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ORIGINAL ARTICLE

Unmet needs in autoimmune hepatitis: Results of the prospective multicentre European Reference Network Registry (R-LIVER)

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Abstract

Background and Aims: The European Reference Network on Hepatological Diseases (ERN RARE-LIVER) launched the prospective, multicentre, quality-controlled R-LIVER registry on rare liver diseases. The aim of this study was to assess the presentation and outcome of autoimmune hepatitis (AIH) after 1 year of treatment.

Methods: Data were prospectively collected at the time of diagnosis and after 6 and 12 months follow-up. Complete biochemical response (CBR) was defined as

Abbreviations: 6-MP, 6-mercaptopurin; AC-AIH, acute-on-chronic AIH; AIH, autoimmune hepatitis; ALT, alanine-aminotransferase; ANA, antinuclear antibodies; anti-LKM-1 or -3, liver-kidney microsomal antibodies-type 1 or -type 3; Anti-SLA/LP, antibodies against soluble liver antigen/liver pancreas; AS-AIH, acute-severe AIH; AST, aspartate-aminotransferase; AUC, area under the curve; BMI, body mass index; CBR, complete biochemical response; CI, confidence interval; ERN RARE-LIVER, European Reference Network on Hepatological Diseases; FU, follow-up; IBD, inflammatory bowel disease; IgG, immunoglobulin G; INR, international normalized ratio; IQR, interquartile range; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; mHAI, modified Hepatitis Activity Index; MMF, mycophenolate mofetil; MTX, methotrexate; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; ROC, receiver operation characteristic; SMA, smooth muscle antibodies; ULN, upper limit of normal.

normalization of alanine aminotransferase (ALT) and immunoglobulin G (IgG) serum levels.

Results: A total of 231 patients from six European centres were included in the analysis. After 6 months of treatment 50% (106/212), and after 12 months 63% (131/210) of patients reached CBR with only 27% (56/211) achieving a steroid-free CBR within the first year.

Overall, 16 different treatment regimens were administered. Change of treatment, mostly due to intolerance, occurred in 30.4% within the first 6 months. In multivariate analysis, younger age at diagnosis (odds ratio [OR] = 1.03 [95% confidence interval (CI) 1.01–1.05]; $p = .007$), severe fibrosis (OR .38 [95% .16–.89], $p = .026$) and change of treatment within the first 6 months (OR .40 [95% CI .2–.86]; $p = .018$) were associated with a lesser chance of ALT normalization at 12 months follow-up.

Conclusion: The landscape of AIH treatment in Europe is highly heterogeneous, even between expert centres. The results from this first European multicentre prospective registry reveal several unmet needs, highlighted by the overall low rates of CBR and the frequent failure to withdraw corticosteroids.

KEYWORDS
autoimmune hepatitis, complete biochemical response, immunosuppression, remission, treatment regime

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory liver disease with variable clinical presentation, ranging from acute severe hepatitis with occasional liver failure to insidious onset chronic liver disease that may lead to fibrosis and development of cirrhosis. Referring to retrospective population-based studies, the incidence of AIH in European countries was estimated to be 1.1–2.2 per 100000 inhabitants per year.[1,2]

The introduction of corticosteroid treatment for remission induction and azathioprine as a first-line steroid-sparing agent for remission maintenance significantly reduced liver-related mortality and morbidity.[3] Serum biomarkers are widely used as surrogate markers of disease activity. The importance of serum immunoglobulin G (IgG) for the diagnosis of AIH is widely acknowledged, however, its value as a surrogate marker for histological activity and disease outcome remains controversial.[3,4] In the last consensus statement by the International AIH Group, the term complete biochemical response (CBR) was defined by the normalization of transaminases, together with the normalization of serum IgG.[4] It should be kept in mind that even though Gerussi et al. demonstrated that normalization of IgG was associated with improved transplant-free survival, no effect of persistent or intermittent IgG elevation on outcome was observed in a more recent study by Díaz-González et al. and no association of IgG elevation during the first year with long-term outcome was shown by Biewenga et al.[5–7]

Drug intolerance, which occurs at approximately 14%–28% for azathioprine in retrospective studies, or an insufficient response to first-line therapy (varying between 2.2% and 25%) necessitates initiation of second- or third-line therapy in AIH.[8–10] In a recent retrospective study, 11.9% of patients switched therapy from first- to second-line within the first year of treatment.[8] Options for second-line treatment include, but are not limited to, 6-mercaptopurine (6-MP) and mycophenolate mofetil (MMF).[11] Prospective and multicentre data on changes in treatment regimens within the first year are largely lacking.[12]

Key points

- After 1 year, 62% of people with autoimmune hepatitis sufficiently respond to treatment but only 27% without the use of steroids.
- We observed a high rate of intolerance to standard treatment within the first 6 months.
- Change of treatment regime was associated with a poorer response to treatment.

Overall, CBR to first-line treatment has been reported to be approximately 60%–80% within the first year in retrospective studies.[3,13] The presence of cirrhosis has been reported as an independent risk factor to predict insufficient response to standard therapy.[14] Whether a younger age at diagnosis is associated with a worse outcome is controversial.[14–17]

Prospective data on adult patients with AIH are scarce and restricted to small-scale single-centre studies, with one exception, namely the Japanese multicentre NHO-AIH study.[18,19] A comparable

correlate in the Caucasian population had not been established until the R-LIVER registry was launched by the European Reference Network on Hepatological Diseases (ERN RARE-LIVER) in 2017. The R-LIVER registry is an ongoing, prospective, quality-controlled and multicentre database on rare liver diseases, that includes patients with newly diagnosed AIH.

The aim of this study was to investigate the clinical presentation, heterogeneity and outcome of therapy for adult AIH patients after 1 year of follow-up across different European expert centres, thus delineating the unmet clinical needs to be addressed in future studies.

2 | METHODS

2.1 | Patient recruitment within the R-LIVER registry

Patients who were referred to a centre participating in the R-LIVER registry with a new diagnosis of AIH within the last 12 months, or who were first diagnosed at the centre, were included in the registry. Written informed patient consent was mandatory for inclusion.

AIH patients enrolled in the R-LIVER registry represented 81.7% of patients with AIH seen at the participating centres (data only available for 5/6 centres, centre with no data available were excluded in this calculation).

Prospective data collection and pseudonymized data entry were conducted at the local sites via Castor Electronic Data Capture. Data management was performed on a superordinate level via the R-LIVER administration located at the University Medical Centre Hamburg-Eppendorf. Approval was obtained from the Ethics Committee of the Hamburg Medical Association (PV5548). Contribution of data to the registry was approved by the respective institutional review boards according to local regulations.

2.2 | Data collection and extraction

Clinical, laboratory and histological observational data were collected at the time of initial diagnosis, and thereafter during the follow-up (FU) visits at the time point of 6 months ± 6 weeks and 12 months ± 12 weeks. Retrospective data from the time of diagnosis was accepted reaching back up to 12 months.

At the time of this analysis, additional annual follow-up continues to be recorded every 12 months ± 12 weeks within the R-LIVER registry. The presence of metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH) and clinical complications were captured according to international definitions at the time of registry design.[20,21] The detailed data collection protocol is displayed in Table S1.

Records of patients were extracted from the R-LIVER registry if they met the following inclusion criteria: (a) verified diagnosis of AIH according to international guidelines[3,22,23]; (b) successful exclusion of concomitant hepatitis B and C viral infection and the absence of concomitant autoimmune liver disease (primary biliary cholangitis [PBC] or primary sclerosing cholangitis [PSC]) and (c) completed 1-year follow-up. Missing values were not imputed.

2.3 | Statistical analysis

Laboratory values were corrected for centre-specific reference values (laboratory value/upper limit of norm [ULN]). For forms of severe presentation, acute-severe AIH (AS-AIH) was defined by elevated serum bilirubin levels above ULN and International Normalized Ratio (INR) ≥1.5 in the absence of, and acute-on-chronic AIH (AC-AIH) in the presence of severe fibrosis (either by imaging or by histology). Fulminant AIH was defined as AS-AIH with hepatic encephalopathy. According to the criteria of the International AIH Group,[4] CBR was defined as the normalization of ALT and IgG below ULN. An insufficient response was defined as failure to achieve CBR whilst a flare was defined as an elevation of ALT and IgG above ULN after initial normalization. For assessing histological disease activity, a modified Hepatitis Activity Index (mHAI) ≥6/18 was regarded as moderate to severe activity, whilst an mHAI <4/18 was seen as equivalent to histological remission. For the assessment of association with CBR, candidate variables were explored via univariate analysis and included in the multivariate regression analysis if the p-value was ≤.1. To correct for centre bias, centre affiliation was included in the multivariate model. To estimate the association between predictors and the dependent variable binary logistic or metric regression analysis was performed. For both individual variables and group differences a two-tailed p-value of ≤.05 was considered significant. If no significant group difference was demonstrated, consideration of pairwise comparisons was omitted.

To explore the predictive value of variables, a receiver operation characteristic (ROC) curve with the associated area under the curve (AUC) was calculated. For combined markers, a predicted probability was derived by binary logistic regression analysis. The difference between AUCs was calculated using DeLonge's test.[24]

Differences between the two groups were compared either via Mann–Whitey U or via Pearson's-Chi-Quadrat test. If the sample size was $n \leq 20$ or the expected cell frequencies were ≤5, Fisher's exact test was used instead of Pearson's-Chi-Quadrat. Wilcoxon test was used for connected samples.

IBM SPSS Statistics 27, R-Studio 2022.12.0 + 353 and GraphPad 10 were used for calculation and visualization. Sankey diagrams were created with SankeyMATIC.

3 | RESULTS

3.1 | Study population

Data were collected prospectively from the launch of the R-LIVER registry in 2017 until 10/2022 from 264 adult patients who either had a complete 1-year follow-up or died within the first year. Of

the 264 patients, 33 patients were excluded for the following reasons: Firstly, 14 patients from centres who overall provided less than five patients due to non-representative recruitment, secondly, 15 patients with incomplete data regarding ALT and thirdly, four patients with first-line treatment as part of a trial (Figure 1). Overall, 231 (81% [187/231] female) patients were included in the analysis with a median age at diagnosis of 55 (IQR 25) years (Table 1). In 88% the simplified AIH Score was reported with 72% having a score of 6 or higher. 11.8% (26/221) of patients presented severely, either with AS-AIH, AC-AIH or fulminant AIH, including four patients who got liver transplanted within the first 8 weeks of whom one died. Patients who either got transplanted or died were considered separately regarding clinical findings, CBR and treatment regimen (see Section 3.7). Liver biopsy at diagnosis was performed in 95.2% (220/231) of patients (Table 1). A 25.1% of biopsies showed histopathological signs of severe fibrosis (defined by fibrosis stage 3 or 4 according to Desmet and Scheuer[25]). In 89.1% (196/220) of liver biopsies, hepatitis activity was assessed using the mHAI. Of those, 81.2% (159/196) presented with moderate to severe activity (mHAI ≥6/18). To compare the value of IgG × ULN, ALT × ULN at baseline and the combination of both for the prediction of moderate to severe mHAI, the AUC-ROC area under the receiver operating characteristic curve (AUC) was calculated. Here, a very good performance could be demonstrated for ALT × ULN (AUC .834, 95% confidence interval [CI] .765–.902), but only a moderate performance for IgG × ULN (AUC .624, 95% CI .513–.735, Figure 2). Of note, as assessed by DeLong's test ($Z = -1.01$; 95% CI −.032 to .010; $p = .310$), there was no significant difference between ALT × ULN and the combination of ALT × ULN and IgG × ULN (AUC .845, 95% CI .775–.915) for the prediction of histological disease activity.

3.2 | Rate of CBR under treatment

After 6 months of treatment, 50% (106/212) of patients reached CBR with 45% (89/199 patients with ALT and IgG available at months 6 and 12) of patients remaining in remission and 6% (11/199) flaring during the following 6 months. 17% (34/199) of patients reached CBR only after 12 months, overall resulting in 62% (131/210) of patients with a CBR at 12 months follow-up. Of note, 33% (65/199) never reached CBR during 12 months of treatment. (Figure 3A, for a comparison of subgroups see Figure S1). Considering only ALT levels, 58% (130/224) of patients responded to treatment with ALT normalization at 6 months, and 69% (155/224) at 12 months.

3.3 | Therapeutic regimens: Choice of corticosteroids

For the induction of remission, most patients (85% [191/224]) received prednisolone with a median dose of 50 mg (IQR 40–60 mg), corresponding to .67 mg/kg bodyweight (IQR .46–.91) per day and 9% (19/224) received budesonide with a median dose of 9 mg (IQR 6–9 mg) per day. 6% (14/224) received no steroids as initial therapy (see Figure 4 for the flow between treatment regimens). After 6 months, 23% (52/224), and after 12 months, 37% (82/224) received a steroid-free treatment. Overall 14% (30/212) were at 6 and 27% respectively at 12-months follow-up (56/211), respectively, being in steroid-free CBR (Figure 3D). Patients treated with azathioprine at 12 months who received no steroids had a median azathioprine dose of 1 mg/kg BW (.8–1.2), and those treated with prednisolone 1.1 mg/kg BW (.8–1.4).

Amongst the patients who did not receive steroids for the induction of remission, 3/14 patients needed treatment with steroids within the first year (Table S2 for details). After 12 months, 8/14 patients achieved CBR (Figure 3E). Of those 14 patients, all patients with ALT values <3 × ULN ($n = 9$) successfully normalized ALT without additional use of steroids.

We next compared the rate of CBR according to the type of steroids used. An equal rate of patients achieved CBR with prednisolone (at 6 months: 50% [89/180]; at 12 months: 62% [111/179]) or budesonide (at 6 months 58% [11/19]; $p = .484$; at 12 months: 66% [12/18]; $p = .697$), respectively, as initial treatment. ALT ($p = .005$) but not IgG ($p = .083$) values significantly differed at baseline between

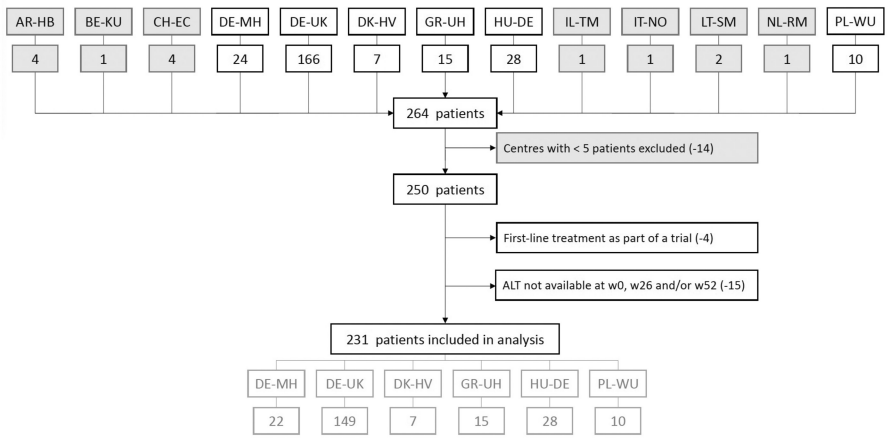

FIGURE 1 Flow chart of patient inclusion. Data on 264 patients were provided by 13 ERN RARE-LIVER centres. Centres with less than 5 patients (light grey) were excluded. Patients were excluded if ALT was missing, or first-line treatment was given as part of a trial. Overall, 231 patients were included in the analysis. DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; PL, Poland.

TABLE 1 Baseline characteristics.

Age at diagnosis, median (IQR)	55 (25) years
Male, *n* (%)	44/231 (19)
Ethnicity Caucasian, *n* (%)	224/229 (97.8)
Pregnancy between baseline and 12 months follow-up, *n* (%)	7/164 (4.3)
BMI at diagnosis in kg/qm, median (IQR), *n* = 214	25.6 (7.6)
BMI at diagnosis >30 kg/qm, *n* (%)	55/214 (25.7)
First-degree relative with autoimmune liver disease, *n* (%)	3/188 (1.6)
AIH type	
Type 1 (ANA ± SMA [F-Actin] positive), *n* (%)	190/225 (84.4)
Type 2 (Anti-LKM-1 ± -3 ± Anti-LC1 positive), *n* (%)	5/225 (2.2)
Type 3 (Anti-SLA/LP positive), *n* (%)	21/225 (9.3)
Seronegative	9/225 (4)
Severe presentation	26/221 (11.8)
AS-AIH, *n* (%)	15/26 (57.7)
AC-AIH, *n* (%)	8/26 (30.8)
Fulminant AIH, *n* (%)	3/26 (11.5)
Liver stiffness at baseline, median (IQR), *n* = 144	11.1 (12.9)
Additional signs of MASLD, *n* (%)	24/217 (11.1)
Additional signs of MASH, *n* (%)	11/217 (5.1)
Alcohol	
None, *n* (%)	107/180 (59.4)
<10 g (women) or 20 g (men) per day, *n* (%)	70/180 (38.9)
>10 g (women) or 20 g (men) per day, *n* (%)	3/180 (1.7)
Smoking	
Current, *n* (%)	39/179 (21.8)
Former, *n* (%)	28/179 (15.6)
Never, *n* (%)	112/179 (62.6)
Concurrent IBD, *n* (%)	6/223 (2.7)
Ulcerative colitis, *n* (%)	3/6 (50)
Crohn's disease, *n* (%)	3/6 (50)
Liver biopsy performed, *n* (%)	220/ 231 (95.2)
Fibrose stage 3-4/4 (Desmet and Scheuer[a]), *n* (%)	49/195 (25.1)
mHAI 0–3, *n* (%)	10/196 (5.1)
mHAI 4–5, *n* (%)	27/196 (13.8)
mHAI 6–18, *n* (%)	159/196 (81.2)
Simplified AIH Score	
≤5 points (possible AIH), *n* (%)	56/203 (27.6)
=6 points (probable AIH), *n* (%)	34/203 (16.7)
≥7 points (definite AIH), *n* (%)	113/203 (55.7)

Note: Baseline characteristics and histological features at diagnosis of AIH patients, including patients receiving liver transplantation.

Abbreviations: AIH, autoimmune hepatitis; ANA, antinuclear antibodies; Anti-LKM-1 or -3, liver-kidney microsomal antibodies-type 1 or -type 3; Anti-SLA/LP, antibodies against soluble liver antigen/liver pancreas; AS-AIH, acute-severe AIH; AC-AIH, acute-on-chronic AIH; BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; SMA, smooth muscle antibodies.

[a]Fibrosis stages by Ishak were converted to a 4-scale as follows: 0 = 0, 1–2 = 1, 3–4 = 2, 5 = 3, 6 = 4.

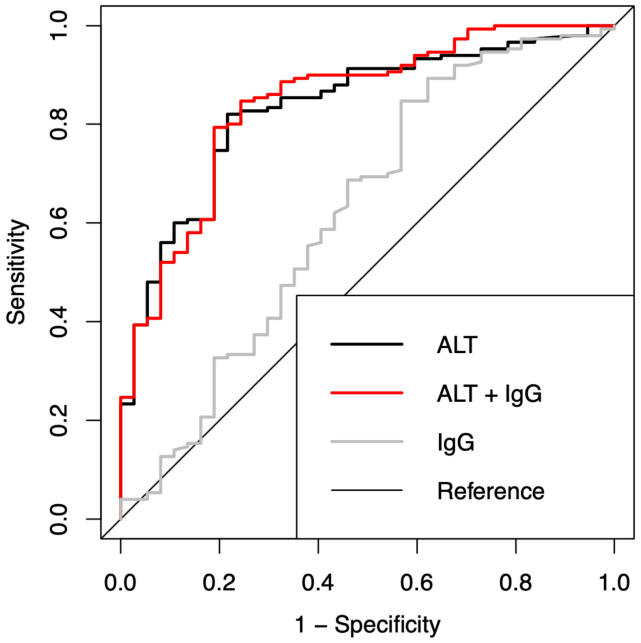

FIGURE 2 Receiver operation characteristic (ROC)-curve for prediction of moderate to high mHAI (6-18/18). Predictive value of ALT × ULN (AUC .834, 95% CI .765–.902) and IgG × ULN (AUC .624, 95% CI .513–.735) at baseline as well as a combination thereof derived by binary logistic regression of both values (AUC .845, 95% CI .775–.915) for prediction of moderate to high mHAI. DeLong's test showed no significant difference comparing the AUC of ALT × IgG and ALT × ULN + IgG × ULN with each other (Z = −1.01; 95% CI −.032 to .010; $p = .310$).

the two groups (Figure S1D). None of the patients initially treated with budesonide had histopathological signs of severe fibrosis at baseline, an equal rate of patients had a mHAI ≥6/18 (budesonide 74% vs. prednisolone 71%). On descriptive analysis, the median (IQR) budesonide dose tended to be higher in those not achieving CBR (6 [6] vs. 6 [3] mg/d at 6 months, 6 [4.5] vs. 3 [.8] mg/day at 12 months). Prednisolone dosing above ($n = 128/180$) or below ($n = 52/180$) .5 mg/kg bodyweight per day was not associated with differences in CBR in univariate analysis (Tables 3 and 4).

3.4 | Comparison of MMF and azathioprine as first-line treatment of AIH

Sixty-nine% (156/224) of patients received azathioprine as an initial treatment with a median dosage of 1 (IQR .5) mg/kg bodyweight. In an exploratory approach and considering the small number of patients receiving MMF ($n = 12$, all with a dose of 2000 mg/day), we investigated the difference between MMF and azathioprine as first-line treatment. A 83% (10/12) of patients who received MMF and 69% (58/83) who received azathioprine at all time points were in CBR at 12 months follow-up ($p = .499$). Considering only the normalization of ALT, 83% (10/12) of patients on MMF responded to treatment and 78% (70/90) of patients to azathioprine (Figure 3B, $p = 1.000$). There was no difference between azathioprine and MMF

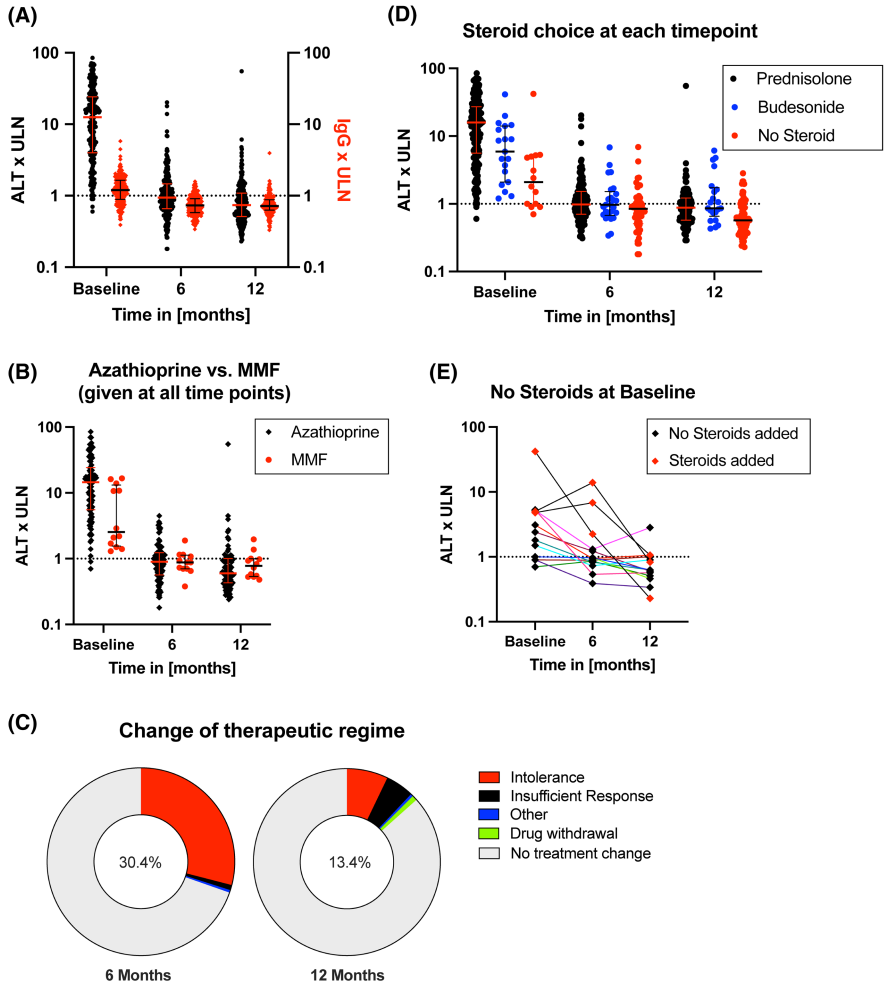

FIGURE 3 Treatment response. Median, IQR and individual IgG and ALT × ULN values at baseline, at 6 and 12 months follow-up (A) with 62.4% CBR at 12 months follow-up, (B) for patients receiving either azathioprine [$n = 90$] or MMF [$n = 12$] ± steroids at all time points with ALT ≤ ULN at 12 months: MMF 83%, azathioprine 77.8%, (D) in dependency of steroid choice at each follow-up. (C) Reason for change of therapeutic regimen shown at 6- ($n = 68/224$) and 12 months ($n = 30/224$) follow-up. (E) Individual ALT × ULN values for patients not initially receiving steroids.

regarding the frequency of additional steroid treatment (baseline 85/90 vs. 12/12 [$p = 1.000$], 6 months-FU 68/90 vs. 9/12 [$p = 1.000$], and 12 months-FU 53/90 vs. 9/12 [$p = .357$]). No intolerance was reported for MMF and none of the patients who were initially treated with MMF changed to another immunosuppressant within the first year of treatment. On the other hand, 37% (58/156) of patients who initially started on azathioprine changed their treatment within the first 6 months ($p = .009$ for comparison with MMF), which was due to intolerance in 98%.

3.5 | Predictors of CBR

Four subgroups were formed based on the CBR pattern to distinguish slow-responders from non-responders as well as sustained response from flare: (i) insufficient response, (ii) sustained CBR since 6 months-follow-up, (iii) CBR achieved only at 12 months-follow-up and (iv) flared at 12 months after CBR at 6 months. Histological signs of severe fibrosis ($p = .001$) and IgG × ULN at baseline displayed a significant group difference ($p = .005$). IgG tended to be higher in those not responding to treatment whilst histopathological signs of severe fibrosis tended to be lower in those reaching CBR within the first 6 months. Descriptive data in dependency of each subgroup are displayed in Table 2, pairwise comparison is shown in Tables S3 and S4.

Univariate and multivariate regression analysis was performed to further explore predictors to achieve CBR at 12 months follow-up (Table 3, for CBR at 6 months follow-up see Table S5): Multivariate analysis, corrected for centre site (overall $p = .864$), confirmed only a significant association for IgG × ULN at baseline (odds ratio [OR] .38 [95% CI .16–.93]; $p = .034$) with CBR. However, as different treatment regimens may have different effects on IgG production independent from disease activity, and since recent studies showed that elevation of IgG during the first year does not predict long-term transplant-free survival, a multivariate analysis corrected for centre site (overall $p = .201$) and considering ALT normalization alone (Table S6) was performed, showing CBR to be associated with treatment change (OR .37 [95% CI .17–.81]; $p = .012$), severe fibrosis (OR .25 [95% .16–.88], $p = .025$) and age at diagnosis (OR 1.03 [95% CI 1.01–1.05]; $p = .023$), but not with IgG × ULN (OR .61 [95% CI .14–2.67], $p = .516$) or IgG × ULN delta between baseline and 12 months follow-up (OR 1.94 [95% CI .23–4.66], $p = .959$). It hence revealed treatment change within the first 6 months as a potentially modifiable risk factor associated with lack of ALT normalization after 12 months of therapy.

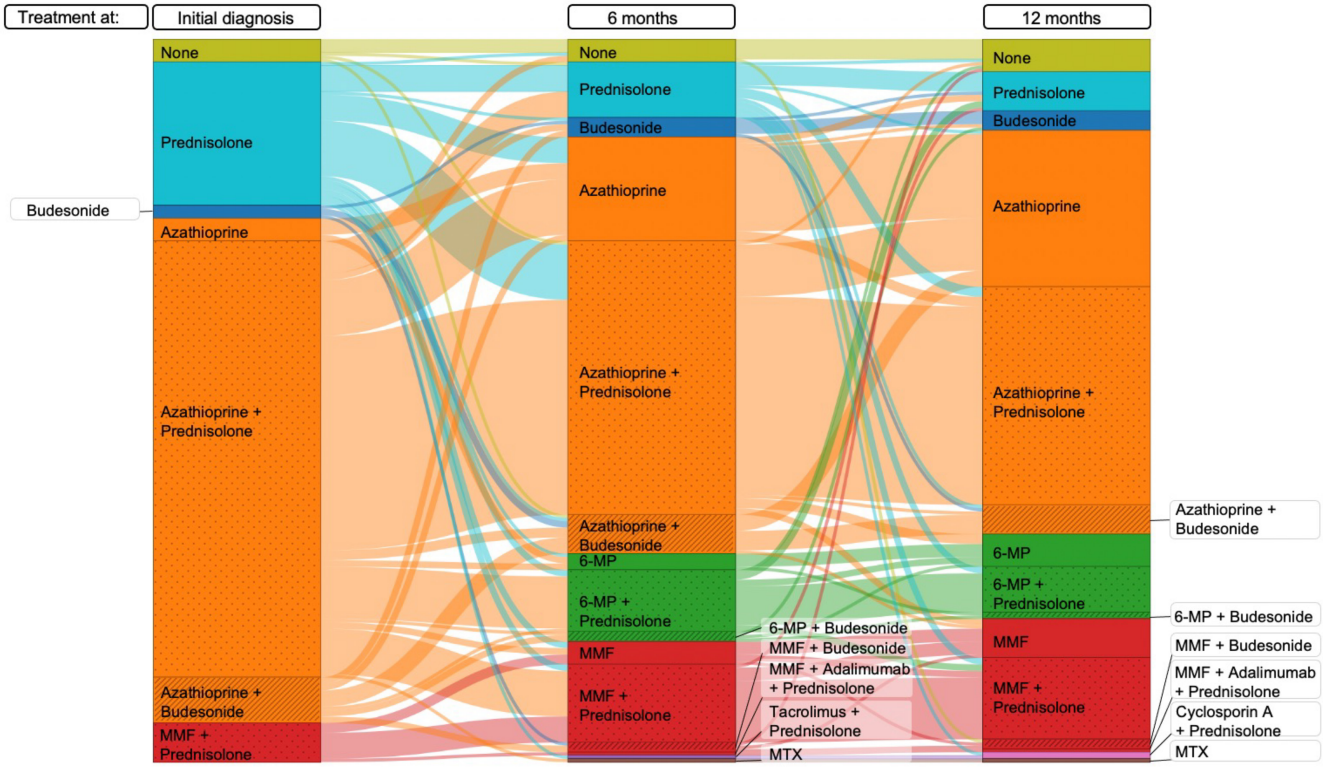

FIGURE 4 Sankey diagram for treatment regimens and flows. Treatment regimens at diagnosis, at 6 months and at 12 months ($n = 224$). Steroids: Prednisolone (dotted), budesonide (striped). Immunosuppressive Treatment: Azathioprine (orange), MMF (red), 6-MP (green), tacrolimus (purple), cyclosporine A (pink), MTX (brown).

In a subgroup analysis, IgG × ULN at baseline was associated with both CBR (OR .24 [95% CI .11–.57], $p = .001$) and ALT normalization (OR .38 [95% CI .17–.85], $p = .018$) in non-cirrhotic patients, which was not statistically significant in cirrhotic patients (CBR: OR .46 [95% CI .15–1.4], $p = .172$; ALT normalization: OR 1.19 [95% CI .60–2.33], $p = .619$), suggesting that unspecific elevation of IgG caused by cirrhosis might impair the value of IgG as a potential biomarker.

3.6 | Heterogeneity of treatment regimens across European centres

This prospective registry enables the analysis of treatment heterogeneity between centres and within patients over time. The most notable finding was that patients who did not change treatment within the first 6 months (regardless of whether they received MMF or azathioprine as first-line treatment) had higher rates of ALT normalization at month 12. After 6 months, 30% (68/224) and between 6 and 12 months 13% (30/224) had a change in therapeutic regimens (excluding dose change and addition of azathioprine or withdrawal of prednisolone according to first-line standard therapy). This was due to intolerance in 96% of cases at 6 months and in 53% at 12 months (Figure 3C). For the characterization of subgroups depending on the change of treatment see Table S7.

A total of 16 different therapeutic regimens were administered within 1 year after initial diagnosis (steroids, azathioprine, 6-MP, MMF, MTX, cyclosporine A, tacrolimus, adalimumab, as well as combinations of those therapies) with 153/224 (68.3%) patients receiving first-line (steroids and/or azathioprine) or no immunosuppressive treatment at 12 months follow-up. Of those, 46% (61/132) reached sustained CBR after 6 and another 20% (27/132) after 12 months (together 67%). Figure S2 shows treatment regimens and their association with CBR. A more detailed analysis comparing the efficacy of different treatment regimens was prohibited by the small number of patients in each group and the high heterogeneity within each treatment group regarding drug dosage.

3.7 | Clinical complications and outcome

Liver-related complications (Table 4 for a detailed listing) besides death or transplantation were reported in 21.9% (49/224) at baseline, of whom 45 (92%) patients had liver imaging consistent with cirrhosis. Seventeen patients had ascites at baseline, in 71% (12/17) ascites resolved within the first year of follow-up. However, three patients newly developed ascites, of whom none reached CBR at any time point. At 6 months follow-up four patients and between 6 and 12 months another four patients newly developed liver-related

TABLE 2 Findings dependent on treatment response status.

	Treatment response status after 12 months, $n=199$				
	Sustained CBR since 6 months, $n=89$ (45%)	CBR at 12 months, $n=34$ (17%)	Flare, $n=11$ (6%)	Insufficient response, $n=65$ (33%)	p-value
Male (%), $n=199$	18	23.5	18.2	18.5	.914
BMI, median (IQR), $n=183$	25.5 (23–29.4)	24.3 (22–28.8)	28.7 (21.2–30.8)	25.5 (22.1–30.9)	.605
Alcohol intake >10/20 g, (%), $n=153$	1.3	4.2	0	2.3	.806
Currently smoking, (%), $n=153$	18.7	26.1	40	22.2	.454
Age at diagnosis, median (IQR), $n=199$	56 (45–65.5)	54 (40–65.75)	51 (29–57)	55 (45.5–66)	.389
Fibrosis 3-4/4, (%) at diagnosis, $n=165$	10.4	35.7	25	42.9	.001 ***
mHAI 6-18, (%) at diagnosis, $n=166$	90.4	75.9	75	80.4	.222
MASLD, (%) at diagnosis, $n=188$	5.9	22.6	20	12.9	.093
MASH, (%) at diagnosis, $n=188$	1.2	12.9	10	6.5	.165
Liver stiffness in kPa at diagnosis, median (IQR), $n=126$	9.4 (6.1–16.3)	14.4 (7.6–22.1)	10.6 (7.6–13)	16.4 (10.2–24.9)	.149
AST × ULN at baseline, median (IQR), $n=193$	9.5 (3.6–25.4)	10.1 (2.9–18.1)	4.5 (2.5–35.1)	11.7 (3.2–24.9)	.579
ALT × ULN at baseline, median (IQR), $n=199$	12.7 (4.9–25.9)	12.3 (4.4–21.6)	6.4 (3.6–28.3)	14.4 (3.9–26.6)	.450
Total bilirubin × ULN at baseline, median (IQR), $n=198$	1.5 (.6–4.1)	1.2 (.7–3.8)	.8 (.5–2.4)	1.3 (.7–4.8)	.878
Severe presentation (%), $n=191$	9.2	15.2	0	9.8	.819
IgG × ULN at baseline, median (IQR), $n=189$	1.1 (.8–1.4)	1.1 (.9–1.7)	1 (.7–1.6)	1.6 (1.2–1.9)	.000***
Prednisolone dose in mg/day at baseline, median (IQR), $n=168$	50 (40–61.3)	50 (40–70)	50 (40–57.7)	50 (40–70)	.994
Budesonide dose in mg/day at baseline, median (IQR), $n=17$	9 (6–9)	6 (3-)		9 (6–9)	.269
Azathioprine dose in mg/day at baseline, median (IQR), $n=141$	75 (50–100)	75 (75–100)	100 (87.5–100)	75 (50–100)	.097

Note: Clinical, laboratory and histological findings (at baseline, unless otherwise specified) depending on response status after 12 months. p-Value for binary or metric logistic regression represents overall group difference. Excluding patients receiving liver transplantation.

Abbreviations: ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; BMI, body mass index; CBR, complete biochemical response; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; mHAI, modified Hepatitis Activity Index; ULN, upper limit of normal.

complications. Of those, 5/8 patients did not reach CBR within the first year, of whom all newly developed signs of cirrhosis.

In the overall cohort, liver stiffness significantly dropped from a median of 10.9 (IQR 12.1) kPa to 8 (IQR 6.3) kPa ($p=.000$). Patients who reached CBR within 6 months had a lower liver stiffness at baseline and at 12 months follow-up (9.4 [IQR 10.2] kPa to 6.3 [IQR 3.6] kPa, $p=.000$) than those responding either only at month 12 (14.4 [IQR 7.7] kPa to 9.7 [IQR 5.8] kPa, $p=.001$) or not reaching CBR at all (16.4 [IQR 14.7] kPa to 9.8 [IQR 11] kPa, $p=.000$). However, a significant overall group difference could not be demonstrated for liver stiffness at baseline ($p=.149$, Table 2) but only at 12 months follow-up ($p=.002$) with pairwise comparison showing a significant difference in liver stiffness between those with a sustained CBR since 6 months and those with no CBR ($p=.000$).

Within the first year, five patients were diagnosed with PBC- and two PSC-Overlap.

During the 1-year follow-up period, five patients died: two due to liver failure of whom one pancreatic carcinoma was suspected, one due to sepsis, one for an unknown reason and one due to post-liver transplant complications. Overall, four patients received liver transplantation after developing liver failure during the first 8 weeks after presentation; one presented with AS-AIH, two with fulminant AIH and one with AC-AIH. The 1-year liver-transplant-free survival of the entire cohort was 97%.

4 | DISCUSSION

We hereby present the results of the first prospective, quality-controlled, multicentre R-LIVER registry of incident AIH patients treated in European expert centres.

The R-LIVER registry is characterized by a high quality of data and reflects adherence to current guidelines in diagnosis and care: liver biopsy was performed in nearly all patients and the mHAI, as the currently recommended histopathological activity score[26] was reported in 89% (196/220) of patients. In 88%, the full simplified AIH score, which allows classification of the likelihood of the presence of AIH, was recorded. The patients recorded in this registry were

TABLE 3 Regression analysis for a complete biochemical response after 12 months.

	Univariate		Multivariate	
	p-Value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)
IgG × ULN at baseline	.000	.27 (.15–.51)	.034	.38 (.16–.93)
Fibrosis 3-4/4 (vs. 0-2/4)	.004	.37 (.19–.73)	.405	.64 (.23–1.83)
Treatment changed between baseline and 6 months FU	.013	.47 (.26–.85)	.370	.66 (.27–1.64)
Liver stiffness 12 months FU	.023	.95 (.91–.99)	.539	.98 (.92–1.05)
R-LIVER centre	.193	0 (0–0)	.864	
IgG × ULN delta (12 months-FU – baseline)	.103	1.5 (.92–2.43)		
AIH type	.166.	0 (0–0)		
Prednisolone dose ≥.5 mgkgBW (vs. <)	.169	.6 (.29–1.24)		
Liver stiffness at diagnosis	.214	.98 (.96–1.01)		
mHAI 6–18 versus <6	.252	1.57 (.73–3.39)		
Age at diagnosis	.326	1.01 (.99–1.03)		
Budesonide versus prednisolone for induction	.582	1.5 (.36–6.35)		
MASH	.602	.72 (.21–2.45)		
BMI	.612	.99 (.94–1.04)		
Severe presentation (vs. non-severe)	.632	1.28 (.47–3.53)		
AST × ULN at baseline	.657	1 (.98–1.01)		
MASLD	.693	.84 (.35–2)		
INR at baseline	.723	1.2 (.44–3.22)		
Male (vs. female)	.763	1.12 (.55–2.25)		
Bilirubin × ULN at baseline	.798	1.01 (.95–1.06)		
ALT × ULN at baseline	.961	1 (.99–1.02)		

Note: Univariate and multivariate analysis for ALT and IgG normalization after 12 months, excluding patients receiving liver transplantation.
Abbreviations: AIH, autoimmune hepatitis; AST, aspartate-aminotransferase; BMI, body mass index; FU, follow-up; IgG, immunoglobulin G; INR, international normalized ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; mHAI, modified Hepatitis Activity Index; ULN, upper limit of normal.

representative with more than 80% of patients newly presenting to centers included in the registry. These findings not only demonstrate a high adherence to guideline-based diagnosis and treatment[3,22] but also indicate that reliable conclusions on the treatment response and outcome of AIH can be derived from this registry.

Our aim was to describe both the presentation and outcome of consecutive and representative patients within the first year of diagnosis to delineate the unmet clinical needs in AIH care. A clear need for treatment optimization could be demonstrated due to the fact, that within the first year of treatment, CBR was only reached in 62% of patients and less than one-third of patients achieved a steroid-free CBR. Change of treatment within the first 6 months, mostly due to intolerance, was identified as a new and potentially modifiable risk factor associated with poor treatment response.

Most of the patients responding to treatment did so within the first 6 months (50%) but a considerable proportion (17.1%) had a slow response and reached CBR only between 6 and 12 months of therapy. Descriptive data suggested that patients with fatty liver disease and/or severe presentation may take longer to reach CBR, and future studies will demonstrate whether these slow responders show different outcomes long-term and might need changes in treatment regimens to improve outcomes early on.

Of note, first-line treatment with MMF showed good response rates, although reported only in a small number of patients. Contrary to the 37% of patients who initially started on azathioprine and changed their treatment within the first 6 months mainly because of intolerance, no intolerance to MMF was recorded in our cohort. MMF as an alternative to azathioprine has been reported as an effective first-line treatment of AIH[10,27] in alliance with the recommendations of the Hellenic Association for the Study of the Liver[28] and has recently been investigated in the CAMARO-Trial.[29] However, teratogenicity is a limiting factor, especially in women of childbearing age.[30]

Multivariate analysis of factors associated with CBR after 12 months confirmed IgG elevation at baseline as a significant risk factor.[31] However, whilst patients with lower IgG levels may present a subgroup with a higher probability of successfully maintaining CBR after drug withdrawal,[32] it has been shown that for the prediction of histological remission, inclusion of IgG only marginally enhanced the diagnostic accuracy, especially in patients with cirrhosis.[33,34] Our results confirm the difference in the predictive value of IgG depending

TABLE 4 Clinical and biochemical features.

	At baseline	At 6 months	At 12 months
Liver-related complications, *n* (%)	49/224 (21.9)	49/224 (21.9)	46/224 (20.5)
Liver imaging consistent with cirrhosis, *n* (%)	45/224 (20.1)	39/224 (17.4)	38/224 (17)
Ascites, *n* (%)	17/224 (7.6)	8/224 (3.6)	8/224 (3.6)
Oesophageal or gastric varices, *n* (%)	9/224 (4.0)	12/224 (5.4)	12/224 (5.4)
Variceal bleeding, *n* (%)	2/224 (.9)	1/224 (.4)	1/224 (.4)
Hepatic encephalopathy, *n* (%)	5/224 (2.2)	0/224 (0)	1/224 (.4)
Hepatorenal-syndrome, *n* (%)	2/224 (.9)	0/224 (0)	0/224 (0)
Spleen size (∅ in mm), median (IQR)	110 (105–124), *n* = 174		110 (100–126), *n* = 83
Concomitant autoimmune liver disease			
Additional diagnosis PBC, *n* (%)	0/224 (0)	4/223 (1.8)	5/221 (1.8)
Additional diagnosis PSC, *n* (%)	0/224 (0)	2/223 (.9)	2/220 (.9)
AST × ULN, median (IQR)	10.07 (3.08–22.14), *n* = 218	.83 (.59–1.24), *n* = 217	.75 (.54–1.03), *n* = 218
ALT × ULN, median (IQR, *n* = 224)	12.56 (3.98–24.21)	.94 (.66–1.46)	.74 (.51–1.08)
ALT ≤ ULN, *n* (%), *n* = 224	9/224 (4)	130/224 (58)	155/244 (69.2)
IgG × ULN, median (IQR)	1.2 (.89–1.65), *n* = 213	.73 (.58–.91), *n* = 212	.72 (.63–.88) *n* = 211
ALT and IgG ≤ ULN, *n* (%)	3/213 (1.4)	106/212 (50)	131/211 (62.1)
Total bilirubin × ULN, median (IQR)	1.32 (.66–4.1), *n* = 222	.58 (.42–.83), *n* = 214	.58 (.42–.82), *n* = 217
ALP × ULN, median (IQR)	1.3 (1.85–.88), *n* = 220	.66 (.52–.94), *n* = 218	.66 (.53–.86), *n* = 219
Albumin in g/L	36 (31.6–40.9), *n* = 200	40.4 (37.8–42.8), *n* = 193	41 (38.9–43.6) *n* = 200
INR, median (IQR)	1.1 (1–1.3), 1.2*n* = 207	1 (1–1.1), *n* = 185	1 (.98–1.016) *n* = 192

Note: Clinical and biochemical features at diagnosis, at 6 months and at 12 months follow-up, excluding patients receiving liver transplantation.
Abbreviations: ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; IgG, immunoglobulin G; IQR, interquartile range; PBC, primary biliary cholangitis; ULN, upper limit of normal.

on the presence of cirrhosis. Of note, in our cohort, serum IgG levels were not accurate predictors of histological disease activity at diagnosis.

The value of IgG as a surrogate marker predicting long-term survival is currently under discussion[7,32,34–36] and different drugs, such as glucocorticoids, may also reduce IgG levels independent of disease activity.[37] We therefore also investigated ALT normalization alone as a biomarker for treatment response. Here, the presence of cirrhosis and a younger age at diagnosis were validated to negatively impact treatment response.[38] In addition, change of treatment regimen was associated with a decreased likelihood of ALT normalization at 12 months follow-up, and continued treatment with first-line medication resulted in higher response rates (Figure 3B). Overall, almost one-third of patients changed therapy after 6 months, which exceeds the number reported in retrospective studies.[39] The most frequent reason for a change of treatment after 6 months was drug intolerance, underlining the need for effective drugs with less side effects and identifying drug intolerance as a modifiable risk factor. Between 6 and 12 months, only a minority of patients changed their treatment regimen; here, the proportion of those who changed due to an insufficient response increased to 36.7%, but intolerance still dominated as the main reason for a change (53.3%).

Even in expert centres in Europe the landscape of AIH therapy is highly heterogeneous, with 16 different treatment regimens administered. On the one hand, this illustrates the complexity of the disease and the local expertise associated with regard to specific immunosuppressive treatment regimens; on the other hand, it also highlights the need for standardized criteria for drug selection, switching and withdrawal and the unmet clinical need of first-line therapy with low rates of drug intolerance.[12,40–42] Here, the results of the CAMARO Trial comparing azathioprine and MMF were in favour of the latter concerning drug tolerance.[29]

The presented study has strengths and limitations. We present the first prospective and quality-controlled European registry of incident AIH, with high rates of data completeness and good representativeness. Limitations include, but are not limited to, the dependency on the accuracy of data entry into the registry, the lack of more frequent data points within the first year after diagnosis, decentral pathology reading and differences in the number of patients included per centre: Multivariate analysis showed no centre effect; however, the majority of patients was contributed by one single centre. Furthermore, inclusion in the registry is also limited by diagnostic challenges, as the diagnosis of AIH can be difficult, especially in differentiation from diagnoses such as drug-induced liver injury. More than a quarter of the patients presented with a

simplified AIH score of 5 or less, in which the diagnosis can only be ascertained over time in accordance. In particular, patients with a new relapse of AIH outside the period covered by the registry might not be recorded. As patients with a simplified AIH score of 5 or less presented with lower transaminases and IgG, had less fibrosis and after 12 months a higher response rate, those patients may present a subgroup with a more benign disease course requiring further research.

Finally, only expert centres contributed to data acquisition, thus limiting the conclusions that can be drawn with regard to overall AIH care in less specialized centres.

Overall, this first report of prospectively acquired data from people with incident AIH in Europe shows a heterogeneous therapeutic landscape within the first year and reveals some of the unmet clinical needs in AIH care such as high rates of treatment change due to intolerance within the first 6 months and low rates of steroid-free treatment response. Further research should address effective first-line therapies with less drug-related side effects, adjustment of steroid choice, dose and requirement to disease activity and the long-term outcome of slow responders, including the value of ALT normalization versus CBR. We are confident that the ongoing R-Liver registry on AIH will provide answers to some of these open questions in the future.

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CONFLICT OF INTEREST STATEMENT

CS: Consultant for Pliant, BiomX, Chemomab, Agomab, sponsored lectures for Falk Foundation, Grants from BiomX, Galapagos. IS: Sponsored lecture for Falk Foundation. BE: Grants from clinician scientist program (PRACTIS) from Hannover Medical School. RT: Consultant for MSD, AET Pharmaceuticals, sponsored lectures for Chiesi, Alexion, Orphalan, Abbvie, Falk Foundation, grants from Oncocyte, other COI patent anti-HIP1R autoantibodies for diagnosis of AIH. JR: Employee of Medical University of Warsaw, Poland. The remaining authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, CS. The data are not publicly available due to ethical restrictions.

ETHICAL APPROVAL STATEMENT

Approval was obtained from the Ethics Committee of the Hamburg Medical Association (PV5548). Contribution of data to the registry was approved by the respective institutional review boards according to local regulations.

PATIENT CONSENT STATEMENT

Written informed patient consent was mandatory for inclusion.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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