Isolated IgG elevation in patients with persistently normal transaminases does not affect the outcome of autoimmune hepatitis

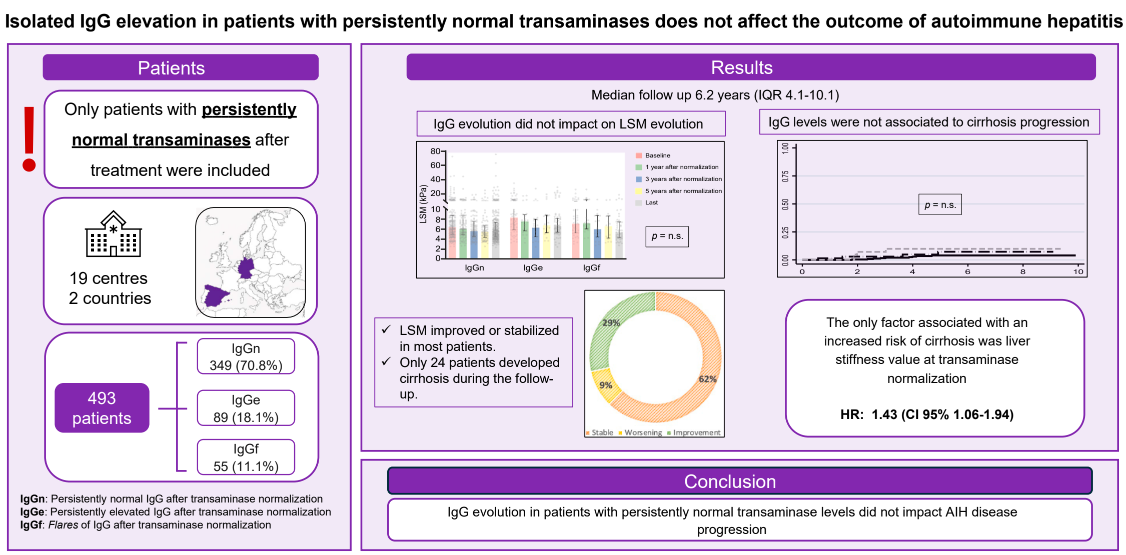
Authors

Álvaro Díaz-González, Ida Schregel, Lorena Carballo, …, Richard Taubert, Christoph Schramm, María-Carlota Londoño

Correspondence

MLONDONO@clinic.cat (M.-C. Londoño), alvaro.diaz@scsalud.es (Á. Díaz-González).

Graphical abstract



Highlights:

- Persistently elevated IgG and IgG flares are relatively common in patients with AIH and persistently normal transaminase levels.
- IgG evolution did not impact AIH outcomes in patients with normal transaminases.
- Only liver stiffness measurement of ≥10 kPa at transaminase normalization was associated with the development of cirrhosis.

Impact and implications:

The body of evidence showing a lesser impact of immunoglobulin G (IgG)values on outcomes in patients with autoimmune hepatitis (AIH) is growing. However, there is still a lack of robust information on the long-term outcomes, especially in patients who achieve persistent transaminase normalization. Persistently elevated IgG or IgG flares in patients with persistently normal transaminases do not seem to affect outcomes in patients with AIH. These results challenge the current definition of complete biochemical response in patients with AIH. Transaminase level normalization appeared to be the best treatment endpoint.

https://doi.org/10.1016/j.jhepr.2025.101562
 JHEP Reports, 2025, 7,

JHEP|Reports

Isolated IgG elevation in patients with persistently normal transaminases does not affect the outcome of autoimmune hepatitis☆

Álvaro Díaz-González[1,*], Ida Schregel[2,3], Lorena Carballo[4], Carmen Álvarez-Navascués[4], Enrique Frisancho-Morales[5], Mireia Miquel[5], Montserrat García Retortillo[6], Judith Gómez[7], Diana Horta[8], Beatriz Mateos[9], Bastian Engel[3,10], Felix Volmer[3,10], María del Barrio[1], Sergio Rodríguez-Tajes[11], Ignasi Olivas[11], Johannes Hartl[2,3], Carla Amaral González[12], Manuel Hernández-Guerra[12], Inmaculada Castello[13], Indhira Pérez-Medrano[14], Jesús M. González-Santiago[15], Ana Arencibía[16], Alberto Gómez[17], Manuel Rodríguez-Perálvarez[17], Javier Crespo[1], Margarita Sala[18], Magdalena Salcedo[19], Ana Barreira-Díaz[3,20], Mar Riveiro-Barciela[3,20], Richard Taubert[3,10], Christoph Schramm[2,3,21], María-Carlota Londoño[3,11,*], ColHai Registry

JHEP Reports **2025**. vol. 7 | 1–8

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Background & Aims: The goal of treatment for autoimmune hepatitis is to achieve a complete biochemical response, defined as normalization of transaminases and immunoglobulin G (IgG) levels. Recent data suggest that IgG normalization does not significantly affect survival. We evaluated the impact of persistently elevated IgG levels (IgGe) and IgG flares (IgGf) on fibrosis progression and cirrhosis development.

Methods: This retrospective multicenter cohort study included 493 patients with autoimmune hepatitis and persistently normal transaminase levels during follow-up. The inverse probability of treatment weighting (IPTW) propensity score method was used to balance the cohorts.

Results: Three hundred forty-nine (70.8%) patients had persistently normal IgG (IgGn) levels, 89 (18.1%) had IgGe, and 55 (11.1%) had IgGf during follow-up. After a median follow-up of 6.2 years (IQR 4.1–10.1 years) with normal transaminase levels, median liver stiffness measurement (LSM) values remained stable, with no significant differences between groups. During the follow-up, 24 patients developed cirrhosis. Predictive factors for cirrhosis were age (hazard ratio [HR] 1.10, p <0.001), albumin (HR 0.20, p <0.001), IgG (HR 1.00, p = 0.001), and platelet count (HR 0.99, p = 0.001) at diagnosis; LSM (HR 1.30, p <0.001) at transaminase normalization; and transaminase normalization at 6 months (HR 0.24, p = 0.025). In the multivariate analysis, only LSM was independently associated with a higher risk of developing cirrhosis. After IPTW application, elevated IgG (IgGe or IgGf) did not affect fibrosis progression (p = 0.275) or cirrhosis development (p = 0.211).

Conclusions: Persistent or temporary serum IgG elevation in patients with normal transaminase levels did not significantly affect autoimmune hepatitis disease progression, thus challenging the current definition of complete biochemical response.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by elevated transaminase levels, hypergammaglobulinemia, autoantibodies, and typical histological findings (interface hepatitis and lymphoplasmacytic portal infiltrates).[1] Treatment consists of a combination of corticosteroids and azathioprine (or mycophenolate mofetil), aimed at achieving disease remission, which refers to the absence of histological activity (modified hepatitis activity index <4).[2] However, follow-up liver biopsies are not routinely performed in clinical practice, and in the absence of other reliable markers, there is consensus that achieving a complete biochemical response (CBR) is an adequate surrogate marker for the absence of clinically relevant histological inflammatory activity.[1,3] CBR is defined as the normalization of alanine aminotransferase (ALT) and immunoglobulin G (IgG) 6 months after starting immunosuppressive treatment,[1,2,3] and it is achieved in ~50–70% of patients.[4–6] According to this definition, patients with CBR have a significantly higher liver transplant-free survival rate. However, recent evidence suggests that IgG normalization might not be necessary to define treatment response in AIH. A multicenter European study

☆ Given their role as Associate Editor, María Carlota Londoño had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to the Guest Editor Diego Vergani.

* Corresponding authors. Addresses: Liver Unit, Hospital Clínic Barcelona, Carrer Villarroel 170, 08036, Barcelona, Spain. Tel.: +34-9322757 (M-C. Londoño); Gastroenterology and Hepatology Department, Clinical and Translational Research in Digestive Diseases Group, Valdecilla Research Institute (IDIVAL), Marqués de Valdecilla University Hospital, Valdecilla Av. s/n, 39008, Santander, Spain. Tel.: +34-942202520 (Á. Díaz-González).
E-mail addresses: MLONDONO@clinic.cat (M.-C. Londoño), alvaro.diaz@scsalud.es (Á. Díaz-González).
https://doi.org/10.1016/j.jhepr.2025.101562

analyzing follow-up liver biopsies found that 88% of patients without cirrhosis and with normal ALT levels were in histological remission. The addition of IgG normalization to the definition of response did not significantly increase the number of patients with histological remission (95%). In patients with cirrhosis, only 26% and 29% of patients with normal transaminase and IgG levels, respectively, were in histological remission.[7] Furthermore, recently published studies have shown that IgG levels were not associated with the probability of survival, whereas elevated aspartate aminotransferase (AST) and ALT levels were associated with a higher risk of mortality.[8,9]

Considering the potentially less relevant role of IgG in the management of AIH, we aimed to assess (1) the frequency of persistently elevated IgG (IgGe) or IgG flares (IgGf) in patients with persistently normal transaminases after induction therapy and (2) the impact of these values on fibrosis progression and cirrhosis development.

Patients and methods

Patients

We performed a retrospective multicenter cohort study of patients diagnosed with AIH and persistently normal transaminases during follow-up at 17 referral centers in Spain participating in the ColHai registry (the Spanish Registry for Cholestatic and Autoimmune Liver Diseases) and two centers in Germany. The inclusion criteria were as follows: (1) diagnosis of AIH based on the simplified International Autoimmune Hepatitis Group criteria (score ≥6), including liver biopsy;[10] (2) standard induction therapy following EASL guidelines;[1] (3) persistently normal transaminase levels after induction therapy, regardless of IgG values; and (4) age >18 years at the time of analysis. The exclusion criteria were as follows: (1) the presence of variant forms of AIH, (2) any other active liver disease that could interfere with treatment response or evaluation, and (3) elevation of transaminase levels during follow-up.

For this project, we defined three cohorts: (1) patients presenting with normal IgG levels after normalization of transaminases (IgGn), defined as patients who consistently maintained normal IgG levels throughout the follow-up period, with no recorded IgG elevations exceeding the upper limit of normal in any follow-up blood tests; (2) patients with persistently elevated levels of IgG after normalization of transaminases (IgGe), defined as those who did not achieve normalization of IgG at any moment during the follow-up; and (3) patients with fluctuating IgG levels, defined as those exhibiting oscillations between normal and elevated IgG values in follow-up blood tests (IgGf) after normalization of transaminases. The usual follow-up intervals at the different centers are presented in Table S1.

The study was approved by the Institutional Review Board of Marqués de Valdecilla University Hospital (internal code: 2021.363) and complied with Good Clinical Practice guidelines and the Declaration of Helsinki and Fortaleza.

Data collected for analysis

Data were anonymized and collected from medical records by each local investigator and centrally compiled and analyzed. In terms of baseline characteristics, we obtained information on demographic variables and the presence of other medical conditions, including autoimmune and metabolic comorbidities, as well as serological, histological, laboratory, liver stiffness measurement (LSM), and treatment parameters. Only reliable LSMs (≥10 valid measurements, ≥60% success rate, and IQR/median ratio <0.30) were included in the analysis.

Adjustments to immunosuppressive drug doses were recorded if made because of fluctuations in IgG or persistently elevated IgG levels.

Definitions

The upper limit of normality at each center was used to define transaminase levels and IgG normalization. Acute severe hepatitis was defined as an acute onset of jaundice and an international normalized ratio (INR) of ≥1.5 in patients without known chronic liver disease.[3] Cirrhosis at baseline was diagnosed based on the histological findings at the time of AIH diagnosis. The development of cirrhosis during follow-up was recorded at each center according to typical clinical, ultrasound, and histological characteristics and/or LSM >16 kPa[11–15] in patients without cirrhosis at baseline. Relevant changes in LSM were defined as an increase or decrease of at least 2 kPa between elastography performed at the time of transaminase level normalization and at the last follow-up. Because of the lack of data on the optimal cut-off point for assessing significant changes in LSM during the follow-up of patients with AIH, we used the 2-kPa value previously described in patients with primary biliary cholangitis.[16]

Statistical analysis

Quantitative variables are expressed as median and IQR (25th–75th percentiles). Categorical variables are presented as absolute frequencies and percentages (%). The inverse probability of treatment weighting (IPTW) propensity score (PS) method was used to balance the cohorts (patients with normal IgG and patients with abnormal IgG). The PS was estimated using a logistic regression model. The parameters included in the final PS model were age (years), baseline INR, baseline alkaline phosphatase, baseline IgG, use of azathioprine (yes *vs*. no), presence of other autoimmune diseases (yes *vs*. no), and presence of anti-soluble liver antigen (SLA) antibodies (positive *vs*. negative). The balance between the baseline parameters of each cohort was assessed before and after the application of IPTW weights and stabilized using standardized mean differences.[17,18] A standardized mean difference of >20% was considered unbalanced.[19] Fisher's exact test and the chi-square (X^2) test were used to compare categorical variables. Depending on the normality of distribution and homoscedasticity, parametric or nonparametric methods were applied for continuous variables. For independent data, Student's *t*/Mann–Whitney *U* test (two groups) or ANOVA/Kruskal–Wallis test (more than two groups) was used. For paired data, the paired Student's *t*/Wilcoxon signed-rank test (two groups) or repeated-measures ANOVA/Friedman test (more than two groups) was used. Logistic and Cox regression analyses were used to elucidate associations and create predictive models of cirrhosis development, respectively. The results of the logistic regression are presented as odds ratios (ORs) and 95% CIs.

The level of significance was set at 5% (two-sided). Analyses and statistical tests were performed using Stata

Statistical Software (Release 14.1; StataCorp LLC, College Station, TX, USA).

Results

Baseline characteristics

Four hundred ninety-three patients with a definitive diagnosis of AIH and persistently normal transaminase levels were included. Of these, 349 (70.8%) had persistently normal IgG (IgGn) levels, 89 (18.1%) had persistently elevated IgG (IgGe) levels, and 55 (11.1%) had fluctuations in IgG levels during follow-up (IgGf). Table 1 shows the baseline characteristics of the patients. Briefly, most patients were women (n = 361, 73%) with a median age at diagnosis of 56.7 years (IQR 45.6 – 66.1 years), 144 (31.3%) had normal IgG levels, 106 (25%) had at least one autoimmune comorbidity, and 71 (15%) had cirrhosis at the time of AIH diagnosis. Disease presentation was acute in 191 patients (46%), chronic in 142 (32%), acute severe in 70 (17%), and acute liver failure in 12 (2.9%), with no differences between the IgG groups (Table S2). Similarly, there were no significant differences in transaminase levels, total bilirubin levels, albumin levels, or platelet counts at the time of diagnosis. Patients with cirrhosis at baseline exhibited elevated IgG levels compared with those without cirrhosis (2,145 *vs.* 1,800 mg/dL, p = 0.002, Table S3). In contrast, patients with IgGf had significantly higher IgG levels at diagnosis (IgGn, 1,711 mg/dl; IgGe, 2,125 mg/dl; IgGf, 2,655 mg/dl; p <0.001) and a higher prevalence of positive antinuclear antibodies (ANA) (IgGn, 80.4%; IgGe, 78.2%; IgGf, 96.1%; p = 0.006), anti-smooth muscle antibodies (ASMA) (IgGn, 43%; IgGe, 31%; IgGf, 55.8%; p = 0.015), and anti-SLA (IgGn, 2.6%; IgGe, 3.5%; IgGf, 13.9%; p = 0.008). In addition, we found that

Table 1. Baseline characteristics of the cohort.

	Whole cohort (N = 493)	IgGn (n = 349)	IgGe (n = 89)	IgGf (n = 55)	*p* value
Women, n (%)	361 (73.2)	254 (72.8)	67 (75.3)	40 (72.7)	0.921
Age at AIH diagnosis (years)	56.7 (45.6–66.1)	56.7 (45.5–66)	56.7 (47.2–65.8)	58.1 (40.5–69.2)	0.852
Alcohol consumption, n (%)*	25 (5.4)	18 (5.5)	3 (3.4)	4 (7.8)	0.487
Metabolic syndrome, n (%)*	113 (24.3)	79 (24.2)	24 (27.3)	10 (19.6)	0.596
AIH presentation, n (%)†					
Acute	191 (46)	139 (49)	32 (36.8)	20 (45.4)	0.376
Chronic	142 (34.2)	91 (32)	35 (40.2)	16 (36.4)	
Acute severe	70 (16.9)	44 (15.5)	19 (21.8)	7 (15.9)	
Acute liver failure	12 (2.9)	10 (3.5)	1 (1.2)	1 (2.3)	
Staging‡					
F0	91 (25.4)	57 (23.5)	20 (27)	14 (34.1)	0.593
F1	75 (20.9)	54 (22.2)	17 (23)	4 (9.8)	
F2	62 (17.3)	43 (17.7)	14 (18.9)	5 (12.2)	
F3	59 (16.5)	40 (16.5)	11 (14.9)	8 (19.5)	
F4	71 (19.8)	49 (20.2)	12 (16.2)	10 (24.4)	
AST (IU/L)	394 (131–985)	399 (126–1,015)	472 (231–958)	299 (128–849)	0.774
AST ×ULN	11.3 (3.9–28.4)	10.9 (3.6–28.4)	13.4 (6.8–28.5)	8.0 (3.5–26.5)	0.551
ALT (IU/L)	510 (180–1,117)	511 (172–1,190)	572 (280–1,096)	419 (172–884)	0.516
ALT ×ULN	14.2 (4.6–29.6)	13.5 (4.2–30.8)	17.1 (8.2–30.4)	10.4 (3.6–25.0)	0.265
ALP (IU/L)	136 (95–201)	135 (93–200)	143 (114–205)	123 (89–208)	0.787
ALP ULN	1.2 (0.8–1.7)	1.2 (0.8–1.7)	1.3 (0.9–1.9)	1.0 (0.7–1.5)	0.073
GGT (IU/L)	165 (80–300)	165 (78–301)	169 (87–319)	133 (62–241)	0.423
GGT ULN	3.9 (1.8–7.0)	4 (1.8–7.1)	4.2 (2.2–7.0)	2.9 (1.4–5.4)	0.196
Total bilirubin (mg/dl)	1.8 (0.8–7.3)	1.8 (0.8–7.4)	2.1 (0.6–7.1)	1.4 (0.9–6.4)	0.561
Albumin (g/dl)	3.7 (3.2–4.2)	3.7 (3.2–4.2)	3.8 (3.2–4.2)	3.8 (3.2–4.2)	0.907
Platelets ($\times 10^9$)	200 (163–248)	200 (163–250)	202 (162–241)	200 (159–250)	0.496
INR	1.1 (1–1.3)	1.1 (1–1.3)	1 (1.2–1.4)	1.2 (1.1–1.3)	**0.018**
ANA ≥1/40, n (%)	389 (81.7)	271 (80.4)	68 (78.2)	50 (96.1)	**0.006**
ASMA ≥1/40, n (%)	200 (42.2)	144 (43)	27 (31)	29 (55.8)	**0.015**
Anti-LKM§, n (%)	13 (2.9)	9 (2.9)	4 (4.6)	0 (0)	0.360
Anti-SLA¶, n (%)	16 (4.1)	7 (2.6)	3 (3.5)	6 (13.9)	**0.008**
IgG (mg/dl)	1,645 (1,013–2,271)	1,711 (1,280–2,230)	2,125 (1,690–2,600)	2,655 (2,064–3,330)	**<0.001**
IgG ×ULN	1.2 (0.8–1.5)	1.1 (0.8–1.4)	1.25 (1.0–1.6)	1.6 (1.3–2.0)	**<0.001**
Normal IgG at diagnosis, n (%)	144 (31.3)	122 (37.6)	20 (23.3)	2 (4)	**<0.001**
Other AI disease, n (%)	106 (25.5)	74 (26.1)	26 (29.9)	6 (13.6)	0.116
Steroids, n (%)	480 (97.4)	340 (97.4)	87 (97.7)	53 (96.4)	0.873
AZA**, n (%)	384 (78.2)	263 (75.6)	80 (90.9)	41 (74.5)	**0.003**
AZA dose (mg/day)	50 (50–50)	50 (50–50)	50 (50–50)	50 (50–50)	0.977

Quantitative values are expressed as median and IQR. Comparisons between groups were performed using the chi-square (X^2) test for categorical variables and ANOVA and the Kruskal–Wallis test for continuous variables. Values in bold denote statistical significance: defined as p <0.05.

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LKM: liver/kidney microsomal antibodies; anti-SLA, anti-soluble liver antigen antibodies; AP, alkaline phosphatase; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; AZA, azathioprine; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; IgGe, persistently elevated IgG; IgGf, IgG flares; IgGn, persistently normal IgG; INR, international normalized ratio; ULN, upper limit of normal.

*Data available in 465 patients.

†Data available in 415 patients.

‡Data available in 358 patients.

§Data available in 442 patients.

¶Data available in 395 patients.

**At the moment of induction, data available in 384 patients.

elevated baseline IgG levels were significantly associated with a higher probability of presenting with IgGe or IgGf during follow-up (OR 3.13, 95% CI 1.88–5.21, p <0.001). The median duration for the initial normalization of transaminase levels was 5.6 months (IQR 2.4–10.3 months), whereas the median time for sustained normalization was 7 months (IQR 3.5–13.8 months). No significant differences were observed between groups. At the time of transaminase normalization, except for IgG values, there were no significant differences in biochemical parameters or LSM among the groups (Table 2).

Isolated IgG elevation led to intensification of immunosuppression in a minority of patients

Considering that patients with IgGe and/or IgGf did not meet the criteria for CBR, treatment was intensified by restarting corticosteroid therapy or increasing azathioprine dose in 21 patients with IgGe (24%) and eight with IgGf (15%). Of these, IgG normalization was only achieved in nine patients formerly classified within the IgGe group and two with former IgGf (43% and 25%, respectively).

Isolated IgGe or IgGf were not associated with fibrosis progression

After a median follow-up of 6.2 years (IQR 4.1–10.1 years) with persistently normal transaminase levels, the median LSM values 1 year after normalization of transaminase levels were 6.3 kPa (IQR 5–8.7 kPa) and 5.8 (IQR 4.5–7.7 kPa) at 3 years, 5.7 kPa (IQR 4.5–7.6 kPa) at 5 years, and 5.8 kPa (IQR 4.6–7.6 kPa) at the last follow-up. In this regard, LSM values presented a significant decrease within each patient group (at transaminase normalization *vs*. last LSM available: IgGn, 6.4 *vs*. 5.7 kPa, p = 0.002; IgGe, 8.3 *vs*. 6.6 kPa, p = 0.003; and IgGf, 7.1 *vs*. 5.4 kPa, p = 0.001). Importantly, when comparing LSM values across the IgGn, IgGe, and IgGf groups at the different time points assessed, no statistically significant differences were found (Fig. 1). We also did not identify any differences when comparing only patients with normal IgG with those with abnormal IgG levels (in any of its forms), both at the time of transaminase normalization (6.4 *vs*. 7.8 kPa; p = 0.124) and at the last elastography performed during follow-up (5.7 *vs*. 6.2 kPa; p = 0.744). Relevant LSM changes (±2 kPa) were observed in 119 patients (37.7 %). Most patients presented a decrease in LSM (n = 90, 28.5%), and only 29 (9.2%) presented a persistent (confirmed in at least one subsequent LSM) increase of >2 kPa in LSM. The only predictive factor associated with increased liver stiffness during follow-up was the absence of transaminase normalization at month 12 (Table S4).

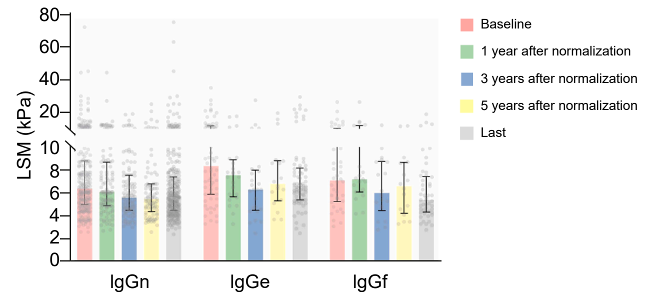

Fig. 1. Individual LSM values at transaminase normalization and at 1, 3, and 5 years after normalization of transaminase levels. Bars represent median values, and whiskers represent the 25th and 75th percentiles (IQR). No significant differences were observed among the groups: 1 year, p = 0.321; 3 years, p = 0.567; 5 years, p = 0.192; last follow-up, p = 0.225. The differences between the first and last LSM values within each group were as follows: IgGn, p = 0.002; IgGe, p = 0.003; and IgGf, p = 0.001. IgG, immunoglobulin G; IgGe, persistently elevated IgG; IgGf, IgG flares; IgGn, persistently normal IgG; LSM, liver stiffness measurement.

Factors associated with cirrhosis development

At the time of AIH diagnosis, 71 patients (14.8%) presented with cirrhosis (as determined histologically). These patients were predominantly women (69.4%), with a median age of 61 years (IQR 50.9–73.9 years), median IgG of 2,145 mg/dl (IQR 1,600–3,045 mg/dl), and LSM of 11.4 kPa (IQR 7.2–20.9 kPa). The presence of cirrhosis at AIH diagnosis did not differ among the IgGn, IgGe, or IgGf groups (p = 0.665).

Table 2. Characteristics of the cohort at the time of transaminase normalization.

	Whole cohort	IgGn	IgGe	IgGf	p value
Time to first transaminase normalization (months)	5.6 (2.4–10.5)	5.6 (2.7–10.5)	5.4 (2.1–9.3)	6.4 (2.1–11.4)	0.766
Time to definite transaminase normalization (months)	7 (3.5–13.8)	7 (3.6–14.6)	6.8 (3.6–13.1)	6.6 (2.8–13.3)	0.717
Follow-up (years)	6.2 (4.1–10.1)	6.5 (4.3–9.8)	5.3 (3.0–9.8)	6.4 (4.5–11.1)	0.109
AST (IU/L)	26 (22–31)	26 (22–32)	25 (22–30)	27 (22–32)	0.225
AST ×ULN	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.8 (0.6–0.8)	0.948
ALT (IU/L)	26 (20–31)	26 (20–32)	24 (19–29)	24 (17–30)	0.101
ALT ×ULN	0.7 (0.5–0.8)	0.7 (0.5–0.8)	0.7 (0.6–0.8)	0.6 (0.4–0.8)	0.303
ALP (IU/L)	68 (55–88)	68 (54–87)	69 (58–90)	71 (54–83)	0.623
ALP ×ULN	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.8)	0.6 (0.4–0.7)	0.124
GGT (IU/L)	31 (20–57)	30 (20–62)	32 (21–42)	31 (21–55)	0.661
GGT ×ULN	0.7 (0.5–1.3)	0.7 (0.5–1.5)	0.7 (0.5–0.9)	0.7 (0.5–1.1)	0.451
Total bilirubin (mg/dl)	0.6 (0.5–0.9)	0.7 (0.5–0.9)	0.6 (0.6–0.6)	1 (0.9–1.1)	0.616
INR	1 (0.9–1.1)	1 (1–1.1)	1 (1–1.1)	1 (1–1.1)	0.170
IgG (mg/dl)	1,150 (959–1,380)	1,100 (922–1,280)	1,633 (1,561–1,945)	1,555 (1,350–1,760)	**<0.001**
IgG ×ULN	0.7 (0.6–0.9)	0.7 (0.6–0.8)	1.1 (1–1.2)	1 (0.8–1.1)	**<0.001**
Liver stiffness (kPa)*	6.7 (5–9.5)	6.4 (5–8.8)	8.3 (5.9–11.8)	7.1 (5.3–9.9)	0.126

Quantitative values are expressed as median and IQR. Comparisons between groups were performed using ANOVA and the Kruskal–Wallis test for continuous variables. Values in bold denote statistical significance: defined as p <0.05.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; IgGe, persistently elevated IgG; IgGf, IgG flares; IgGn, persistently normal IgG; INR, international normalized ratio; ULN, upper limit of normal.

*Data available at normalization in 339 patients.

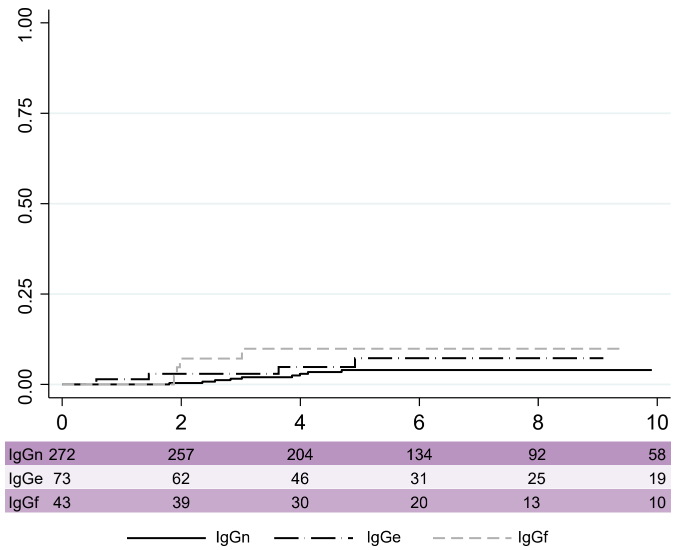

Fig. 2. Kaplan–Meier curve displaying the time to cirrhosis development across the different IgG groups. IgG, immunoglobulin G; IgGe, persistently elevated IgG; IgGf, IgG flares; IgGn, persistently normal IgG.

During follow-up, 24 patients progressed to cirrhosis in a median time of 3 years (IQR 1.9–4.1 years). The time to cirrhosis development is shown in Fig. 2. There were no differences in the baseline characteristics of these patients based on the evolution of IgG, except for IgG levels, which were significantly higher in patients with IgGe and IgGf than in those with IgGn (Table S5). However, patients who developed cirrhosis during follow-up were older (69.6 *vs*. 55.9 years; p <0.001), had lower albumin levels (3.3 *vs*. 3.8 g/dl; p <0.001), lower platelet counts (176 × 10^9 *vs*. 211 × 10^9; p <0.001), higher IgG values at diagnosis (2,454 *vs*. 1,780 mg/dl; p = 0.009), and higher AST (28 *vs*. 25; p = 0.017), GGT (47 *vs*. 28 IU/L; p = 0.017), and LSM (11.2 *vs*. 6.1 kPa; p <0.001) at the time of transaminase normalization (Table S6).

In multivariate analysis, only LSM at the time of transaminase normalization was independently associated with the risk of developing cirrhosis during follow-up (HR 1.43, 95% CI 1.06-1.94, p = 0.019). Conversely, different evolutionary categories of IgG (HR 1.49, 95% CI 0.26–8.40), IgG values at diagnosis (HR 0.99, 95% CI 0.99–1.01), and IgG values at the time of transaminase level normalization (HR 1.00, 95% CI 0.99–1.00) were not associated with the risk of developing cirrhosis (Table 3). After identifying the predictive ability of liver elastography for cirrhosis development during follow-up, we determined the optimal cut-off point associated with that risk. We identified 10.1 kPa as the optimal cut-off point for this prediction, with an AUC of 0.898 (95% CI 0.855–0.931; Fig. S1).

Only three of the 95 patients (1%) with cirrhosis decompensated during follow-up, and one required liver transplantation. No patient developed hepatocellular carcinoma during follow-up.

Considering the retrospective design of the study and the participation of a large number of centers, IPTW PS analysis was performed, with the aim of minimizing the risk of potential selection bias. After IPTW application, the cohort was adequately balanced for comparison among the groups. The pre- and post-IPTW data are shown in Fig. S2. We found that the presence of elevated IgG (either IgGe or IgGf) had no impact on either the risk of increasing liver stiffness during follow-up (OR 1.38, 95% CI 0.77–2.49, p = 0.275) or the risk of developing cirrhosis (HR 2.74, 95% CI 0.62–12.06, p = 0.181). Kaplan–Meier curves after IPTW application are shown in Fig. S3.

Discussion

The present study demonstrated that in real-world clinical practice, isolated IgG elevation in patients with persistently normal transaminase levels does not negatively impact the course of AIH. Only LSM at the time of normalization of transaminase levels was significantly associated with the development of cirrhosis during follow-up.

CBR, defined as the normalization of transaminases and IgG levels, has been recommended as the primary treatment goal for AIH, as it is considered the best surrogate for the absence of histological activity. However, it is not uncommon to find patients with persistently elevated or fluctuating IgG

Table 3. Univariate and multivariate Cox regression analyses of cirrhosis development.

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Female sex	0.76 (0.25–2.30)	0.634		
Age	1.10 (1.05–1.14)	**<0.001**	1.01 (0.94–1.08)	0.690
Albumin at baseline	0.20 (0.08–0.47)	**<0.001**	0.33 (0.08–1.47)	0.147
Platelets at baseline	0.99 (0.99–0.99)	**0.001**	0.99 (0.99–1.00)	0.577
INR at baseline	2.56 (0.75–8.76)	0.135		
IgG at diagnosis	1.00 (1.00–1.01)	**0.001**	0.99 (0.99–1.01)	0.719
AST >20 IU/L at transaminase normalization	4.53 (0.60–34.05)	0.142		
ALT >20 IU/L at transaminase normalization	0.44 (0.18–1.13)	0.089		
Transaminase normalization at 6 months	0.24 (0.07–0.84)	**0.025**	0.33 (0.05–2.03)	0.232
IgG at transaminase normalization	1.00 (0.99–1.00)	0.086		
IgG categories (elevated/flares *vs.* normal)	2.26 (0.92–5.58)	0.078	1.49 (0.26–8.40)	0.679
Liver stiffness at transaminase normalization	1.30 (1.18–1.42)	**<0.001**	1.43 (1.06–1.94)	**0.019**
Other AI disease	1.06 (0.37–2.98)	0.910		
Baseline metabolic syndrome	0.95 (0.31–2.86)	0.926		

Only patients without cirrhosis at baseline were included in the analysis. The variable “IgG categories” was included in the multivariate model because of its relevance to the present study. Univariate and multivariate analyses were performed using the Cox proportional hazards regression. Values in bold denote statistical significance: defined as p <0.05.
AI, autoimmune; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; IgG, immunoglobulin G; INR, international normalized ratio.

levels during the course of the disease despite having normal transaminase levels. In fact, in our cohort, IgG levels did not normalize during follow-up in nearly one-third of the patients. This could lead to the unnecessary intensification of immunosuppression, resulting in an increased risk of adverse events. Previous studies have suggested that in patients with normal transaminase levels, with and without cirrhosis, normalization of IgG levels did not significantly increase the probability of being in histological remission.[7,20]

Interestingly, patients with IgGf presented higher baseline IgG levels, as well as a significantly higher prevalence of autoantibody positivity, compared with the other groups. However, histological activity did not significantly differ between patients with IgGf or IgGn during follow-up (data not shown). Furthermore, no differences were observed between the groups concerning the presentation of AIH, presence of cirrhosis at diagnosis, or prevalence of other autoimmune comorbidities, indicating that these factors did not account for the elevated levels of IgG. Although IgG levels were not associated with an increased risk of disease progression, higher levels at diagnosis were associated with a higher probability of maintaining elevated IgG or presenting IgG flares during follow-up. These results confirmed those of a previous publication showing that IgG levels at the time of AIH diagnosis did not negatively affect the course of the disease in terms of fibrosis progression.[21]

The primary objective of our work was not solely to characterize this patient population but to ascertain whether patients with IgGe or IgGf during follow-up present a worse prognosis. To this end, we focused our analysis on a robust endpoint, such as the development of cirrhosis, and a pertinent surrogate marker commonly used in clinical practice, LSM. Considering the recommendation to avoid elastography within the initial 6 months after starting immunosuppressive therapy,[22] the first liver stiffness value we deemed for analysis was the one recorded during the first year after the normalization of transaminase levels. Although patients with IgGe presented with significantly higher LSM values at transaminase normalization, these differences disappeared during the follow-up. In contrast to what has been published,[23] in which a sub-cohort of 13 patients with normal transaminase and IgG levels exhibited a 1.6% annual increase in liver stiffness, our cohort displayed stable or even decreasing LSM during follow-up. More importantly, these results remained unchanged when IPTW analysis was used to balance the potential confounding characteristics of patients with normal or elevated IgG levels.

In addition to LSM stability, we observed that only 24 patients developed *de novo* cirrhosis during follow-up and more than half had persistently normal IgG levels. In fact, only LSM after transaminase level normalization was independently associated with an increased risk of cirrhosis during follow-up. This interesting result confirms our previous observation,[24] indicating the important prognostic role of LSM in AIH, as has been previously described in other autoimmune and cholestatic liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis.[25] It is important to acknowledge that the assessment of any association with cirrhosis development may be influenced by the limited occurrence of events during the follow-up period. Nevertheless, this consideration also applies to the consistency observed in our findings with previous publications showing the crucial role of liver stiffness in predicting cirrhosis development in AIH.[22,24] Moreover, the scarcity of events in a cohort comprising nearly 500 patients monitored for over 6 years substantiates our hypothesis regarding the minimal impact of IgG during follow-up in patients with persistently normal transaminase levels.

As elevated IgG during follow-up was not associated with worse outcomes, one might argue whether elevated IgG reflects histological activity in patients with AIH. Although the lack of liver biopsies during follow-up in the current study made it impossible to completely rule out this association, other studies have shown a weak correlation between IgG levels and disease activity in the setting of normal IgG values at diagnosis.[21] Therefore, alternative explanations for elevated IgG levels should be considered, including the possibility of genetic variants that could affect IgG levels, the presence of comorbidities associated with high IgG levels,[21,23] or a potential sign of hepatic immune regulation mediated by B cells.[26] Furthermore, biochemical response, defined as transaminase normalization and resolution (or improvement) of hepatic necroinflammatory activity, may not parallel immunological remission. In this context, elevated IgG levels could potentially indicate the persistence of immune cell dysregulation despite effective treatment of AIH.

Our study is not free of limitations. (1) It was a retrospective study and lacked follow-up liver biopsies to confirm the absence of histological activity or the development of cirrhosis. However, we aimed to minimize this limitation by including multiple centers with expertise in the management of patients with AIH and with the use of strict criteria for including patients in the study. (2) We did not know the baseline normal IgG levels (before AIH diagnosis) for each patient, which makes it impossible to exclude the possibility of IgG elevation (despite being within the normal range) in some patients. (3) Because of unclear recommendations on how to monitor disease progression in AIH, LSM was not consistently performed at the same time points in all the patients, and the clinical evidence of disease progression could have potentially biased the decision to perform this test. (4) In the present study, we included patients who did not exhibit any elevation of transaminase levels during follow-up, with analytical monitoring conducted every 3–6 months in most centers, as shown in Table S1. As in real-world clinical practice, it is not possible to rule out an elevation in transaminases or a variation in IgG levels between monitoring intervals, as these data are unavailable. (5) Lastly, the number of negative hepatic events was very low, making it difficult to analyze the potential role of IgG elevation in the risk of decompensation or the need for liver transplantation. However, this low event rate reflects the expertise of the centers in managing patients with AIH.

In conclusion, this study showed that complete IgG normalization in patients with persistently normal transaminases did not significantly impact disease progression in AIH, highlighting the need to validate these results and potentially revise the definition of CBR.

Affiliations

[1]Gastroenterology and Hepatology Department, Clinical and Translational Research in Digestive Diseases Group, Valdecilla Research Institute (IDIVAL), Marqués de Valdecilla University Hospital, Santander, Spain; [2]Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]European Reference Network on Hepatological Diseases (ERN RARE-LIVER); [4]Digestive Diseases Department, Hospital Universitario Central de Asturias, Oviedo, Spain; [5]Liver Unit, Digestive Diseases Department, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain; [6]Digestive Diseases Department, Hospital del Mar-Parc de Salut Mar, Barcelona, Spain; [7]Digestive Diseases Department, Hospital Universitario de Burgos, Burgos, Spain; [8]Digestive Diseases Department, Hospital Universitari Mutua de Terrassa, Terrassa, Spain; [9]Digestive Diseases Department, Hospital Universitario Ramón y Cajal, CIBERehd, IRYCIS, Madrid, Spain; [10]Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology, Hannover Medical School, Hannover, Germany; [11]Liver Unit, Hospital Clínic Barcelona, Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Universitat de Barcelona, Centro de investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [12]Digestive Diseases Department, Hospital Universitario de Canarias, La Laguna, Spain; [13]Digestive Diseases Department, Hospital General Universitari de Valencia, Valencia, Spain; [14]Department of Hepatology, Complexo Hospitalario Universitario de Pontevedra, Instituto de Investigación Sanitaria Galicia Sur (IISGS) Pontevedra, Spain; [15]Digestive Diseases Department, Complejo Asistencial Universitario de Salamanca, Laboratorio de Hepatología Experimental y Vectorización de Fármacos (HEVEPHARM), CIBERehd, IBSAL, Salamanca, Spain; [16]Digestive Diseases Department, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain; [17]Department of Hepatology and Liver Transplantation, Hospital Universitario Reina Sofía, IMIBIC, CIBERehd, Córdoba, Spain; [18]Liver Unit, Digestive Diseases Department, Hospital Universitari Doctor Josep Trueta, IDIBGI (Institut d'Investigació Biomèdica de Girona), CIBEREHD, Girona, Spain; [19]Digestive Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [20]Liver Unit, Internal Medicine Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Centro de investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [21]Martin Zeitz Center for Rare Diseases, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Abbreviations

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; CBR, complete biochemical response; HR, hazard ratio; IgG, immunoglobulin G; IgGe, persistently elevated IgG; IgGf, IgG flares; IgGn, persistently normal IgG; INR, international normalized ratio; IPTW, inverse probability treatment weighting; LSM, liver stiffness measurement; OR, odds ratio; PS, propensity score; SLA, soluble liver antigen.

Financial support

MCL received support from the Instituto de Salud Carlos III (ISCIII) through the project 'PI21/00800' co-funded by the European Union and 'Beca de Intensificación para Investigadores' by the Spanish Association of the Study of the Liver (AEEH). IO was funded by Contractes Clínic de Recerca 'Emili Letang—Josep Font' 2022, granted by the Hospital Clínic Barcelona. BE was supported by the PRACTIS—Clinician Scientist program of Hannover Medical School, funded by the German Research Foundation (DFG, ME 3696/3). ADG received support from the Instituto de Investigación Valdecilla through the project 'NVAL 21-10'.

Conflicts of interest

The authors declare that they have no conflicts of interest related to this study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, visualization, writing—original draft**:** ADG, MCL.

Resources, visualization, and writing—review and editing: all authors.

Data availability

Data are available upon reasonable request to the corresponding authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101562.

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Keywords: Autoimmune hepatitis; Complete biochemical response; Immunoglobulin G.
Received 29 January 2025; received in revised form 7 August 2025; accepted 13 August 2025; Available online 29 August 2025