



### CONSENSUS DOCUMENT

## [Translated article] Common Approach to Metabolic-Associated Fatty Liver Disease in Patients With Psoriasis: Consensus-Based Recommendations From a Multidisciplinary Group of Experts



J.M. Carrascosa <sup>a,\*</sup>, E. Vilarrasa <sup>b</sup>, I. Belinchón <sup>c</sup>, P. Herranz <sup>d</sup>, J. Crespo <sup>e</sup>, F. Guimerá <sup>f</sup>, A. Olveira <sup>g</sup>, on behalf of the Working Group for the Common Approach to Psoriasis and MAFLD (GACPE) <sup>◊</sup>

<sup>a</sup> Departamento de Dermatología, Hospital Universitario Germans Trias i Pujol, Universitat Autònoma de Barcelona, IGTP Badalona, Barcelona, Spain

<sup>b</sup> Departamento de Dermatología, Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>c</sup> Departamento de Dermatología, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica (ISABIAL), Universidad Miguel Hernández de Elche, Alicante, Spain

<sup>d</sup> Departamento de Dermatología, Hospital Universitario La Paz, Madrid, Spain

<sup>e</sup> Servicio de Gastroenterología y Hepatología, Hospital Universitario Marqués de Valdecilla, IDIVAL, Escuela de Medicina, Universidad de Cantabria, Santander, Spain

<sup>f</sup> Servicio de Dermatología y Patología, Hospital Universitario de Canarias, La Laguna, Spain

<sup>g</sup> Servicio de Aparato Digestivo, Hospital Universitario La Paz, Madrid, Spain

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**Abstract** Recent years have seen concerted efforts to understand the relation between psoriasis and metabolic-associated fatty liver disease (MAFLD). Not only is MAFLD diagnosed more often in patients with psoriasis, but its clinical course is also more aggressive. A common approach is therefore needed to enable early detection of liver disease coincident with psoriasis. Especially important is an analysis of risks and benefits of potentially hepatotoxic treatments. This consensus paper presents the recommendations of a group of experts in dermatology and hepatology regarding screening for MAFLD as well as criteria for monitoring patients and referring them to hepatologists when liver disease is suspected.

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\* Corresponding author.

E-mail address: [jmcarrascosac@hotmail.com](mailto:jmcarrascosac@hotmail.com) (J.M. Carrascosa).

◊ All the members of the Working Group for the Common Approach to Psoriasis and MAFLD (GACPE) are listed in the Appendix.

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## PALABRAS CLAVE

Psoriasis;  
Esteatosis hepática metabólica;  
EHmet;  
Hepatotoxicidad

## Abordaje común del paciente con psoriasis y riesgo de esteatosis hepática metabólica: recomendaciones de un grupo de expertos multidisciplinar

**Resumen** En los últimos años se están haciendo notables esfuerzos para entender la relación existente entre la psoriasis y la esteatosis hepática metabólica (EHmet). Este trastorno no solo se presenta con una mayor prevalencia en pacientes psoriásicos, sino que además se acompaña de una mayor gravedad. Con este precedente se evidencia la necesidad de establecer un protocolo de abordaje precoz de la enfermedad hepática en los pacientes con psoriasis. Asimismo, es de especial relevancia la evaluación del riesgo y del beneficio en referencia al uso de tratamientos con potencial hepatotóxico. En el presente manuscrito se exponen las recomendaciones de un panel de expertos en dermatología y hepatología para el cribado, el diagnóstico, la monitorización y los criterios de derivación en pacientes con psoriasis, en caso de sospecha de esteatosis hepática metabólica.

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## Introduction

Approximately 125 million people worldwide (1%–3% of the world's population) have psoriasis, and more than 1 million of these are in Spain (2.69% of the country's population).<sup>1,2</sup> Psoriasis is a systemic inflammatory disease that works synergistically with other immune-mediated inflammatory diseases.<sup>2,3</sup> Understanding the impact of associated comorbidities is essential for enabling comprehensive clinical management.<sup>2</sup>

One of the comorbidities associated with psoriasis is what has to date been known as *nonalcoholic fatty liver disease*. In this review, we will refer to this disease using the new term agreed on by the Spanish Association for the Study of the Liver (AEEH) following a Delphi process: *metabolic-associated fatty liver disease*, or MAFLD.<sup>4</sup> MAFLD comprises a spectrum of hepatic lesions ranging from fat accumulation in the liver, which is a metabolic disorder considered to have a low risk of progression, to steatohepatitis, an inflammatory disorder that can progress to cirrhosis and its complications. MAFLD is generally asymptomatic and occurs in association with metabolic syndrome (MetS).<sup>5</sup> It is in fact recognized as the hepatic manifestation of this syndrome and can precede other manifestations.<sup>6,7</sup> MetS is a group of metabolic disorders among which hepatic disorders are considered particularly significant.<sup>6,7</sup> MAFLD has a wide clinical spectrum (Fig. 1) with a dynamic course characterized by periods of progression, regression, and stability.<sup>8,9</sup> This variability can in part be explained by genetics and lifestyle changes, but factors such as age, sex, race, alcohol consumption, and gut microbiota also influence clinical presentation and responses to treatment.<sup>5</sup>

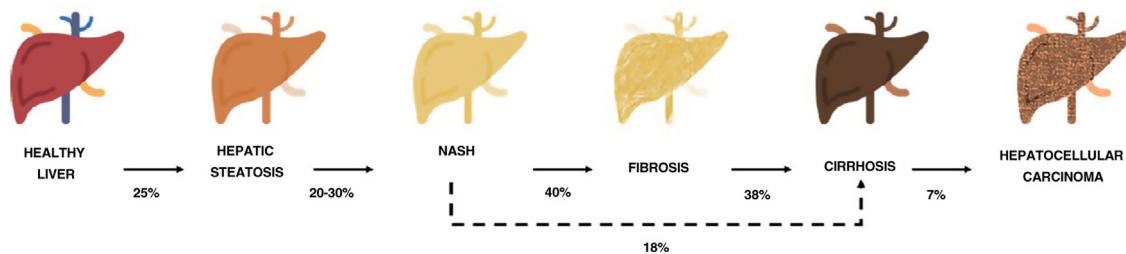
The prevalence of MAFLD is rising progressively, in line with that of MetS, obesity, and type 2 diabetes.<sup>8,10</sup> MAFLD is estimated to affect 25% of the population and 55.5% of people with type 2 diabetes. Although the percentage of patients with MAFLD who develop nonalcoholic steatohepatitis (NASH) is unknown, it is in excess of 10%. The prevalence of biopsy-proven NASH in patients with MAFLD appears to have increased in recent years from 29.9% to 59.1%.<sup>5</sup>

NASH progresses to fibrosis in 40.76% of cases.<sup>8</sup> The estimated prevalence of MAFLD in Spain is 25.8%, while that of significant fibrosis estimated by sequential combination of transition elastography (TE) and liver biopsy is 2.8%.<sup>10</sup>

Prognosis in MAFLD is influenced by progression to NASH, fibrosis, and comorbidities. Advanced fibrosis increases the risk of liver-related morbidity and mortality.<sup>10,11</sup> MAFLD thus constitutes a significant health problem and a major reason for liver transplantation.<sup>9,12</sup>

The evidence supporting the relationship between psoriasis and MAFLD is substantial.<sup>15</sup> In general, MAFLD is more common in patients with more severe psoriasis.<sup>16,17</sup> Phan et al.,<sup>15</sup> corroborating previous findings,<sup>18</sup> showed that patients with psoriasis were twice as likely to have MAFLD as those without psoriasis. In Spain, the percentage of patients with psoriasis and MAFLD is 42.3%.<sup>19</sup> A direct correlation has also been observed between psoriasis severity and liver disease severity.<sup>20</sup> One cross-sectional study found that advanced fibrosis was more common in patients with psoriasis than in healthy controls, and that psoriasis was a significant predictor of advanced liver fibrosis independently of age, sex, body mass index, hypertension, and diabetes.<sup>21</sup> Psoriasis is currently recognized as an independent risk factor for MAFLD.<sup>22,23</sup> Likewise, hypertension, hyperglycemia, and obesity are the main risk factors for MAFLD in patients with psoriasis. The association between psoriasis and MAFLD is independent of confounders, confirming a shared pathophysiology involving inflammatory pathways and genetic predisposition.<sup>15</sup> Psoriasis and MAFLD have a common etiology of low-intensity chronic inflammation involving adipokines that participate in energy balance and inflammatory cytokines (interleukin [IL] 17, tumor necrosis factor- $\alpha$ , and IL-6).<sup>3,24,25</sup>

The above findings suggest that early screening for MAFLD is necessary in patients with psoriasis.<sup>26</sup> The AEEH recently published a consensus statement on the detection of prevalent occult liver diseases and referral criteria. Among its conclusions with clinical implications were 1) chronic liver disease should be screened for and monitored in patients with immune-mediated skin disorders and 2) chronic liver disease is more common in this setting due to immunological and inflammatory mechanisms and hepatotoxicity.<sup>26</sup>



**Figure 1** Progression of metabolic-associated fatty liver disease. From steatosis (stable, with little risk of progression, characterized by the accumulation of intracellular fat in the hepatocyte) to nonalcoholic steatohepatitis (NASH) (fat accumulation accompanied by inflammatory changes and cell damage) and hepatic fibrosis (collagen deposition in the form of fibrous septa that cause architectural remodeling and progressive hepatocyte dysfunction). Fibrosis predisposes to the development of cirrhosis (fibrotic septa and regeneration nodules) and hepatocellular carcinoma and/or liver failure. [6,8,10,12-14](#)

To encourage multidisciplinary management and update current recommendations on screening, diagnosis, monitoring, and referral for MAFLD in patients with psoriasis, we formed an expert panel to design a set of consensus-based recommendations based on current evidence and real-world experience.

## Methodology

A working group of 12 experts with experience in the management of psoriasis and MAFLD—7 dermatologists and 5 hepatologists—was formed to prepare this document. The methodology was based on the so-called *formal method*.<sup>27,28</sup> The group began by reviewing the current evidence and completing several purpose-designed questionnaires on psoriasis and risk of liver disease to identify key points related to detection, screening, diagnosis, and management. Over the course of 3 meetings, the group analyzed clinical aspects related to the definition and management of at-risk patients. At a final meeting, they agreed on an algorithm for managing these patients, which included practical diagnostic and monitoring recommendations based on the main clinical practice guidelines (CPGs) and the clinical experience of the members of the panel.

## Identifying Risk Factors for Liver Disease in Patients With Psoriasis

The expert panel recommends screening for liver disease in patients with psoriasis according to current Spanish CPGs,<sup>29,30</sup> regardless of treatment or time since diagnosis, if at least 1 of the criteria accompanying steatosis in a diagnosis of MAFLD is present<sup>31</sup>: overweight or obesity, T2D, and/or evidence of metabolic dysregulation. These criteria are as follows:

- Waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women
- Blood pressure  $\geq 130/85$  mm Hg or specific drug treatment
- Plasma triglycerides  $\geq 150$  mg/dL ( $\geq 1.70$  mmol/L) or specific drug treatment
- Plasma HDL cholesterol  $< 40$  mg/dL ( $< 1.0$  mmol/L) for men and  $< 50$  mg/dL ( $< 1.3$  mmol/L) for women, or specific drug treatment

- Prediabetes (fasting glucose levels 100–125 mg/dL [5.6–6.9 mmol/L] or 2-h postload glucose levels 140–199 mg/dL [7.8–11.0 mmol/L] or HbA1c 5.7%–6.4% [39–47 mmol/mol])
- HOMA-IR (homeostatic model of assessment for insulin resistance) score  $\geq 2.5$
- Plasma high-sensitivity C-reactive protein level  $> 2$  mg/L

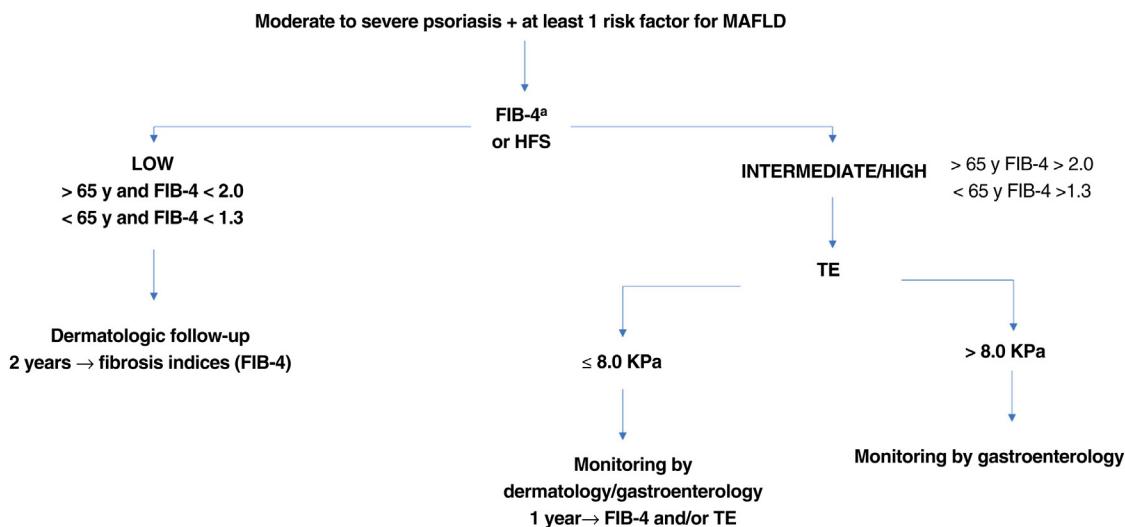
Patients with psoriasis and at least 1 risk factor for MetS should be screened for the risk or presence of liver disease. As MAFLD is a silent disease, national and international CPGs recommend using noninvasive methods such as the Fibrosis-4 Index for Liver Fibrosis (FIB-4) for the early detection of risk factors for the different stages of MAFLD (from steatosis to advanced stages such as fibrosis).<sup>10,30,31</sup> Transaminases should not be explored in isolation for the early diagnosis of MAFLD, as levels can be normal, even in patients with advanced fibrosis.<sup>32</sup>

## Screening Recommendations for MetS

Once an at-risk patient is identified, the first step in the proposed screening and follow-up algorithm (Fig. 2) should be applied.

Consensus is lacking on which noninvasive diagnostic tools, or cutoffs (Table 1), should be used instead of liver biopsy to screen for MAFLD.<sup>10,22,31</sup> Liver biopsy is the current gold standard,<sup>33</sup> but it is not without complications. The CPGs recommend combining serum-based testing and TE, as this reduces the need for biopsy by approximately 50% to 60% and secures an accurate diagnosis.<sup>34</sup> Serum-based fibrosis tests are the first-choice option for screening purposes, with TE to be used in patients considered at high risk.

**Table 1** lists a number of noninvasive liver fibrosis screening tests. The expert panel considers FIB-4 to be most suitable test for initial screening in dermatology units: it has been externally validated for fibrosis screening in patients with fatty liver disease, is readily available and easy to process, and is recommended by CPGs.<sup>10,22,31</sup> FIB-4 takes account of platelet count, age, and aspartate aminotransferase and alanine aminotransferase values. It has high negative predictive value (NPV) for the diagnosis of advanced fibrosis (stage F3-F4), meaning that liver biopsy can be avoided.<sup>35,36</sup> A score of less than 1.30 rules out advanced fibrosis with an NPV of 85%. Scores of more than



**Figure 2** Screening algorithm for patients at risk of MAFLD. Depending on the situation of each hospital and test availability, the dermatology department can order TE or refer the patient to the gastroenterology department. MAFLD indicates metabolic-associated fatty liver disease; FIB-4, Fibrosis-4 Index for Liver Fibrosis; HFS, Hepatome Fibrosis Score; TE, transient elastography.  
<sup>a</sup>TE should be performed to evaluate the risk of fibrosis in patients with a low FIB-4 score and under a potentially hepatotoxic treatment.

**Table 1** Noninvasive Tests for Diagnosing Metabolic-Associated Fatty Liver Disease.

Test	Stage	Parameters	Risk of advanced fibrosis according to cutoff values			
			Fibrosis		Steatosis	
HSI <sup>41</sup>	Steatosis	ALT/AST, BMI, sex, diabetes	< 30: low			
			> 36: high			
FLI <sup>42</sup>	Steatosis	Waist circumference, BMI, triglycerides, GGT	< 30: low			
			30–59: intermediate			
			≥ 60: high			
NAFLD-FS <sup>43</sup>	Fibrosis	Fasting blood glucose or diabetes mellitus, age, BMI, ALT, AST, platelets, albumin	< -1.455: F0-F2, low			
			-1.455–0.675: indeterminate			
			> 0.675: F3-F4, high			
FIB-4 <sup>44</sup>	Fibrosis	Age, ALT, AST, platelets	< 1.30: F0-F2, low			
			> 2.67: F3-F4, high			
HFS <sup>40</sup>	Fibrosis	Sex, age, diabetes, glucose, insulin, HOMA-IR (no diabetes), AST, albumin, platelets	HFS score	F2-F4	F3-F4	F4
			< 0.12	23.6%	8.1%	0.9%
			0.12–0.47	57.1%	33.7%	7.4%
			> 0.47	86.4%	76.3%	35.5%
APRI <sup>45</sup>	Fibrosis	AST, platelets	F0-F2: < 0.5; 72.7%			
			F3-F4: > 1.5; 54.2%			
BARD score <sup>46</sup>	Fibrosis	ALT, AST, diabetes, BMI	0–1: low			
			2–4: high			
ELF <sup>47</sup>	Fibrosis	HA, PIIINP, TIMP-1	< 7.7: zero or low			
			≥ 7.7–9.7: moderate			
			≥ 9.8: high			

Abbreviations: ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; ELF, enhanced liver fibrosis test; GGT, gamma-glutamyl transferase; HFS, Hepatome Fibrosis Score; HOMA, homeostatic model assessment for insulin resistance; HSI, hepatic steatosis index; NAFLD-FS, nonalcoholic fatty liver disease fibrosis score; PIIINP, procollagen III amino-terminal peptide; TIMP-1, tissue inhibitor of matrix metalloproteinase 1.

**Table 2** Clinical trials evaluating treatments for metabolic-associated fatty liver disease.

Target	Drug	Action	Phase	Ref.
Diabetes, insulin resistance	Semaglutide	GLP-1 receptor analog	II	54
	Canagliflozin	SGLT2 inhibitor	Pilot	55
	BMS-986036	Recombinant FGF21	II	56
Dyslipidemia	Aramcol	SCD inhibitor	III	57
	Firsocostat (GS-0976)	ACC inhibitor	II	58
Nuclear receptor	Obeticholic acid	FXR agonist	III	59
	Elafibranor	PPAR $\alpha$ / $\delta$ agonist	III	60
	Resmetirom (MGL-3196)	TR $\beta$ agonist	III	61
Apoptosis Inflammation, fibrosis	Emricasan	Caspase inhibitor	II	62
	Selonsertib	ASK1 inhibitor	III	63
	Cenicriviroc	CCR2/5 antagonist	III	64
	GR-MD-02	Galectina-3 inhibitor	I	65
	JKB-121	TLR4 antagonist	II	66
	ND-LO2-s0201	HSP47 siRNA	II	67

Adapted from.<sup>53</sup>

Abbreviations: ACC, acetyl-coenzyme A carboxylase; ASK1: apoptosis signal-regulatory kinase 1; CCR2/5, chemokine coreceptor type 2/5; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; GLP1, glucagon-like peptide 1; HSP47 siRNA: heat shock protein 47 small interfering ribonucleic acid; PPAR $\alpha$ / $\delta$ , peroxisome proliferator-activated receptor $\alpha$ / $\delta$ ; SCD, stearoyl-coenzyme A desaturase; SGLT2, sodium-glucose cotransporter type 2; TLR4, toll-like receptor 4; TR $\beta$ , thyroid hormone receptor  $\beta$ .

2.67 indicate advanced fibrosis with a positive predictive value (PPV) of 79%.<sup>37</sup> A number of factors, however, must be considered, including the risk of false positives from PPVs, a relatively high probability (1 in 3) of intermediate scores (1.30–2.67), and the influence of age on the accuracy of predictions (a threshold score of 2 is recommended for people aged over 65 years).<sup>38</sup>

The accuracy of FIB-4 depends on age: the index is not suitable for people younger than 35 years, and more tailored cutoffs are needed to improve its specificity in those older than 65 years.<sup>39</sup> Another serum-based tool, the HEP-AMET Fibrosis Score (HFS), offers greater specificity (higher predictive values than FIB-4) and accuracy, resulting in less diagnostic uncertainty. Its only limitation is that it includes HOMA-IR, which is generally not a routinely ordered test.<sup>40</sup>

When serum-based testing indicates a low risk, twice-yearly dermatologic follow-up with reassessment of risk is recommended.<sup>31</sup> TE is recommended in patients with a medium to high risk.<sup>31,38,48</sup> It has proven effective for monitoring disease severity, has high diagnostic accuracy for advanced stages of fibrosis (F3-F4), correlates with clinical findings,<sup>49,50</sup> and, as a noninvasive test, does not increase risk. It should be noted that a high FIB-4 score indicates increased risk, regardless of TE results. Decisions to refer a patient for TE should therefore be based on availability and expected usefulness (whether or not it will influence outcomes). Patients with an intermediate FIB-4 score should be referred for TE due to the high level of uncertainty.

Wong et al.<sup>51</sup> showed that a TE cutoff of 7.9 kPa had the highest accuracy (sensitivity, 91%; specificity, 75%; and positive predictive power, 97%) for the diagnosis of advanced fibrosis and cirrhosis in patients with MAFLD. The recommended cutoff for high-risk patients is therefore 8 kPa. Patients with a high FIB-4 score and a TE value of 8 kPa or lower should be reassessed annually using FIB-4 and/or a repeat TE if available.

Patients with a TE value of more than 8 kPa and a risk of advanced fibrosis (F3-F4) should be referred to the gastroenterology department for evaluation of the most appropriate management strategy (Fig. 2). If TE is not available, patients with a high FIB-4 score should be referred to a gastroenterologist.

### Current Treatments for Psoriasis and Their Impact on MAFLD

The expert panel recommendations are general guidelines for common clinical situations that should be applied according to the criteria of each specialist.

CPG diet and exercise recommendations are the mainstay treatment for MAFLD.<sup>31</sup> Weight reductions of 10% or more can resolve NASH and reduce fibrosis severity by at least 1 stage. Minor weight loss (5%–10%) can improve certain components of MAFLD. A Mediterranean diet, even without weight loss, reduces liver fat content.<sup>52</sup>

A number of drugs are currently under development for MAFLD. Details of clinical trials evaluating their efficacy and safety are summarized in Table 2.

Mets factors should be evaluated in patients without severe liver disease who have a TE value of 6 to 8 kPa, regardless of FIB-4 score. Determining the degree of metabolic disease is important for estimating the risk of progression to advanced fibrosis or cirrhosis.<sup>7</sup> The results of this assessment will determine the need for follow-up and further tests in accordance with the respective recommendations (annual follow-up and repeat FIB-4).

Patients with psoriasis and liver disease have an increased risk of drug-induced hepatotoxicity (Table 3).<sup>68</sup> Methotrexate is the most widely used conventional systemic drug in moderate to severe psoriasis due to its cost-effectiveness and the extensive experience with its use. It is, however, hepatotoxic and can cause fibrosis.<sup>69–71</sup>

**Table 3** Drugs Used to Treat Psoriasis and Their Impact on the Liver.

Drug	Toxicity	Type of damage	Liver failure	Increased risk of liver damage
Methotrexate <sup>69-73</sup>	+++	Oxidative damage	Use with precaution Contraindicated if TBIL > 5 mg/dL	MAFLD/obesity, leflunomide, alcohol
Acitretin <sup>74,75</sup>	++	Mitochondrial dysfunction	Contraindicated	Elevated transaminases 15%-30% <sup>75</sup>
TNF inhibitors <sup>76-78</sup>	++	Liver failure, noninfectious hepatitis, hepatic insufficiency	NA	Increased risk of liver damage with adalimumab <sup>79</sup> and autoimmune hepatitis with infliximab <sup>78</sup>
IL-12/23 antibodies <sup>79</sup>	+	NA	N/A	NA
IL-23 antibodies <sup>80-82</sup>	+	Elevated transaminases <sup>a</sup>	NA	NA
IL-17 antibodies <sup>83-85</sup>	NA	NA	NA	Possible protective effect against inhibition of IL-17A in animal models <sup>86</sup>
Apremilast <sup>87</sup>	NA	NA	NA	NA
Cyclosporine <sup>88</sup>	Rare	Oxidative damage	Safe	Obesity
				Dose reduction required

Adapted from.<sup>25,69-88</sup>

Abbreviations: IL, interleukin; NA, not applicable (no studies); TBIL, total bilirubin.

The group of TNF inhibitors includes etanercept, adalimumab, and infliximab. The group of IL-17A inhibitors includes brodalumab, ixekizumab, and secukinumab. The group of IL-23 inhibitors includes tildrakizumab, guselkumab, and risankizumab.

<sup>a</sup> Only guselkumab in psoriatic arthritis studies, according to summary of product characteristics.**Table 4** Characteristics of Moderate to Severe Psoriasis in Candidates for Systemic Treatment According to the Definitions of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology (AEDV).<sup>29</sup>

Psoriasis severity scores	BSA <sup>a</sup> 10% or PASI <sup>b</sup> > 10 or DLQI <sup>c</sup> > 10
Location	Visible areas (face and dorsum of hands), palms, soles, genitals, scalp, nails, and also recalcitrant plaques with a functional or psychological impact
Previous treatment failure	Not controlled by topical therapy or phototherapy

<sup>a</sup> Body surface area (BSA) is one of the most widely used scales to assess psoriasis severity.<sup>91</sup> BSA is calculated from the arithmetic mean of the affected skin surface weighted according to the total area occupied by each part of the body evaluated: the head represents 10% of the total body surface, the upper extremities 20%, the trunk 30%, and the extremities less than 40%.<sup>92</sup>

<sup>b</sup> The Psoriasis Area Severity Index (PASI) is the most widely used measurement scale for assessing the extent and severity of psoriasis and guiding treatment decisions. This index combines a severity score ranging from 0 to 4 assigned to each psoriasis lesion (0 = none, 1 = mild, 2 = moderate, 3 = marked, 4 = very marked) in 4 parts of the body (head, trunk, upper limbs, and lower limbs). The score is based on 3 parameters: erythema, induration, and desquamation.<sup>92,93</sup>

<sup>c</sup> The Dermatology Life Quality Index (DLQI) is composed of 10 questions on the extent to which a person's skin problem has affected their life over the past week. Each question has 4 possible answers: not at all (0), a little (1), a lot (2), very much (3). The scores (0-3) are added to obtain a total score. A higher score indicates worse quality of life.<sup>94</sup>

A recent study of patients with moderate to severe psoriasis treated with methotrexate in Spain showed a correlation between treatment duration and risk of liver fibrosis.<sup>72</sup> The percentage of patients with a high risk (FIB-4 > 1.3) increased from 18.2% when patients received methotrexate for 16 to 24 weeks to 27.3% when they were treated for 52 to 104 weeks and 32.3% when they were treated for longer.<sup>72</sup> Shetty et al.<sup>71</sup> suggested that the intensity and frequency of monitoring should be tailored to individual risk factors and emphasized the increased risk of methotrexate-induced liver damage in patients with NASH or NASH-fibrosis.

Patients under treatment with steatogenic drugs should also be monitored for liver damage.<sup>68</sup> According to a recent CPG, amiodarone, methotrexate, tamoxifen, and the chemotherapeutic agents 5-fluorouracil and irinotecan

are risk factors for MAFLD and should be maintained or withdrawn based on their potential to protect against progression to liver disease (grade B recommendation based on extrapolation from level 1 evidence studies).<sup>89</sup>

TE is recommended in patients with a low FIB-4 score under hepatotoxic treatment.<sup>70,89,90</sup> The decision whether to continue treatment with a hepatotoxic drug in patients with moderate to severe psoriasis and a TE value of 8 kPa or lower (tested because of a high FIB-4 score or reevaluated with a low FIB-4 score due to treatment) should be based on an individual risk-benefit analysis and the recommendations of the hepatologist. Hepatotoxic drugs are not recommended in patients with a high FIB-4 score and/or a TE of more than 8 kPa due to the risk of advanced fibrosis (F3-F4) (Table 4).

## Discussion

Agreement among dermatologists and hepatologists on simple, evidence-based, criteria to identify, diagnose, and monitor at-risk individuals is essential for the efficient management of MAFLD. General recommendations should be tailored to the specific characteristics, needs, and organizational and care delivery set-ups of different hospital and health care providers.

Potential interactions between psoriasis treatments and MAFLD must be taken into account, with consideration of both the prevalence of liver disease and the potential and diverse impacts of these treatments. Decisions on whether to continue with a potentially hepatotoxic treatment in patients with a risk of liver fibrosis should be taken after weighing up the risks and benefits. Individual evaluation and follow-up is necessary.

Of all the treatments investigated, methotrexate is the only one associated with an increased risk of new-onset or worsening MAFLD. There is no evidence that phototherapy or certain new-generation conventional treatments cause hepatotoxicity in patients with hepatic steatosis. Although most biologic therapies have a favorable risk-benefit profile in patients with steatosis and varying degrees of fibrosis, their hepatotoxic potential is diverse (Table 3).<sup>92</sup>

## Conclusions

Considering the prevalence of MAFLD in patients with psoriasis and the interconnections between these diseases, we recommend screening for liver disease and certain components of MAFLD in patients with psoriasis, regardless of the presence or extent of liver biochemistry abnormalities. This screening should be a routine part of psoriasis care in dermatology departments and clinics. The first-choice strategy is to use a combination of FIB-4 and TE and to refer patients to the hepatology department when a significant risk of advanced fibrosis is detected.

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## Conflicts of Interest

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Salvador Benlloch Pérez has participated as a researcher, speaker, or consultant in projects and clinical trials sponsored by Novartis, Novo Nordisk, and Gilead.

Jorge Alonso Suárez Pérez has served on a steering committee and/or participated as a guest speaker for Novartis, LEO Pharma, Abbvie, Lilly, Janssen, UCB, Amgen, and Almirall.

José Manuel Carrascosa has served as a principal investigator/co-investigator and/or was a guest speaker for Novartis, LEO Pharma, Abbvie, Lilly, Janssen, UCB, Sandoz, Mylan, Amgen, Almirall, Bristol-Myers-Squibb, and Boehringer Ingelheim.

Javier Ampuero declares that he has no conflicts of interest.

Francisco Guimerà declares that he has no conflicts of interest.

## Appendix. Working Group for a Common Approach to Psoriasis and MAFLD (GACPE)

GACPE, the Working Group for a Common Approach to Psoriasis and MAFLD, is composed of 7 dermatologists and 5 hepatologists with experience in managing psoriasis and MAFLD. The respective experts are listed below.

### Dermatologists

Jorge Alonso Suárez-Pérez. Departamento de Dermatología, Hospital Universitario Virgen de la Victoria, Málaga, Spain.

Susana Armesto Alonso. Departamento de Dermatología, Hospital Universitario Marqués de Valdecilla, Santander, Spain.

Isabel Belinchón Romero. Departamento de Dermatología, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica (ISABIAL), Universidad Miguel Hernández de Elche, Alicante, Spain.

José Manuel Carrascosa Carrillo. Departamento de Dermatología. Hospital Universitario Germans Trias i Pujol. Universitat Autònoma de Barcelona. IGTP Badalona, Spain.

Francisco Guimerá Martín-Neda. Servicio de Dermatología y Patología, Hospital Universitario de Canarias, La Laguna, Spain.

Pedro Herranz Pinto. Departamento de Dermatología, Hospital Universitario La Paz, Madrid, Spain.

Eva Vilarrasa Rull. Departamento de Dermatología, Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain.

## Hepatologists

Javier Ampuero Herrojo. Departamento de Enfermedades Digestivas, Hospital Universitario Virgen del Rocío. Laboratorio 213, Instituto de Biomedicina de Sevilla (IBIS). Departamento de Medicina, Universidad de Sevilla. Centro Biomédico en Red de Enfermedades Hepáticas y Digestivas (CIBERehd). Sevilla, Spain.

Salvador Benlloch Pérez. Servicio de Enfermedades Digestivas, Hospital Arnau de Vilanova. Valencia. Centro Biomédico en Red de Enfermedades Hepáticas y Digestivas (CIBERehd). Valencia, Spain.

Javier Crespo García. Servicio de Gastroenterología y Hepatología. Hospital Universitario Marqués de Valdecilla. IDIVAL. Escuela de Medicina. Universidad de Cantabria. Santander, Spain.

Antonio Olveira Martín. Servicio de Aparato Digestivo, Hospital Universitario La Paz, Madrid, Spain.

## References

- Puig L, Ruiz de Morales JG, Dauden E, Andreu JL, Cervera R, Adán A, et al. Prevalence of ten immune-mediated inflammatory diseases (IMID) in Spain. *Rev Esp Salud Pública*. 2019;93:e201903013.
- Takeshita J, Grewal S, Langan SM, Mehta NN, Oggie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases. *J Am Acad Dermatol*. 2017;76:377-90.
- Mantovani A, Gisondi P, Lonardo A, Targher G. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel Hepato-Dermal axis? *Int J Mol Sci*. 2016;17:217.
- Romero-Gómez M, Ampuero J. Looking for a new name for non-alcoholic fatty liver disease in Spanish: esteatosis hepática metabólica (EHmet). *Rev Esp Enferm Dig*. 2021;113:161-3.
- Juanola O, Martínez-López S, Francés R, Gómez-Hurtado I. Non-alcoholic fatty liver disease: metabolic, genetic, epigenetic and environmental risk factors. *Int J Environ Res Public Health*. 2021;18:5227.
- Reccia I, Kumar J, Akladios C, Virdis F, Pai M, Habib N, et al. Non-alcoholic fatty liver disease: a sign of systemic disease. *Metabolism*. 2017;72:94-108.
- Kanwar P, Kowdley KV. The metabolic syndrome and its influence on nonalcoholic steatohepatitis. *Clin Liver Dis*. 2016;20:225-43.
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73-84.
- Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. *Transplantation*. 2019;103:22-7.
- Aller R, Fernández-Rodríguez C, Lo Iacono O, Bañares R, Abad J, Carrión JA, et al. Consensus document. Management of non-alcoholic fatty liver disease (NAFLD). Clinical practice guideline. *Gastroenterol Hepatol*. 2018;41:328-49.
- Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology*. 2019;69:2672-82.
- Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol*. 2019;70:151-71.
- Drew L. Fourth, the progression of liver disease in NASH is not linear and can be manifested by periods of progression, regression and stability. *Nature*. 2017;550:S102.
- Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547-55.
- Phan K, Onggo J, Charlton O, Smith SD. Relationship between psoriasis and non-alcoholic fatty liver disease – updated systematic review and adjusted meta-analysis. *Aust J Dermatol*. 2019;60:e352-5.
- Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. *J Hepatol*. 2009;51:758-64.
- Madanagobalane S, Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: a study from South India. *Aust J Dermatol*. 2012;53:190-7.
- Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia F, Méndez-Sánchez N, Arrese M, et al. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2015;29:656-62.
- Belinchón-Romero I, Bellot P, Romero-Pérez D, Herráiz-Romero I, Marco F, Frances R, et al. Non-alcoholic fatty liver disease is associated with bacterial translocation and a higher inflammation response in psoriatic patients. *Sci Rep*. 2021;11:1-12.
- Olveira A, Herranz P, Montes ML. Psoriasis and fatty liver: a harmful synergy. *Rev Esp Enfermedades Dig*. 2019;111:314-9.
- Gisondi P, Barba E, Girolomoni G. Non-alcoholic fatty liver disease fibrosis score in patients with psoriasis. *J Eur Acad Dermatol Venereol*. 2016;30:282-7.
- Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328-57.
- Vandervoort EAM, Koehler EM, Nijsten T, Stricker BH, Hofman A, Janssen HL, et al. Increased prevalence of advanced liver fibrosis in patients with psoriasis: a cross-sectional analysis from the Rotterdam study. *Acta Derm Venereol*. 2016;96:213-7.
- Prussick RB, Miele L. Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? *Br J Dermatol*. 2018;179:16-29.
- Fiore M, Leone S, Maraolo AE, Berti E, Damiani G. Liver illness and psoriatic patients. *Biomed Res Int*. 2018;2018:1-12.
- Romero Gómez M, Aller J, Fernández Rodríguez C, Augustín S, Latorre R, Rivera-Esteban J, et al. Consenso sobre métodos de detección y derivación de enfermedades hepáticas prevalentes ocultas. *Consenso AEEH. Gastroenterol Hepatol*. 2022;46:236-47.
- Martínez-Sahuquillo Amuedo ME, Echevarría Ruiz De Vargas MC. Métodos de consenso Uso adecuado de la evidencia en la toma de decisiones. «Método RAND/UCLA». *Rehabilitación*. 2001;35:388-92.
- James D, Warren-Forward H. Research methods for formal consensus development. *Nurse Res*. 2015;22:35-40.
- Carrascosa JM, Puig L, Belinchón Romero I, Salgado-Boquete L, Del Alcázar E, Andrés Lencina JJ, et al. Practical update of the recommendations published by the psoriasis group of the Spanish Academy of Dermatology and Venereology (GPs) on the treatment of psoriasis with biologic therapy. Part 1. Concepts and general management of psoriasis with biologic therapy. *Actas Dermosifiliogr*. 2022;113:261-77, <http://dx.doi.org/10.1016/j.ad.2021.10.003>.
- Carrascosa JM, Puig L, Romero IB, Salgado-Boquete L, Del Alcázar E, Lencina JJA, et al. Practical update of the guidelines published by the psoriasis group of the Spanish Academy of Dermatology and Venereology (GPs) on the treatment of psoriasis with biologic agents: Part 2 – Management of special populations patients with comorbid

conditions, and risk. *Actas Dermosifiliogr.* 2022;113:583–609, <http://dx.doi.org/10.1016/j.ad.2022.01.024>.

31. Guerra-Ruiz AR, Casals G, Irizubia P, Lalana M, Leis A, López RM, et al. Valoración bioquímica en la enfermedad hepática grasa asociada a la disfunción metabólica. *Adv Lab Med.* 2021;2:209–19.

32. European Association for the Study of the Liver (EASL). European Association for the Study of Diabetes (EASD). European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol.* 2016;64:1388–402.

33. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology.* 2003;37:1286–92.

34. Tafur Sánchez CN, Durá Gil M, Alamán Domínguez A, Hernández Pérez CM, Mora Cuadrado N, Gómez de la Cuesta S, et al. Utilidad práctica de los índices no invasivos en la esteatosis hepática metabólica. *Endocrinol Diabetes Nutr.* 2022;69:418–25, <http://dx.doi.org/10.1016/j.endinu.2021.08.001>.

35. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L, et al. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. *World J Gastroenterol.* 2018;24:3361–73.

36. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006;43:1317–25.

37. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut.* 2010;59:1265–9.

38. Petta S, Wong VW, Cammà C, Hiriart JB, Wong GL, Vergniol J, et al. Serial combination of non-invasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. *Aliment Pharmacol Ther.* 2017;46:617–27.

39. European Association for the Study of the Liver. Clinical Practice Guideline Panel. EASL Governing Board representative. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. *J Hepatol.* 2021;75:659–89.

40. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gómez M, Allison M, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol.* 2017;112:740–51.

41. Ampuero J, País R, Aller R, Gallego-Durán R, Crespo J, García-Monzón C, et al. Development and validation of hepmet fibrosis scoring system – a simple noninvasive test to identify patients with nonalcoholic fatty liver disease with advanced fibrosis. *Clin Gastroenterol Hepatol.* 2020;18, 216–25.e5.

42. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis.* 2010;42:503–8.

43. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol.* 2006;6:33.

44. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology.* 2007;45:846–54.

45. Sumida Y, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. *BMC Gastroenterol.* 2012;12:2.

46. Peleg N, Issachar A, Sneh-Arbib O, Shlomai A. AST to Platelet Ratio Index and fibrosis 4 calculator scores for non-invasive assessment of hepatic fibrosis in patients with non-alcoholic fatty liver disease. *Dig Liver Dis.* 2017;49:1133–8.

47. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. *Gut.* 2008;57:1441–7.

48. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology.* 2008;47:455–60.

49. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol.* 2003;29:1705–13.

50. Murad Gutiérrez V, Romero Enciso JA. Liver elastography: what it is, how it is done, and how it is interpreted. *Radiología.* 2018;60:183–9.

51. Wong VWS, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology.* 2010;51:454–62.

52. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol.* 2017;67:829–46, <http://dx.doi.org/10.1016/j.jhep.2017.05.016>.

53. Tanaka N, Kimura T, Fujimori N, Nagaya T, Komatsu M, Tanaka E, et al. Current status, problems, and perspectives of non-alcoholic fatty liver disease research. *World J Gastroenterol.* 2019;25:163–77, <http://dx.doi.org/10.3748/wjg.v25.i2.163>.

54. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratiu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384:1113–24.

55. Akuta N, Watanabe C, Kawamura Y, Arase Y, Saitoh S, Fujiyama S, et al. Effects of a sodium-glucose cotransporter 2 inhibitor in nonalcoholic fatty liver disease complicated by diabetes mellitus: preliminary prospective study based on serial liver biopsies. *Hepatol Commun.* 2017;1:46–52.

56. Sanyal A, Charles ED, Neuschwander-Tetri BA, Loomba R, Harrison SA, Abdelmalek MF, et al. Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet.* 2019;392:2705–17.

57. ClinicalTrials.gov. A clinical study to evaluate the efficacy and safety of aramchol in subjects with NASH (ARMOR). Available from: <https://clinicaltrials.gov/ct2/show/NCT04104321> [accessed 1.7.22].

58. Alkhouri N, Lawitz E, Noureddin M, DeFrondo R, Shulman GI. GS-0976 (Firsocostat): an investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH). *Expert Opin Investig Drugs.* 2020;29:135–41.

59. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet.* 2015;385:956–65.

60. Ratiu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. *Gastroenterology.* 2016;150:1147–59.e5.

61. Harrison SA, Bashir M, Moussa SE, McCarty K, Pablo Frias J, Taub R, et al. Effects of resmetirom on noninvasive endpoints in a 36-week phase 2 active treatment extension study in patients with NASH. *Hepatol Commun.* 2021;5:573–88.

62. Barreyro FJ, Holod S, Finocchietto PV, Camino AM, Aquino JB, Avagnina A, et al. The pan-caspase inhibitor Emricasan (IDN-6556) decreases liver injury and fibrosis in a murine model of non-alcoholic steatohepatitis. *Liver Int.* 2015;35:953-66.

63. Schuster S, Feldstein AE. NASH: novel therapeutic strategies targeting ASK1 in NASH. *Nat Rev Gastroenterol Hepatol.* 2017;14:329-30.

64. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. *Hepatology.* 2018;67:1754-67.

65. Harrison SA, Marri SR, Chalasani N, Köhli R, Aronstein W, Thompson GA, et al. Randomised clinical study: GR-MD-02, a galectin-3 inhibitor, vs. placebo in patients having non-alcoholic steatohepatitis with advanced fibrosis. *Aliment Pharmacol Ther.* 2016;44:1183-98.

66. Diehl AM, Harrison S, Caldwell S, Rinella M, Paredes A, Moylan C, et al. JKB-121 in patients with nonalcoholic steatohepatitis: a phase 2 double blind randomized placebo control study. *J Hepatol.* 2018;68:S103.

67. ClinicalTrials.gov. JUNIPER: a phase 2 study to evaluate the safety, biological activity, and PK of ND-L02-s0201 in subjects with IPF. Available from: <https://clinicaltrials.gov/ct2/show/NCT03538301> [cited 2022, Jul 1].

68. Mikhaylov D, Hashim PW, Nektalova T, Goldenberg G. Systemic psoriasis therapies and comorbid disease in patients with psoriasis: a review of potential risks and benefits. *J Clin Aesthet Dermatol.* 2019;12:46-54.

69. Maybury CM, Jabbar-Lopez ZK, Wong T, Dhillon AP, Barker JN, Smith CH. Methotrexate and liver fibrosis in people with psoriasis: a systematic review of observational studies. *Br J Dermatol.* 2014;171:17-29.

70. NICE. Psoriasis: assessment and management (CG153). Clinical Guideline 84, no pagination, 2015.

71. Shetty A, Cho WK, Alazawi W, Syn WK. Methotrexate hepatotoxicity and the impact of nonalcoholic fatty liver disease. *Am J Med Sci.* 2017;354:172-81.

72. Rivera R, Vilarrasa E, Ribera M, Roe E, Kueder-Pajares T, Zayas AI, et al. Unmet needs in patients with moderate-to-severe plaque psoriasis treated with methotrexate in real world practice: FirST study. *J Dermatolog Treat.* 2022;33:1329-38.

73. Agencia Española de Medicamentos y Productos Sanitarios. Ficha Técnica de Metotrexato.

74. Ficha técnica de Acitretina. Agencia Europea de Medicamentos, 2020.

75. Silva FS, Ribeiro MP, Santos MS, Rocha-Pereira P, Santos-Silva A, Custódio JB, et al. Acitretin affects bioenergetics of liver mitochondria and promotes mitochondrial permeability transition: potential mechanisms of hepatotoxicity. *Toxicology.* 2013;306:93-100.

76. Ficha técnica de Humira. Agencia Europea de Medicamentos, 2009.

77. Ficha técnica de Cimzia. Agencia Europea de Medicamentos, 2019.

78. Ficha técnica de Remicade. Agencia Europea de Medicamentos, 2014.

79. Agencia Española de Medicamentos y Productos Sanitarios. Ficha Técnica de Ustekinumab, Stelara®, 2013.

80. European Medicines Agency Tremfya (Guselkumab): summary of product characteristics. *Agencia Eur Med.* 2019:1-71.

81. Ficha técnica de Skyrizi. Agencia Europea de Medicamentos, 2014.

82. Ficha técnica de Tremfya. Agencia Europea de Medicamentos, 2009.

83. Ficha técnica de Cosentyx. Agencia Europea de Medicamentos, 2019.

84. Ficha técnica de Kyntheum. Agencia Europea de Medicamentos, 2014.

85. Ficha técnica de Taltz. Agencia Europea de Medicamentos, 2019. [doi:10.2307/j.ctvdf0dxq.12](https://doi:10.2307/j.ctvdf0dxq.12).

86. Gomes AL, Teijeiro A, Burén S, Tummala KS, Yilmaz M, Waisman A, et al. Metabolic inflammation-associated IL-17A causes non-alcoholic steatohepatitis and hepatocellular carcinoma. *Cancer Cell.* 2016;30:161-75, <http://dx.doi.org/10.1016/j.ccr.2016.05.020>.

87. Agencia Española de Medicamentos y Productos Sanitarios. Ficha Técnica de Apremilast.

88. Agencia Española de Medicamentos y Productos Sanitarios. Ficha Técnica Ciclosporina, 2020.

89. Andrade RJ, Aital GP, Björnsson ES, Kaplowitz N, Kullak-Ublick GA, Larrey D, et al. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol.* 2019;70:1222-61, <http://dx.doi.org/10.1016/j.jhep.2019.02.014>.

90. Taylor WJ, Korendowych E, Nash P, Helliwell PS, Choy E, Krueger GG, et al. Drug use and toxicity in psoriatic disease: focus on methotrexate. *J Rheumatol.* 2008;35:1454-7.

91. Reolid A, Servitje O, Ginarte M, Pérez-Ferriols A, Vélez A, Aragüés M, et al. Validación del método de cuantificación del área corporal afectada por la psoriasis mediante lápiz óptico. *Actas Dermosifiliogr.* 2020;111:143-8.

92. Henseler T, Schmitt-Rau K, Kiel D. A comparison between BSA, PASI, PLASI and SAPASI as measures of disease severity and improvement by therapy in patients with psoriasis. *Int J Dermatol.* 2008;1019-23.

93. Chalmers RJG. Assessing psoriasis severity and outcomes for clinical trials and routine clinical practice. *Dermatol Clin.* 2015;33:57-71.

94. Adaptación transcultural al español del cuestionario Dermatology Life Quality Index (DLQI): El Índice de Calidad de Vida en Dermatología. *Actas Dermo-Sifiliogr.* Available from: <https://www.actasdermo.org/es-adaptacion-transcultural-al-espanol-del-articulo-13003408> [cited 2022, Jul 1].