- Jordi Llaneras, Mar Riveiro Barciela, Eulalia Pericas , Nuria Boixareu , Jordi Navarro , Juan Ignacio Esteban, Lluis Castells , **Cristina Marcos** , Maria Buti, Rafael Esteban. Impact of the universal access to direct-acting antivirals in the profile of hepatitis C treated patients. The International Liver Congress (EASL). Virtual meeting, 2020. Póster.

Background and Aims: The role of sofosbuvir (SOF) based direct acting antivirals (DAAs) in waitlisted liver transplant candidates with Hepatitis C virus (HCV) is controversial, because of the concern that DAA use may disadvantage patients under the MELD system. Waitlist outcome data to date has been limited to select centers. The purpose of this study was to determine the prevalence of SOF containing DAA regimen use in liver transplant candidates in a nationwide registry and the associated impact on outcomes.
Method: Using the Scientific Registry of Transplant Recipients database, we examined all adult candidates on the national liver transplant waitlist from January 1, 2014 to December 31, 2017 waiting for their first transplant with HCV as the primary or secondary indication for listing. This cohort was linked to a national database of pharmacy claims, to identify patients treated with SOF containing regimens (sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir) during the study period. Subjects were followed from listing date or January 1, 2014 if they were listed before the study period until the first occurrence of removal from the waitlist, transplant, death, or December 31, 2017. The final cohort consisted of 1420 subjects. The SOF treated group was compared to a matched historical cohort of candidates waitlisted from January 1, 2010 to December 31, 2013 who were not treated with SOF based regimens. The groups were matched on several factors using incidence density without replacement sampling of 1 case up to 3 controls. Both univariate Cox proportional hazards models and cumulative incidence curves were done using competing risks methodology.

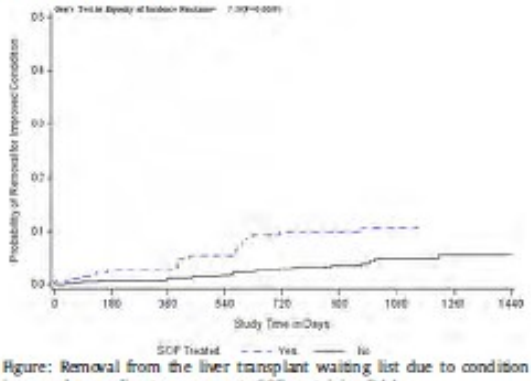

Figure: Removal from the liver transplant waiting list due to condition improved, according to exposure to SOF containing DAA

Results: During the study period, 208 patients (14.6%) were treated with a SOF containing DAA regimen during liver transplant listing. There were 787 subjects in the matched cohort. Treatment with SOF based regimens was associated with a lower risk of all-cause mortality compared to non-treatment (HR 0.47, 95% CI 0.26–0.83, P = 0.0094). Patients treated with SOF based regimens were more likely to be removed from the waitlist due to improved condition compared to untreated subjects (HR 2.65, 95% CI 1.41–4.99, P = 0.0025). Liver transplant incidence (HR 1.02, 95% CI 0.78–1.34, P = 0.8719) and removal from the waitlist due to worsened condition (HR 0.84, 95% CI 0.50–1.40, P = 0.4941) did not differ between SOF treated and untreated groups.
Conclusion: In a contemporary national cohort, only a minority of waitlisted HCV positive liver transplant candidates were treated with SOF containing DAAs. However, SOF use was associated with reduced all-cause mortality and increased removal from the waitlist due to improved condition which suggests that HCV treatment should be considered in all HCV infected liver transplant candidates.

THU416

Factors associated with efficacy of retreatment with grecaprevir/pibrentasvir therapy in prior DAA failed patients - nationwide multicenter study in Japan

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Background and Aims: To identify factors associated with the efficacy of retreatment with grecaprevir/pibrentasvir (GLE/PIB) therapy in patients who failed prior DAA therapy.
Method: This was a nation-wide multicenter study involving 83 regional core centers for the treatment of liver disease and related hospitals. A total of 526 patients who failed prior DAA therapy and retreated with GLE/PIB were registered. Serum was obtained before GLE/PIB therapy and the RAS in NS3/NS5A region was determined by population sequencing. Factors associated with SVR12 were analyzed.
Results: The overall SVR12 rate was 96.5%; the SVR12 rate of genotype 1a, 1b, 2a, 2b patients was 100%, 96.5%, 100% and 100%, respectively. Among the genotype-1b patients, the SVR12 rate in 4 patients with P32deletion RAS in NS5A region was 25%, which was significantly lower than 97% of patients without this unique RAS ($p < 0.01$). Among patients without P32deletion RAS, presence of A92 K RAS in NS5A (odds ratio 15.3, 95% confidence interval 2.3–101, $p < 0.01$), R30H in NS5A (OR 9.1, 95%CI 1.8–46, $p < 0.01$), prior failure of multiple DAA regimens (OR 8.3, 95%CI 1.9–37, $p < 0.01$), and age over 76 (OR 4.5, 95% CI 1.2–17, $p = 0.03$) independently affected SVR. The SVR12 was 99% in 193 patients who had none of the above four factors, whereas it was 97% in 92 patients who had only one factor, and 76% in 21 patients who had 2–3 factors.
Conclusion: This nation-wide study revealed high rate of SVR by retreatment with GLE/PIB. The unique RAS P32deletion in NS5A significantly attenuated the efficacy. Other than this unique RAS, R30H RAS in NS5A, Y92 K in NS5A, prior failure of multiple DAA regimens, and age were factors to lower SVR rates. In patients without these factors, the rate of SVR was 99%.

THU417

Impact of the universal access to direct-acting antivirals in the profile of hepatitis C treated patients

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Background and Aims: Treatment with direct-acting antivirals (DAAs) was limited to patients with advanced fibrosis until 2017. Since then, access to DAAs was allowed to all subjects with chronic hepatitis C (CHC), regardless of the degree of fibrosis. Our aim was to analyse the impact of universal access to DAAs in the profile of subjects treated for CHC.
Method: Retrospective study based on the pharmacy register of all patients with CHC treated during two periods: restrictions (2014–2016) and universal access (2017–2019). Baseline clinical and virological characteristics, type of therapy and Sustained Virological response (SVR) were collected.
Results: 2,384 combinations of interferon-free oral DAAs were administered to 2,327 patients with CHC within these periods. The percentage of patients with advanced fibrosis (F3-F4) receiving therapy significantly decreased over time, although 23% of treated subjects in 2019 had significant fibrosis and 2% were decompensated. Baseline characteristics of subjects treated during each period are shown in the table. An increase in treated HIV-infected patients was observed, probably due to lower interactions with the new DAAs

Table: (abstract: THU417)

	Period with restrictions 2014–2016 (n= 1094)	Universal Access Period 2017–2019 (n=1290)	Total (n= 2384)	
Male	613 (56%)	716 (56%)	1329 (56%)	p = 0.8
Age (years)	61 ± 13	57 ± 14	59 ± 14	p < 0.001
Fibrosis				p < 0.001
F0-F1	60 (6%)	538 (42%)	598 (25%)	
F2	241 (22%)	405 (31%)	646 (27%)	
F3	253 (23%)	154 (12%)	407 (17%)	
F4	540 (49%)	193 (15%)	733 (31%)	
Decompensated cirrhosis	38 (4%)	25 (2%)	63 (3%)	p = 0.2
Hepatocarcinoma	17 (2%)	4 (0.3%)	21 (1%)	p < 0.001
Liver transplant	52 (5%)	21 (2%)	73 (3%)	p < 0.001
HIV Coinfection	116 (11%)	238 (19%)	354 (15%)	p = 0.002
Genotype 1b	693 (63%)	558 (43%)	1251 (53%)	p < 0.001
Non- pangenotypic DAAs	1094 (100%)	605 (47%)	1709 (71%)	
Pangenotypic DAAs	–	675 (53%)	675 (29%)	
SVR 12	782/820 (95%)	983/1015 (97%)	1765/1835 (96%)	p = 0.1

Median, SD; n (%).
DAAs, Direct-Acting Antivirals. SVR12, Sustained virological response at week 12.

combinations. Genotype 1b was the most prevalent (53%) in the first period and decreased in the second period, due to an increase of patients infected by GT 1a, 3 and 4. Seven patients relapsed after DAA and were retreated with SOF/VEL/VOX, all of them achieving SVR. Pangenotypic regimens used in the second period slightly increased SVR rates.

Conclusion: Despite universal access to high efficacy pangenotypic DAAs combinations, 23% of patients treated in 2019 still had advanced fibrosis. This result highlights the need to improve and increase screening and linkage to care in order to eliminate HCV infection.

THU418

Hepatitis C therapy with grazoprevir/elbasvir and glecaprevir/pibrentasvir in patients with advanced chronic kidney disease - data from the German hepatitis C-registry (DHC-R)

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Background and Aims: Grazoprevir/elbasvir (EBR/GZR) and glecaprevir/pibrentasvir (G/P) are the two licensed treatment options with direct antiviral agents (DAA) for patients with chronic hepatitis C virus (HCV) infection and a baseline glomerular filtration rate (GFR) <30 ml/min. Real world data in this special patient population is sparse so far. Thus, we analyzed safety and effectiveness data within the German Hepatitis C-Registry (DHC-R).

Method: The DHC-R is a prospective national real-world registry including about 16,500 chronic hepatitis C patients recruited by more than 250 centers. Data were analyzed as of Jun 30, 2019. The analysis is based on 2,773 patients with documented GFR at baseline treated with EBR/GZR (N = 1,041), EBR/GZR + ribavirin (N = 53) and G/P (N = 1,679), respectively. For the per protocol analysis, non-adherent patients, patients with missing data and patients lost to follow-up were excluded.

Results: The baseline characteristics of the total study cohort were as follows: (70%/4%/21%/5% HCV-genotype 1/2/3/4; 64.7% male; age 50 ± 14 years, 96% Caucasian, 83% treatment-naïve,12% cirrhosis). 94 (3.4%) patients with baseline GFR <30 ml/min initiated antiviral therapy with EBR/GZR (N = 57), EBR/GZR + ribavirin (N = 4), or G/P (N

	End of treatment GFR			
Baseline GFR	**0-15**	**>15-30**	**>30-60**	**>60**
0-15 (n=79)	97.5% (n=77)	1.3% (n=1)	0	1.3% (n=1)
>15-30 (n=7)	14.3% (n=1)	57.1% (n=4)	14.3% (n=1)	14.3% (n=1)
>30-60 (n=83)	0	3.6% (n=3)	65.1% (n=54)	31.3% (n=26)
>60 (n=1,894)	0	0	2.4% (n=46)	97.6% (n=1,848)

Patients with documented GFR at baseline and end of treatment were considered in this analysis (N=2,063).

Figure: (abstract: **THU418**): Comparison between baseline and end-of-treatment glomerular filtration rate.

- **Cristina Marcos-Fosch**, Lara Grau-López, Raúl-Felipe Palma-Alvarez, Constanza Daigre, Ariadna Rando-Segura, Jordi Llaneras, Mar Riveiro-Barciela, Francisco Rodriguez-Frias, Joan Colom, Rafael Esteban, Maria Buti. Low attendance of people with substance use disorders to addiction centers jeopardized hepatitis C screening and treatment during the COVID-19 pandemic. American Association for the Study of Liver Diseases (AASLD). Virtual meeting, 2021. Póster.

(7%) with GT4 infection were included, the median sampling point after EOT was 7.6 months (0.0-63.0). The patients had not responded to LDV/SOF (39%, 289/749), DCV/SOF (17%, 124/749), PrO±D (13%, 95/749), VEL/SOF (12%, 93/749), GZR/EBR (8%, 61/749), SMV/SOF (6%, 48/749) or G/P (5%, 39/749). The frequencies of NS3 RASs were 70-90% after EOT in protease inhibitor-experienced patients and RASs disappeared rapidly in GT1b, GT3 and GT4 after follow-up month 3 (FU3), which was largely due to the loss of variants at position 168. RASs in GT1a were stable due to Q80K. In NS5B, nucleotide RASs were very rare and S282T only occurred in with GT3a. NS5A RASs were very common in NS5A inhibitor-experienced patients across all GT (90-95% after EOT) and were detectable in 70% of patients even after FU24. L31M and Y93H were most common in GT1b. In GT1a and GT4 different RASs at positions 28, 30, 31 and 93 were detected. A30K and Y93H were frequent in GT3. While NS5A RASs remained stable in GT1b, RASs slightly decreased in GT1a and GT3 after FU24 (GT1a, 71%, GT1b, 95%, GT3, 73%), which was mainly caused by the decline of Y93H. For GT4, data sets are not yet competed at later time points, but there was also a trend towards an Y93H decrease. **Conclusion:** NS3 and NS5B RASs quickly disappeared, whereas high rates of persistent NS5A RASs were observed more than two years after end of DAA treatment in all GT with only slow decline in certain HCV GTs. This may have an impact on retreatment with first generation DAAs in resource-limited settings and for the achievement of the global HCV elimination aims.

Disclosures:

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Peter Buggisch – Abbvie: Grant/Research Support; Falk: Grant/Research Support; Gilead: Grant/Research Support; Intercept: Grant/Research Support; Merck/MSD: Grant/Research Support; Norgine: Grant/Research Support; AbbVie: Speaking and Teaching; Falk: Speaking and Teaching; Gilead: Speaking and Teaching; Intercept: Speaking and Teaching; Merck/MSD: Speaking and Teaching; Norgine: Speaking and Teaching; AbbVie: Consulting; Falk: Consulting; Gilead: Consulting; Intercept: Consulting; Merck/MSD: Consulting; Norgine: Consulting

Jörn M Schattenberg – Echosens: Consulting; Genfit: Consulting; Bristol Myers Squibb: Consulting; Boehringer Ingelheim: Consulting; Boehringer Ingelheim: Grant/Research Support; Gilead Sciences: Grant/Research Support; Siemens Healthcare GmbH: Consulting; Sanofi: Consulting; Roche: Consulting; Pfizer: Consulting; Novartis: Consulting; Nordic Bioscience: Consulting; Madrigal: Consulting; Intercept Pharmaceuticals: Consulting; Gilead Sciences: Consulting; MSD Sharp & Dohme GmbH: Speaking and Teaching; Falk Foundation: Speaking and Teaching; Siemens Healthcare GmbH: Grant/Research Support

Georg Dultz – Abbvie: Speaking and Teaching

Thomas Berg – Bayer: Consulting; Eisai: Consulting; Ipsen: Consulting; MSD/Merck: Consulting; Roche: Consulting

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LOW ATTENDANCE OF PEOPLE WITH SUBSTANCE USE DISORDERS TO ADDICTION CENTERS JEOPARDIZED HEPATITIS C SCREENING AND TREATMENT DURING THE COVID-19 PANDEMIC

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Background: Elimination of Hepatitis C Virus (HCV) infection in individuals with substance use disorders (SUD) is key to achieve the WHO goal by 2030. However, HCV screening and treatment of these subjects is challenging . The aim of this study was to assess the level of attendance and the incidence of HCV infection during the COVID-19 pandemic in a cohort of subjects with SUD who had previously been screened in an addiction center. **Methods:** Prospective study conducted in an addiction center that included subjects with SUD, previously (2018-2019) screened for HCV, who were offered treatment by a multidisciplinary team in the addiction center. After 18 months, during the COVID-19 pandemic, they were offered HCV screening again to assess the incidence of new infections and reinfections. **Results:** In the first study, HCV screening was offered to 528 individuals with SUD but only 401 accepted. Of these, 112 (30%) were anti-HCV positive and 42 (10%) HCV-RNA positive and elegible for therapy. Direct-acting antivirals (DAAs) were started in 15 (24%) and all achieved sustained virological response. The main reason for non starting DAAs was loss of follow-up. After 18 months, only 242 (60%) of the 401 previously tested were still linked to the center and 176 (72%) agreed to be screened. Anti-HCV antibodies were detected in 58 (33%) and HCV-RNA was detected in 6 (3.4%): 4 with known infection who had previously refused therapy and 2 (1.1%) new infections. Among those previously treated no case of HCV reinfection was detected.Attendance to the addiction center was lower in young subjects (44 ± 12 vs 47 ± 11, p=0.02) in those not receiving opiod substitution therapy (30% vs 70%, p=0.008) and among cocaine users (45% vs 55%, p=0.049). Previous psychiatric disorders were associated with higher linkage to the addiction center during follow-up (66% vs 34%, p=0.003). **Conclusion:** Despite a descentralized model of care, a high number of individulas with SUD do not accept HCV screening. The HCV prevalence and incidence of new infection is high in this population and the attendance to addiction centers low, with a 40% dropout rate. There are significant differences in terms of demographic, clinical and substance use variables between attending patients and those who abandon follow-up.

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- Joan Martinez-Camprecios, Raquel Domínguez-Hernández, **Cristina Marcos-Fosch**, Ariadna Rando, Mar Riveiro-Barciela, Francisco Rodriguez Frias, Miguel Ángel Casado, Rafael Esteban, Maria Buti. Active search to retrieve lost-to follow-up HCV patients (RELINK-C strategy): health and economic value. The International Liver Congress (EASL). Virtual meeting, 2021. Póster.

patients who underwent EGD screening gained the highest life expectancy of 5.47 years per patient. Compared to the Baveno VI criteria strategy, the incremental cost-effectiveness ratio of EGD strategy was $89.28 per quality-adjusted life-year. The results were sensitive to the probability of low-risk patients detected by EGD. In terms of cost-effectiveness ratio, the strategies of EGD and Baveno VI criteria were both cost-effective according to the threshold. Additionally, the possibility of selecting EGD screening is 93.4%, however, if the capability of Baveno VI criteria of detecting high-risk patients improved or the willingness-to-pay was lower than $91.4 per patient per quality-adjusted life-year, screening with Baveno VI criteria will emerge as a preferred strategy.

Conclusion: Scenarios of screening with EGD or Baveno VI criteria are both cost-effective. The preference of decision depends on the variation of key parameters and the willingness-to-pay of decision makers. The consideration of spared endoscopy rate and dynamic follow-up will improve the screening value of Baveno VI criteria in routine practice.

PO-1341

Active search to retrieve lost-to follow-up HCV patients (RELINK-C strategy): health and economic value

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Background and aims: Spain is on track to eliminate Hepatitis C (HCV) infection by 2030 after treating more than 140, 000 chronic infected individuals in the last six years. This public health challenge

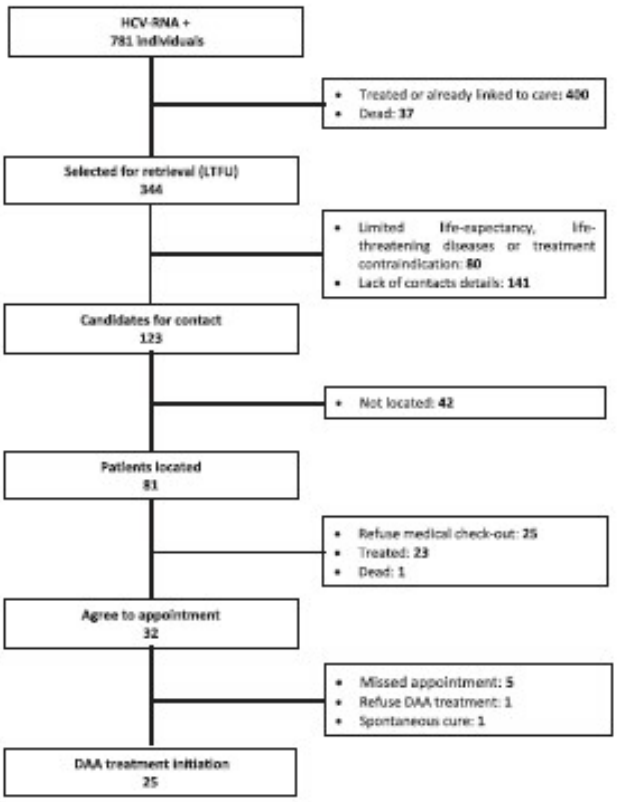

Figure 1. Flowchart of HCV viremic cases from year 2019, patients selected for retrieval or lost to follow-up (LTFU), candidates for contact, patients located and patients who finally initiate direct-acting antiviral (DAA) treatment.

Figure: (abstract: PO-1341)

is leading physicians and authorities to design new strategies in order to increase diagnosis of unknown HCV cases or to retrieve untreated or lost-to-follow-up (LTFU) patients. The aim of this study was to retrieve LTFU HCV viremic patients who could benefit from treatment (RELINK-C strategy) and to evaluate its effectiveness and economic value.

Method: The RELINK-C strategy is based on a retrospective search (January to December 2019) for HCV-RNA+ve cases from the central laboratory department of the Barcelona north health area (450, 000 inhabitants) followed by medical records review. Individuals who were LTFU or with an unresolved infection were selected for retrieval. Candidates were contacted by phone (5 maximum attempts) for diagnosis and treatment assessment. Cost of RELINK-C was estimated along with lifetime health and economic outcomes of RELINK-C vs non-intervention through a Markov model based on candidates for HCV treatment with available contact information.

Results: 781 HCV-RNA+ve cases were detected. Of those, 344 (44%) were LTFU and selected for retrieval and among them, 123 were candidates for contact. Reasons for not contacting 80 of the cases were limited life expectancy, life-threatening diseases or HCV treatment contraindication and patients lack of contact details among 141 cases. Upon the phone calls, 81 patients were located, of whom 32 agreed to an appointment with the physician (25 refused medical check out, 23 were already treated and 1 had died). Finally, 27 patients attended the appointment and 25 started DAA treatment (1 spontaneous cure, 1 refused treatment) (Figure 1).

The investment associated to RELINK-C strategy (search and diagnosis) was €13, 877. Model based on the 123 patients, excluding 23 patients already treated, 1 death and 1 spontaneous cure, showed that treating 25 patients in RELINK-C strategy vs no patients treated in non-intervention decreases mortality by 23% and liver complications by 22–27% (greater impact on decompensated cirrhosis), generating €278, 534 savings associated to liver complications management.

Conclusion: RELINK-C enabled 25 of the 81 located patients to receive HCV treatment and has shown to be an efficient strategy to help in achieving Hepatitis C elimination.

PO-1374

Optimizing diagnostic algorithms to advance HCV elimination in Italy: A cost effectiveness evaluation

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Background and aims: Italy is the country with the greatest burden of hepatitis C virus (HCV) infection in Western Europe. There is a political will for HCV elimination and 71.5 million euros have been allocated to a free-of-charge screening in the 1969–1989 birth cohorts and the key populations. We aimed to evaluate the cost effectiveness of different diagnostic algorithms considering the complete patient journey from screening to treatment completion, within the available screening budget in Italy.

Method: A Cost-effectiveness analysis, simulating six screening diagnostic algorithms to detect HCV active infection in the targeted birth cohort (1969–1989) was conducted (Figure). A Markov model for liver disease progression with a 20-years' time horizon and health care system perspective was used. The diagnosis of active HCV infection is made by the detection of antibodies (HCV-Ab), either by rapid or phlebotomy-based assays, followed by HCV-RNA or HCV core antigen (HCV-AG) confirmatory testing either on a second sample (2 visits) or by Reflex testing (1 visit). The rate of individuals that will end up as undiagnosed and unlinked to care has been evaluated by the estimates of false negatives by each assay and by the patient re-attendance drop-off at each screening step based on literature data. Age, fibrosis stage, treatment effectiveness, DAA costs and liver disease costs were used to evaluate the quality-adjusted life-years (QALY) and the incremental cost-effectiveness ratios (ICER) of

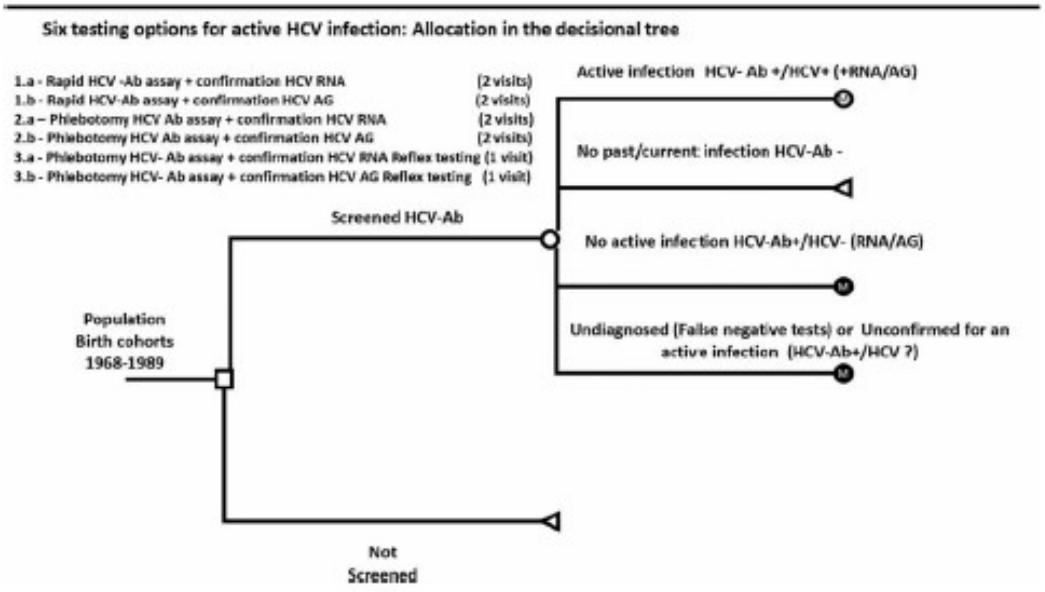

Figure: (abstract: PO-1374)

- Beatriz Mateos Muñoz , Maria Buti , Inmaculada Fernández Vázquez, Marta Hernández Conde, Vanesa Bernal Monterde , Fernando Diaz , Rosa Morillas, Luisa Garcia-Buey, Esther Badia-Aranda, Mireia Miquel, Alberto Amador, Sergio Rodriguez-Tajes, Lucía Ramos Merino, Antonio Madejón, Montserrat García-Retortillo, Juan Arenas, Joaquin Cabezas, Jesús González Santiago, Conrado Fernández-Rodríguez, Patricia Cordero, Moises Diago, Antonio Mancebo, Albert Pardo, Manuel Rodríguez, Elena Hoyas, José Juan Moreno, Juan Turnés, Miguel Angel Simón, **Cristina Marcos-Fosch**, José Luis Calleja Panero, Rafael Bañares, Sabela Lens, Javier Crespo, Manuel Romero Gomez, Enrique Rodríguez-Santiago , Santiago Moreno Guillén , Agustin Albillos. Tenofovir reduces the severity of COVID-19 infection in chronic hepatitis B patients. The International Liver Congress (EASL). Virtual meeting, 2021. Póster.

Conclusion: These are the first real life data on bulevirtide therapy in Germany. Overall, we observed a favorable safety profile as well as a marked biochemical and virological response in the majority of our patients. However, middle- and long-term data are needed to evaluate the impact of bulevirtide on clinical end points in hepatitis delta patients.

PO-1448

Excellent virological and clinical responses maintained over 3 years of continuous Bulevirtide treatment in patients with HDV compensated cirrhosis and clinically significant portal hypertension

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Background and aims: Treatment with Bulevirtide (BLV) for 48 weeks in compensated HDV cirrhotic patients is safe and effective, but its long-term effects in a real-life setting even after dose reduction/discontinuation have not been investigated yet.

Method: Three difficult-to-treat compensated HDV cirrhotic patients with clinically significant portal hypertension added BLV 10 mg/day (high dose) to ongoing TDF. Case 1: 69 years, female, HDV-RNA 23, 600 IU/ml, HBsAg 10 IU/ml, ALT 140 U/L; Case 2: 51 years, male, HDV-related autoimmune hepatitis, small esophageal varices, platelets 74, 000/mmc, HDV-RNA 392, 000 IU/ml, ALT 232 U/L; Case 3: 58 years, female, HDV-RNA 104, 803 IU/ml, ALT 244 U/L. HDV-RNA was quantified by RoboGene 2.0 (LLOQ 6 IU/ml). In first two patients, HDV/HBV-specific T cells were analyzed in blood by direct ex-vivo IFN-γ ELISPOT methods, up to last follow-up

Results: In Case 1, HDV-RNA became undetectable by week 36 and ALT normalized by week 20. After BLV withdrawn (week 52), HDV-RNA became rapidly detectable, peaked at week 16 (13, 655 IU/ml), and then declined at week 32 (421 IU/ml), remaining stable <1, 000 IU/ml afterwards. ALT level increased from week 14 to 30 (41→333 U/L) and then declined to persistent normal values. At 101-weeks off therapy: HDV-RNA 87 IU/ml, ALT 26 U/L, HBsAg 0.49 IU/ml. Two patients were treated continuously for 3 years: undetectable HDV-RNA and normal ALT levels were achieved after 28 and 12 weeks in Case 2, and 52 and 28 weeks in Case 3. Virological and biochemical response were maintained through the following 2 years of therapy, even after BLV dose reduction to 5 and 2 mg/day. At last visit: both patients had undetectable HDV-RNA and ALT 22 U/L. In one patient, virological response was associated with an excellent clinical response: esophageal varices disappeared, histological/lab features of autoimmune hepatitis resolved, AFP normalized, platelets and albumin improved. Overall, no safety issues were recorded, as bile salt increase was asymptomatic. Circulating HDV/HBV-specific T cells were tested in 2 patients at baseline and every 2 months during and off-therapy: no changes were observed, neither after HDV reactivation (Case 1) nor in 2.5 years of BLV continuative treatment (Case 2).

Conclusion: Continuous administration of BLV for 3 years provides excellent virological and clinical response in HDV cirrhotic patients with clinically significant portal hypertension.

PO-1449

Tenofovir reduces the severity of COVID-19 infection in chronic hepatitis B patients

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Background and aims: HIV-positive patients on Tenofovir (TDF)/FTC have a lower risk for COVID-19 and related hospitalization than those on other therapies (Ann Intern Med 2020;173:536). We hypothesize that TDF reduces the incidence and severity of COVID-19 in patients with chronic hepatitis B (CHB). Our aim was to analyze the incidence and severity of COVID-19 in patients with CHB on antiviral treatment, TDF or entecavir (ETV).

Method: Search of patients with COVID-19 infection between 1st February to 30th November in the database of adult (>18 yr) CHB patients on TDF or ETV from 28 Spanish hospitals. COVID- 19 infection was defined by a positive polymerase chain reaction, and severe infection by bilateral severe pneumonia, acute respiratory distress syndrome, sepsis or septic shock (WHO criteria). The effect of antiviral treatment on the risk of severe COVID-19 was estimated by the inverse probability of treatment weighting propensity score (IPTW) method. Need for intensive care unit (ICU) and ventilatory support, and mortality were explored by bivariate analysis.

Results: The database search of 4736 CHB patients identified 117 with COVID-19 (2.5%, 95%CI 2.1–2.9%), 67 on TDF and 50 on ETV. Forty-one (35%), 5 (4.3%) and 6 (5.1%) out of the 117 patients with COVID-19 were hospitalized, admitted to ICU or died, respectively. Compared with patients on TDF, those on ETV had significantly ($p<0.05$) greater rates of obesity (22 vs. 9%), diabetes (32 vs. 12%), ischemic cardiopathy (14 vs. 3%) and arterial hypertension (44 vs. 18%). There was a trend for greater severitiy of advanced (F3–F4) fibrosis in the ETV groups (35 vs. 18%, $p=0.06$). The incidence of COVID-19 in patients on TDF or ETV was similar (0.023 vs. 0.026, $p=0.44$). Table shows that, compared with those on TDF, patients on ETV more often had severe COVID-19, required ICU, ventilatory support, had longer hospitalization or died. In multivariate logistic regression adjusted by age, sex, obesity, comorbidities and fibrosis stage, TDF reduced by 6-fold the risk of severe COVID-19 (adjusted-IPTW-OR 0.17, 95%CI 0.04–0.67, $p=0.01$).

Table: Characteristics of COVID-19 by treatment groups

	ETV (50)	TDF (67)	p
Severe COVID-19	18 (36%)	4 (6%)	<0.01
ICU admission	5 (10%)	0 (0%)	0.01
Ventilatory support	10 (20%)	2 (3%)	<0.01
Hospitalization days	10.8 ± 19	3.1 ± 7	<0.01
Death	5 (10%)	1 (1.5%)	0.08

Conclusion: Patients with CHB on TDF have a lower risk of severe COVID-19 infection than those on ETV. TDF seems to exert a protective effect in patients with CHB infected by COVID-19.

PO-1628

Comparison of hepatitis B virus relapses between hepatitis B e antigen-negative chronic hepatitis B patients who discontinue tenofovir disoproxil fumarate with or without switching to alafenamide

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Background and aims: Previous studies showed that hepatitis B virus (HBV) relapse after the cessation of tenofovir disoproxil fumarate (TDF) occurs much earlier than that after the cessation of entecavir. Prior study showed the clinical relapse pattern goes along with the ended-up nucleos (t)ide analogues (Peng CW AASLD 2020 abstract). Tenofovir alafenamide (TAF) is a new prodrug of tenofovir, TAF was non-inferior to TDF in efficacy. However, the incidence of HBV relapse after the cessation of TAF therapy remains unclear. The aim of this study is to compare HBV relapse rates between hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients who discontinued TDF with or without switching to TAF.

Method: A total of 442 HBeAg-negative patients who received TDF monotherapy and 31 HBeAg-negative patients who received TDF at the start treatment and switching to TAF at least 12 weeks (range 20–69 weeks) were recruited. The patients all had post-treatment follow-up for at least 4 months. All patients fulfilled the stopping criteria of the Asia-Pacific Association for the Study of the Liver of 2012. The propensity score-matching method was used by creating a ratio of 1:3 to adjust age, sex, cirrhosis, HBV DNA at entry, treatment and consolidation duration and end-of-treatment (EOT) HBsAg. Thus, 31 and 93 patients who discontinued TDF with (Group I) and without (Group II) switching to TAF were included in this study.

Results: There were no significant differences in terms of clinical features or HBsAg levels between the two groups. In the Group I and Group II patients, the incidences of virological relapse at post-treatment 12 and 24 weeks were 50.5% versus 36.6% and 71.4% versus 59.1% ($p=0.211$), respectively, and the clinical relapse rates were 34.4% versus 30.1% and 62.1% versus 52.7% ($p=0.259$), respectively. There was no significant difference in virological and clinical relapse rates between the two groups. Multivariate analysis showed that old age, NA-naïve status and lower EOT HBsAg levels were independent predictors of virological and clinical relapse.

Conclusion: HBV relapse rate might be comparable between HBeAg-negative CHB patients who discontinued TDF with or without switching to TAF.

PO-1661

Outcomes and characteristics of hepatocellular carcinomas (HCC) in Caucasian chronic hepatitis B (CHB) patients treated with long-term entecavir (ETV) or tenofovir disoproxil fumarate (TDF) therapy

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Background and aims: HCC can develop in CHB patients under long-term oral antiviral therapy even in reduced rates, but the characteristics of this occurrence have not been adequately studied. This study aimed to assess patient and tumour characteristics as well as outcomes in adult Caucasian CHB patients, with or without compensated cirrhosis, who developed HCC during long-term therapy with ETV or TDF.

Method: In total, 1951 adult Caucasian CHB patients treated with ETV/TDF were included in the PAGE-B cohort (baseline age 53 ± 14 years, males 71%, HBeAg-positive 18%, cirrhosis 28%). Patients with