External validation of the IAIHG autoimmune hepatitis response criteria in a multicentric real-world cohort
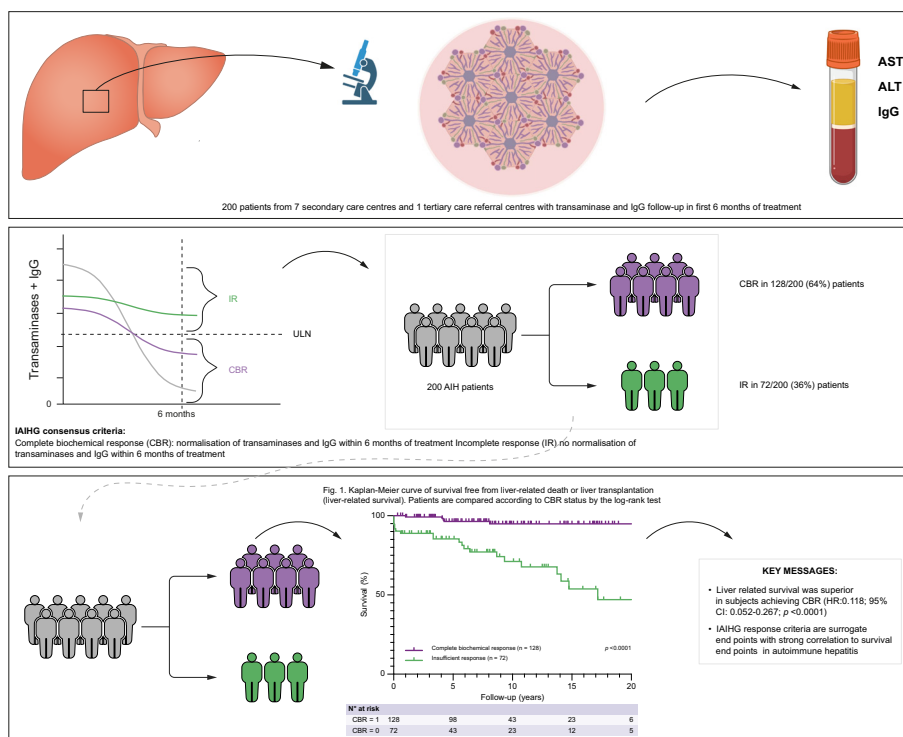
Authors

Lorenz Grossar, Sarah Raevens, Christophe Van Steenkiste, ..., Anja Geerts, Hans Van Vlierberghe, Xavier Verhelst

Correspondence

Lorenz.grossar@ugent.be (L. Grossar).

Graphical abstract

200 patients from 7 secondary care centres and 1 tertiary care referral centres with transaminase and IgG follow-up in first 6 months of treatment

CBR in 128/200 (64%) patients

IR in 72/200 (36%) patients

200 AIH patients

IAIHG consensus criteria:
Complete biochemical response (CBR): normalisation of transaminases and IgG within 6 months of treatment Incomplete response (IR):no normalisation of transaminases and IgG within 6 months of treatment

Fig. 1. Kaplan-Meier curve of survival free from liver-related death or liver transplantation (liver-related survival). Patients are compared according to CBR status by the log-rank test

KEY MESSAGES:
- Liver related survival was superior in subjects achieving CBR (HR:0.118; 95% CI: 0.052-0.267; p <0.0001)
- IAIHG response criteria are surrogate end points with strong correlation to survival end points in autoimmune hepatitis

Complete biochemical response (n = 128)
Insufficient response (n = 72)
p <0.0001

N° at risk					
CBR = 1	128	98	43	23	6
CBR = 0	72	43	23	12	5

Highlights

- Follow-up in autoimmune hepatitis treatment relies mainly on biochemical parameters.
- CBR is defined as normalisation of transaminases and IgG within 6 months.
- Achieving CBR is strongly associated with superior liver-related survival.
- Further validation of IAIHG response criteria will enable comparisons in future studies.

Impacts and Implications

Corticosteroids remain the cornerstone of treatment to induce remission of disease activity in autoimmune hepatitis (AIH), and the majority of patients require long-term corticosteroid treatment to achieve sustained remission. Definitions of response to treatment have varied over the years, and consistently used intermediate endpoints are needed to facilitate advancements in non-corticosteroid treatment for autoimmune hepatitis. The International Autoimmune Hepatitis Group (IAIHG) defined consensus criteria on endpoints in the treatment of AIH, for which further external validation is needed. Here, we demonstrate the usefulness of the IAIHG consensus criteria and corroborate their correlation to primary endpoints, such as liver-related survival and native liver survival in a multicentric, real-world setting. The design of future studies can rely on the IAIHG consensus criteria as intermediate endpoints.

External validation of the IAIHG autoimmune hepatitis response criteria in a multicentric real-world cohort

Lorenz Grossar[1,2,*], Sarah Raevens[2,3], Christophe Van Steenkiste[4,5], Isabelle Colle[6], Charlotte De Vloo[7], Hans Orlent[8], Jeoffrey Schouten[9], Marie Gallant[10], Annelien Van Driessche[11], Sander Lefere[1,2], Lindsey Devisscher[2,12], Anja Geerts[2,3], Hans Van Vlierberghe[2,3], Xavier Verhelst[2,3]

Check for updates

Background & Aims: The goal of treatment in autoimmune hepatitis (AIH) is induction of remission to prevent the development of liver fibrosis, cirrhosis, and its related complications. Various definitions of treatment response and remission have been used. The International Autoimmune Hepatitis Group (IAIHG) recently defined consensus criteria for treatment response. We aimed to validate the IAIHG response criteria in our cohort and establish correlations with survival endpoints.

Methods: We performed a retrospective, multicentric cohort study in one tertiary and seven secondary care centres in Belgium. Eligible patients were at least 18 years of age at data collection and were diagnosed with AIH by a simplified IAIHG score of ≥6. Complete biochemical response (CBR) was defined according to the IAIHG consensus criteria as normalisation of transaminases and serum IgG within the first 6 months of treatment. The primary endpoint was liver-related survival – defined as freedom from liver-related death or liver transplantation. Secondary endpoints were overall mortality and transplant-free survival. Outcomes were compared between patients attaining CBR and those with insufficient response.

Results: Biochemical response status could be determined in 200 patients with AIH: CBR was achieved in 128 (64.0%) individuals. Patients not achieving CBR more frequently presented with cirrhosis on initial histology (22.2% *vs*. 10.9%, *p* = 0.036). Liver-related mortality or liver transplantation as a primary outcome occurred in 26 patients (13.0%). Patients achieving CBR exhibited superior liver-related (hazard ratio 0.118; 95% CI 0.052-0.267; *p* <0.0001) and overall (hazard ratio 0.253; 95% CI 0.111-0.572; *p* = 0.0003) survival.

Conclusions: We externally validated the IAIHG consensus criteria for CBR and confirmed their correlation with survival endpoints in a multicentric, real-world cohort. Patients with AIH achieving CBR as an intermediate endpoint have significantly superior liver-related and overall survival.

Introduction

Autoimmune hepatitis (AIH) was first described in the 1950s as a chronic liver disease in young women.[1,2] Diagnosis is based on clinical suspicion assisted by diagnostic criteria, which rely on the presence of circulating non-organ specific autoantibodies, elevation of serum IgG, histopathology, exclusion of other causes of chronic hepatitis, and response to immunosuppressive treatment.[2] With prevalence rates ranging from 16 to 18 cases per 100,000 inhabitants in Europe, it is considered a rare disease.[3] Since implementation of treatment with systemic corticosteroids, disease activity can be controlled, improving prognosis.[4]

The main goal of treatment in AIH is remission induction and prevention of disease progression, which, if left untreated, leads to development of fibrosis, cirrhosis, and its related complications.[5,6] Stable biochemical response predicts resolution of histological disease activity,[3] and treatment is mainly guided by evolution of serum transaminases and IgG.[2,7] A broad array of definitions for treatment response and varying time intervals to achieve biochemical response have been used

previously, and definition of response to therapy was frequently based on less stringent improvement of biochemical parameters.[8] The recently described international autoimmune hepatitis group (IAIHG) response criteria[9] are consensus-based intermediate endpoints that were developed to enable comparison between studies. Furthermore, an external validation of these response criteria was performed in the consensus statement, demonstrating superior survival in individuals achieving biochemical response. The IAIHG response criteria are defined to further guide developments in the field of AIH and therefore, further external validation is needed to correlate these surrogate endpoints with clinical endpoints. We aimed to externally validate the IAIHG response endpoints in a retrospective, multicentric cohort.

Patients and methods

Study design

We performed a Belgian retrospective, multicentric cohort study in one tertiary centre (Ghent University Hospital), and

seven secondary care centres (Maria Middelares Ghent, ASZ Aalst, AZ Delta Roeselare, AZ Sint-Jan Brugge, VITAZ Sint-Niklaas, Jan Yperman Ieper, AZ Glorieux Ronse).

Setting and patients

The case finding strategy consisted of a keyword- and diagnosis-based search in the electronic health system of the respective hospitals, with a time frame starting from the earliest available retrieved file in the system as of July 1990, up to 31 December 2022. Case validation was performed by revision of the individual patient files and determination of the simplified autoimmune hepatitis score, as defined by the IAIHG.[10] Patients in follow-up for AIH were included if they had undergone liver biopsy with findings compatible with or typical of AIH before the start of treatment, had a simplified IAIHG score of ≥6 (probable or definite AIH) and were at least 18 years of age at time of data collection. Individuals diagnosed with primary sclerosing cholangitis-AIH or primary biliary cholangiopathy-AIH variant syndromes, fulfilling the Paris criteria,[11] were excluded from analysis. Data collection was performed up to 1 August 2023.

Data collection

The following baseline clinical characteristics were retrieved from the medical records: age at diagnosis, gender, treating centre, and the presence of any known extrahepatic autoimmune disease. Follow-up time was calculated as time from diagnosis to last outpatient visit, death, or liver transplantation. Collected laboratory variables at time of diagnosis and start of treatment included serum levels of aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, alkaline phosphatase, bilirubin, IgG, and international normalised ratio, as well as presence of autoantibodies. Presence of cirrhosis at diagnosis was defined by histopathology only. Acute severe autoimmune hepatitis (AS-AIH) was defined as an acute (<26 weeks) manifestation of AIH, with coagulopathy (international normalised ratio ≥1.5) without histological evidence of chronic liver disease. Patients with AS-AIH were further subdivided as AS-AIH with or without acute liver failure (ALF), based on the presence or absence of encephalopathy, as reported elsewhere.[12,13] Serial follow-up of transaminase and serum IgG levels was performed during the first 6 months of treatment, and afterwards during further follow-up. Patients with peak IgG levels above 16 g/L, or above the age-specific upper limit of normal when diagnosed in childhood, were considered as having a IgG elevation. As for treatment data, we recorded the type and dose of corticosteroids ((methyl)prednisolone or budesonide) and steroid-sparing agents administered for remission induction and maintenance immunosuppressive therapy. Doses of budesonide and methylprednisolone were converted to their prednisolone equivalent dose, assuming that 3 mg of budesonide equals 10 mg of prednisolone[14,15] and 4 mg of methylprednisolone equals 5 mg of prednisolone.[16] Intolerance to immunosuppressive therapy leading to discontinuation of the specific drug was also assessed.

Patients were categorised according to their response to treatment, as defined by the IAIHG consensus statement.[9] According to this definition, complete biochemical response (CBR) is achieved in case of normalisation of serum transaminases and IgG within the first 6 months of treatment,

insufficient response (IR) as the lack of CBR within 6 months, and non-response as less than 50% decrease of serum transaminases after 4 weeks of treatment. Normalisation of transaminase levels was defined according to reference values of the treating centre. As an additional analysis, biochemical response was assessed in all individuals regardless of the 6-month timeframe, to report on overall biochemical response rates. Time-to-event analysis was performed for the following outcome measures: all-cause mortality, liver-related mortality, liver transplantation, and occurrence of hepatocellular carcinoma. The primary endpoint was liver-related survival, defined as survival free from liver transplantation or liver-related death, as described elsewhere.[17] Liver-related death was defined as death due to ALF or complications of chronic liver disease and cirrhosis.[18]

Statistical analysis

Baseline characteristics were reported with the appropriate measure of central tendency according to their distribution: continuous variables were summarised as means ± SD or medians and IQR, as appropriate. Categorical variables were reported as percentages and frequencies. Univariable comparisons were performed using the Chi-square test for comparisons between categorical variables and the Mann-Whitney or Student's t tests for comparison between continuous explanatory variables, where appropriate. To identify independent risk factors for CBR status, multivariable analysis was performed using binary logistic regression if $p <0.1$ after univariable analysis. Time-to-event analysis was performed using the Kaplan-Meier method with log-rank testing, with results reported as hazard ratios (HRs) with their corresponding 95% CIs. Univariable and multivariable survival regression were then performed using the Cox proportional hazards method to determine associations between predictor variables and liver-related survival. Significance level was set at $p <0.05$. Statistical analysis was performed using SPSS version 29 (IBM Corp., Armonk, NY) and GraphPad Prism version 9.0 (GraphPad Software Inc., Boston, MA).

Ethical aspects

This study complies with the Declaration of Helsinki from 1975 and was performed in compliance with local ethics committee approval.

Results

After exclusion of 28 patients with established AIH-PBC and 25 with AIH-PSC variant syndrome, the final cohort consisted of 213 individuals. Follow-up data were sufficient to determine CBR status for 200 patients, who were included in CBR vs. IR subgroup comparisons. The median age at diagnosis and median follow-up duration of the whole population were 47 years (interquartile range: 29-59) and 7.8 years (interquartile range: 4.1-13.0), respectively. There was a female predominance of 74.2%, and 150 individuals (70.4%) were followed-up in a tertiary centre. CBR was achieved in 128 (64.0%) individuals, whereas 72 patients (36.0%) were classified as IR. Non-response occurred in 15 individuals (7.5%). Eight individuals had follow-up of less than 6 months due to liver-related death or liver transplantation (two and six individuals,

respectively) in the first 6 months without achievement of biochemical response, and were classified as IR. At the end of data collection, regardless of time to achievement of biochemical response, 170 of all 213 patients (79.8%) had achieved biochemical response, including three for whom CBR status could not be assessed within the 6-month time frame. Fig. S1 depicts the cumulative proportion of individuals achieving biochemical response as a function of time.

Baseline characteristics for the whole cohort and CBR vs. IR comparisons are outlined in Table 1. Peak transaminase and IgG levels were comparable between the two subgroups. Elevation of serum IgG at diagnosis was present in 70.8% of the population and was similar in both subgroups. Diagnosis of cirrhosis on initial histology was more frequent in the IR group compared to the CBR group (22.2% in the IR vs. 10.9% in the CBR subgroup, p = 0.032), and this association persisted after multivariable analysis (p = 0.036).

In one-fourth of patients, at least one concurrent autoimmune disease was present, listed by frequency: autoimmune thyroid disease,[25] inflammatory bowel disease,[13] rheumatoid arthritis,[10] type 1 diabetes mellitus,[9] vitiligo,[4] lupus,[3] keratoconjunctivitis sicca,[2] mixed connective tissue disease,[2] and autoimmune gastritis.[2] Concurrent autoimmune disease was similarly distributed in both biochemical response subgroups.

One-hundred and fifty patients (70.1%) were treated in a tertiary care referral centre. A comparison of baseline characteristics between patients treated in a secondary and tertiary care hospital is detailed in Table S1. Patients treated in tertiary care more frequently presented with cirrhosis (17.3% vs. 6.3%; p = 0.044 after multivariable logistic regression). Conversely, patients in secondary care were more frequently classified as 'definite AIH' according to the simplified IAIHG score (p = 0.016

and p = 0.017 for IAIHG score ≥7 after univariable and multivariable analysis, respectively).

Treatment and outcome

Treatment data are detailed in Table 2. All patients received corticosteroids for remission induction, which consisted of (methyl)prednisolone in almost two-thirds of the population. In one-third of the whole population, maintenance therapy consisted of corticosteroids without a steroid-sparing agent. In the remaining proportion, first-line steroid-sparing therapy consisted of azathioprine in virtually all individuals except for four in the CBR group and two in the non-CBR group. Intolerance leading to drug discontinuation occurred in 22 patients (11.0%) of the whole population, which was due to azathioprine intolerance in 13 individuals (6.5%) and corticosteroid intolerance in 9 (4.5%). Cumulative corticosteroid doses at 6 and 12 months after treatment initiation, comparing individuals receiving either (methyl)prednisolone or budesonide for remission induction, are outlined in Table 3. On average, budesonide-treated individuals received higher cumulative steroid-equivalent doses compared to their counterparts receiving (methyl)prednisolone. No difference could be established in cumulative steroid doses between CBR and IR subgroups.

We next performed time-to-event analysis comparing CBR vs. IR subgroups. The primary outcome, liver-related death or transplantation, occurred in 26 individuals for whom CBR status was known (13.0%), with 21 events (29.2%) occurring in the IR group and five events (3.9%) in the CBR group (HR 0.118; 95% CI 0.052-0.267; p <0.0001). The resulting Kaplan-Meier curve for liver-related survival is outlined in Fig. 1.

Overall mortality was 14.0% (28 individuals: 9 in the CBR group and 19 in the IR group), and survival was superior for the

Table 1. Comparison of baseline variables of the study population, according to CBR status.

	Whole population (N = 200)	CBR (n = 128)	IR (n = 72)	Univariable comparison p value (if <0.05)*	Multivariable comparison p value (if <0.05)*
Median age at diagnosis (years)	48 (29-60)	49 (31-62)	45 (29-59)	0.494	
Median follow-up time (years)	7.8 (4.1-12.2)	7.8 (5.1-12.0)	6.5 (2.9-12.6)	0.279	
Female gender (%)	146/200 (73.0%)	96/128 (75.0%)	50/72 (69.4%)	0.549	
Female-to-male ratio	2.70:1	3.0:1	2.3:1		
Acute severe AIH (%)	20/193 (10.4%)	11/125 (8.8%)	9/68 (13.2%)	0.334	
Acute severe AIH without ALF (%)	11/193 (5.7%)	8/125 (6.4%)	3/68 (4.4%)	0.569	
Median AST (U/L, normalised to ULN)	10.7 (3.6-34.1)	10.5 (4.1-28.2)	13.4 (3.1-36.8)	0.850	
Median ALT (U/L, normalised to ULN)	15.2 (4.9-36.0)	15.2 (4.9-39.6)	14.0 (4.1-35.3)	0.531	
Median INR at diagnosis	1.1 (1.0-1.3)	1.1 (1.0-1.2)	1.2 (1.0-1.4)	**0.011**	0.821
Median albumin at diagnosis (g/L)	36.0 (27.0-42.0)	37.0 (30.9-42.0)	34.0 (17.0-41.0)	**0.022**	0.090
Median TSB at diagnosis µmol/L)	20.5 (10.1-104.3)	18.8 (8.6-94.1)	29.1 (10.3-119.7)	0.410	
Median GGT at diagnosis (U/L, normalised to ULN)	6.7 (2.8-14.0)	5.9 (2.6-13.9)	8.0 (3.1-15.2)	0.355	
ALP at diagnosis (U/L)	145.0 (99.0-236.0)	136.0 (97.0-242.0)	164.0 (122.5-225.8)	0.320	
Median IgG value before treatment (g/L)	19.5 (15.2-26.4)	19.2 (14.9-24.2)	21.1 (15.2-29.1)	0.850	
IgG elevation (%)	136/197 (70.8%)	88/124 (71.0%)	48/68 (70.6%)	0.974	
IAIHG score					
Definite AIH (%)	109/200 (54.5%)	75/128 (58.6%)	34/72 (47.2%)		
Probable AIH (%)	91/200 (45.5%)	53/128 (41.4%)	38/72 (52.8%)	0.116	
Cirrhosis at initial histology (%)	30/200 (15.0%)	14/128 (10.9%)	16/72 (22.2%)	**0.032**	**0.036**
Concurrent autoimmune diseases	52/200 (26.0%)	37/128 (28.9%)	15/72 (20.8%)	0.212	

Whole population denotes all 200 individuals with sufficient data available for assessment of CBR status. Categorical variables are reported as absolute values with denominators indicating available data and with percentages between brackets.

n.s.: not significant. AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CBR, complete biochemical response; GGT, gamma-glutamylaminotransferase; IAIHG, international autoimmune hepatitis group; INR, international normalised ratio; IR, insufficient response; TSB, total serum bilirubin; ULN, upper limit of normal.

*Differences between CBR and non-CBR group. Medians are compared using the Mann-Whitney U test, percentages are compared using the Pearson Chi-square test.

Table 2. Comparison of treatment characteristics according to CBR status.

	Whole population (N = 200)	CBR (n = 128)	IR (n = 72)	Univariable comparison (p value)
Corticosteroid induction regimen				
Methylprednisolone (%)	128/200 (64.0%)	79/128 (61.7%)	46/72 (63.9%)	0.668
Budesonide (%)	72/200 (36.0%)	49/128 (38.3%)	26/72 (36.1%)	0.668
Maintenance therapy				
Azathioprine + corticosteroids (%)	123/200 (61.5%)	80/128 (62.5%)	43/72 (59.7%)	0.064
Corticosteroids only (%)	67/200 (33.5%)	44/128 (34.4%)	23/72 (31.9)	0.064
Other combination regimen (%)	6/200 (3.0%)	4/128 (3.1%)	2/72 (2.8%)	0.064
No maintenance therapy (%)	4/200 (2.0%)	0	4/72 (5.6%)	0.064
Intolerance (%)	22/200 (11.0%)	11/128 (8.6%)	11/72 (15.3%)	0.099
Azathioprine intolerance (%)	13/200 (6.5%)	6/128 (4.7%)	7/72 (9.7%)	0.212
Corticosteroid intolerance (%)	9/200 (4.5%)	5/128 (3.9%)	4/72 (5.6%)	0.212
Median steroid-sparing agent maintenance dose (mg/day)[a]				
Azathioprine[b]	100 (60-100)	100 (75-100)	100 (50-100)	0.196
Mycophenolate mofetil	1,500 (1,000-2,000)	1,500 (1,000-2,000)	1,500 (1,000)	0.857

Continuous variables are reported as mean (SD) or median (IQR), as appropriate. Categorical variables are reported as absolute values with denominators indicating available data and with percentages between brackets. Mean values are compared using the independent sample's t test. Percentages are compared using Pearson Chi-square test.
CBR, complete biochemical response; IR, insufficient response.
[a]Doses of two individuals requiring third-line treatment with tacrolimus are not reported because of individualised dosing.
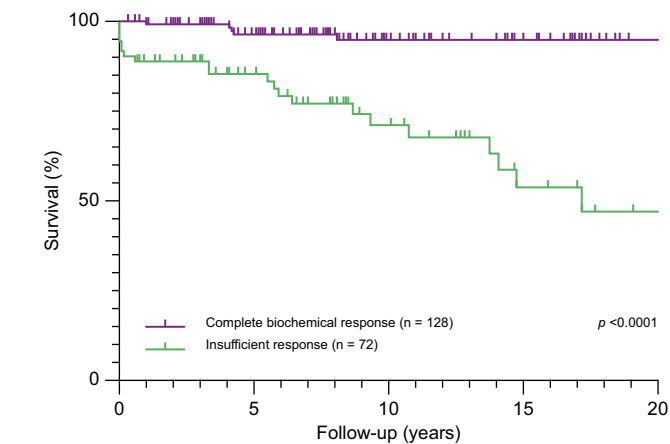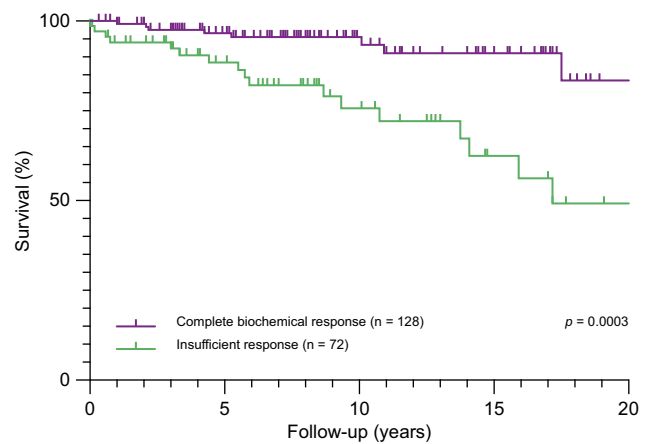[b]Azathioprine maintenance therapy was generally dosed at 1-2 mg/kg/day.

Table 3. Steroid dose comparison between (methyl)prednisolone and budesonide-treated individuals.

	(Methyl)prednisolone	Budesonide	p value
Median steroid dose at induction (mg)	40 (30-40)	9 (9-9)	
Median steroid dose at 6 months (mg)	5 (1.25-10)	3 (0-6)	
Mean cumulative steroid dose at 6 months (mg)			
Whole population (n = 200)	2,223.3 (1,432.7)	3,227.4 (1,129.0)	**<0.001**
CBR (n = 128)	2,240.9 (1,002.1)	3,184.9 (1,094.8)	**<0.001**
IR (n = 72)	2,183.1 (1,361.3)	3,318.2 (1,225.9)	**0.0002**
Mean cumulative steroid dose at 12 months (mg)			
Whole population (n = 200)	2,934.6 (1,926.4)	4,896.4 (2,366.3)	**<0.001**
CBR (n = 128)	3,041.0 (1,953.0)	4,563.7 (1,986.0)	**<0.001**
IR (n = 72)	2,686.5 (1,871.7)	5,551.4 (2,892.2)	**<0.001**

Continuous variables are reported as mean (SD) or median (IQR), as appropriate. Categorical variables are reported as absolute values with denominators indicating available data and with percentages between brackets. Mean values are compared using the independent sample's t test. Percentages are compared using Pearson Chi-square test.
CBR, complete biochemical response; IR, insufficient response.

Fig. 1. Kaplan-Meier curve of survival free from liver-related death or liver transplantation (liver-related survival). Patients are compared according to CBR status by the log-rank test. CBR, complete biochemical response.

Fig. 2. Kaplan-Meier curve of overall survival. Patients are compared according to CBR status by the log-rank test. CBR, complete biochemical response.
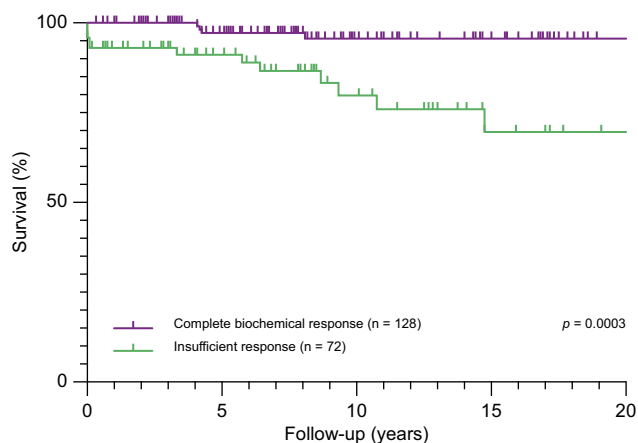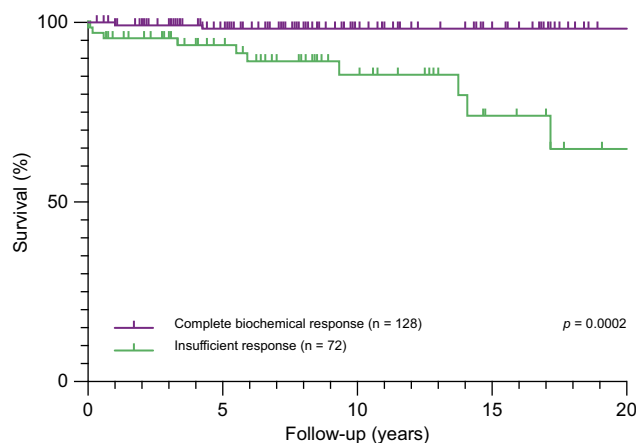
Fig. 3. **Kaplan-Meier curve of transplant-free survival.** Patients are compared according to CBR status by the log-rank test. CBR, complete biochemical response.

Fig. 4. **Kaplan-Meier curve of survival free from liver-related death (liver-related mortality).** Patients are compared according to CBR status by the log-rank test. CBR, complete biochemical response.

CBR group compared to the IR group (HR 0.253; 95% CI 0.111-0.576; *p* = 0.0003). Liver transplantation was performed in 16 individuals (8.0%), with superior transplant-free survival in the CBR group compared to the IR group (HR 0.163; 95% CI 0.058-0.463; *p* = 0.0003). Liver-related mortality alone occurred in nine individuals (12.5%) from the IR group compared to one (0.8%) from the CBR group (HR 0.099; 95% CI 0.030-0.330; *p* = 0.0002). Finally, hepatocellular carcinoma occurred in one and four individuals from the CBR and IR subgroups, respectively (HR 0.122; 95% CI 0.019-0.791; *p* = 0.0248). The resulting Kaplan-Meier curves are outlined in Figs 2–4 for overall survival, transplant-free survival, and survival free from liver-related death, respectively. Eight patients died (all-cause and liver-specific mortality) or underwent liver transplantation within the first 6 months and were considered as IR. To assess for possible confounding, we performed an additional time-to-event analysis excluding these eight individuals, which did not impact our results (data not shown).

We further performed an additional univariable analysis for the primary outcome based on the individual constituents of CBR alone. Both transaminase normalisation and IgG normalisation were associated with superior liver-related survival, with a HR of 0.267 (95% CI 0.133-0.630; *p* = 0.0372) for transaminase normalisation, and 0.202 (95% CI 0.052-0.790; *p* =

0.0007) for IgG normalisation, respectively. The associated Kaplan-Meier curves are available in Fig. S2.

Finally, multivariable Cox regression analysis was performed to reveal independent associations with the primary outcome endpoint, as outlined in Table 4. Specifically, age at diagnosis, gender, AS-AIH without ALF, transaminase and IgG levels at diagnosis, elevated IgG at diagnosis as a dichotomous variable, and cirrhosis on initial histology, were analysed together with transaminase normalisation and IgG normalisation, to identify additional explanatory variables for outcome endpoints. Of the included covariates, only transaminase normalisation and IgG normalisation remained statistically significant predictors of liver-related survival.

Discussion

In this study, we demonstrated that patients achieving CBR, defined as normalisation of serum transaminases and IgG within first 6 months of treatment, have superior liver-related survival as a primary endpoint. Furthermore, patients achieving CBR also had superior overall survival and hepatocellular carcinoma-free survival. By establishing the association between CBR and survival endpoints, we validate the IAIHG consensus criteria for treatment response.

Table 4. Adjusted hazard ratios according to Cox proportional hazards model for the primary outcome point liver-related death or liver transplantation.

Variable	Adjusted hazard ratio[*]	95% CI	*p* value
Age at diagnosis	0.991	0.962-1.020	0.5168
Gender	1.951	0.593-7.860	0.3005
Acute severe AIH, no ALF	1.503	0.071-11.700	0.7320
AST level at diagnosis	1.001	0.999-1.003	0.4955
ALT level at diagnosis	0.999	0.997-1.001	0.3879
IgG level at diagnosis	0.964	0.889-1.030	0.3278
Elevated IgG at diagnosis	1.067	0.228-5.429	0.9352
Cirrhosis at diagnosis	1.512	0.391-4.909	0.5109
Transaminase normalisation	0.203	0.043-0.743	**0.0241**
IgG normalisation	0.179	0.049-0.670	**0.0090**

AIH, autoimmune hepatitis; ALF, acute liver failure; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*Adjusted hazards ratios and their associated 95% CIs are calculated with the Cox proportional hazards regression model to determine the independent contribution of each of the explanatory variables to experience liver-related death or liver transplantation. Variables listed in bold are considered statistically significant (*p* <0.05).

As expected,[2,7,19–21] symptoms and disease severity at initial diagnosis were heterogeneous, ranging from an incidental finding of elevated transaminases to ALF with need for liver transplantation. In contrast to other reports,[22–24] high peak transaminase levels at initial diagnosis did not predict biochemical remission, nor were they associated with superior survival.

AS-AIH is a poorly characterised presentation of AIH, with higher probability of therapy failure and frequent evolution to ALF with need for liver transplantation.[25,26] In a large, retrospective, multicentric Spanish study, assessing early predictors of corticosteroid response in AS-AIH, patients with ALF had the worst corticosteroid response rate and transplant-free survival.[25] In our cohort, AS-AIH patients with ALF also exhibited poor liver-related survival, whereas this association was not present in those with AS-AIH without ALF. It should be noted that our study was not primarily designed to assess the evolution and outcome of this particular subgroup and that the limited number of patients precludes robust statistical analysis.

Cirrhosis is reported to be detected on initial histology in 23 to 33% of patients and is associated with inferior biochemical response and survival in AIH.[21,27–29] Our cohort consisted of a lower proportion of patients presenting with cirrhosis. Nevertheless, these patients showed lower rates of biochemical response, as expected from previous reports.[22,27,29]

Compared to other reports,[21,23,30,31] we had a considerably larger fraction of patients without IgG elevation at diagnosis. This might be explained by the lower proportion of cirrhosis in our cohort, which is a well-known contributing factor to hypergammaglobulinemia.[32]

We outline a well-described and representative real-world cohort, hallmarked by the contribution of both secondary care hospitals and a tertiary care institution. Application of the IAIHG consensus criteria for treatment response is feasible in this cohort and allows for correlation of the surrogate endpoint with survival endpoints. In our cohort, patients achieved CBR more frequently than in the multicentric cohort the initial validation of the IAIHG response criteria is based on.[9,22] However, in the initial external validation cohort, more patients had cirrhosis at initial diagnosis, which could explain the inferior CBR rate compared to our population. Except for the lower proportion of elevated IgG and cirrhosis at diagnosis, our cohort very well reflects the characteristics of other reports.[21,22,33,34]

Furthermore, we report on differences in cumulative steroid doses, with budesonide-treated individuals receiving on average higher cumulative doses compared to those treated with (methyl)prednisolone. These findings are in contrast with another recent study,[15] and could reflect local practice in corticosteroid treatment. Moreover, biochemical response rate is comparable between these two subgroups in our populations, which conflicts with several other reports.[35–37] Our patient mix was derived from both secondary and tertiary care settings and consisted of a lower proportion of patients with cirrhosis, which might explain the higher biochemical response rate under budesonide than observed in many other studies.[15,35] Regardless, the role of budesonide in patients with AIH is part of a broader debate that moves beyond corticosteroid efficacy and rather focuses on advances in nonsteroidal therapies.[38,39]

Our study has several limitations. First, the retrospective nature and prerequisite of response assessment within 6 months implies selection bias of individuals for whom at least 6 months of follow-up is available. However, our case finding strategy allowed us to identify patients with AIH regardless of follow-up time. Second, our cohort is characterised by heterogeneity both in terms of treatment era and clinical phenotype. It is now well-established that persistence of even slightly elevated transaminases and IgG are associated with progressing disease activity.[38] Application of the current, more stringent response criteria to patients classified as treatment responders according to earlier guidance[8,40] could have led to prompt treatment adaptations. Nonetheless, this further reinforces the utility of broadly implemented response criteria to enable comparison between subgroups and studies.

In conclusion, with our study, we aimed to apply the IAIHG consensus criteria for treatment response in a multicentric, real-world cohort. Our results confirm the predictive value of achieving normalisation of serum transaminases and IgG for survival endpoints in patients with AIH. Regardless of interpatient heterogeneity, efforts to achieve and maintain CBR strongly mitigate the risk of adverse survival outcomes. We thus provide an external validation of the response criteria and corroborate their usefulness in clinical practice. Future studies should consist of large samples to further confirm these criteria as surrogate markers for survival outcomes and address the heterogeneity of patients with AIH, with regards to their potential for response to therapy. Biochemical response could further guide efforts to tailor treatment, balancing remission of disease and intolerance to treatment.

Affiliations

[1]Department of Internal Medicine and Paediatrics, Hepatology Research Unit, Ghent University, Ghent, Belgium; [2]Liver Research Centre Ghent, Ghent University, Ghent University Hospital, Ghent, Belgium; [3]Department of Gastroenterology and Hepatology, Ghent University Hospital, Ghent, Belgium; [4]Department of Gastroenterology and Hepatology, AZ Maria Middelares, Ghent, Belgium; [5]Department of Gastroenterology and Hepatology, University Hospital Antwerp, Antwerp, Belgium; [6]Department of Gastroenterology and Hepatology, ASZ Aalst, Aalst, Belgium; [7]Department of Gastroenterology and Hepatology, AZ Delta Roeselare, Roeselare, Belgium; [8]Department of Gastroenterology and Hepatology, AZ Sint Jan Brugge, Brugge, Belgium; [9]Department of Gastroenterology and Hepatology, VITAZ, Sint-Niklaas, Belgium; [10]Department of Gastroenterology and Hepatology, Jan Yperman Ziekenhuis, Ieper, Belgium; [11]Department of Gastroenterology and Hepatology, AZ Glorieux, Ronse, Belgium; [12]Department of Basic & Applied Medical Sciences, Gut-Liver Immunopharmacology Unit, Ghent University, Ghent, Belgium

Abbreviations

AIH, autoimmune hepatitis; ALF, acute liver failure; AS-AIH, acute severe AIH; CBR, complete biochemical response; HR, hazard ratio; IR, insufficient response.

Conflict of interest

The authors of this study declare that they do not have any conflict of interest.
   Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation, writing, original draft, review and editing, data analysis, visualisation: LG. Conceptualisation, critical appraisal: XV. Critical appraisal: SR, CVS, IC, CDV, HO, JS, MG, AVD, SL, LD, AG, HVV.

References

Author names in bold designate shared co-first authorship

[1] Waldenstrom J. [Liver, blood proteins and nutritive protein]. Dtsch Z Verdau Stoffwechselkr 1953;9:113–119.

[2] EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol 2015;63(4):971–1004.

[3] Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. Gut 2021;70(10):1989–2003.

[4] Soloway RD, Summerskill WH, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology 1972;63(5):820–833.

[5] Kirk AP, Jain S, Pocock S, et al. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut 1980;21(1):78–83.

[6] Mieli-Vergani G, Vergani D, Czaja AJ, et al. Autoimmune hepatitis. Nat Rev Dis Primers 2018;4:18017.

[7] Mack CL, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American association for the study of liver diseases. Hepatology 2020;72(2):671–722.

[8] Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31(5):929–938.

[9] **Pape S**, **Snijders R**, Gevers TJG, et al. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol 2022;76(4):841–849.

[10] Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology (Baltimore, Md) 2008;48(1):169–176.

[11] Chazouillères O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28(2):296–301.

[12] Yeoman AD, Westbrook RH, Zen Y, et al. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J Hepatol 2014;61(4):876–882.

[13] Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. Dig Dis Sci 2013;58(4):897–914.

[14] Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. Clin Pharmacokinet 2004;43(12):803–821.

[15] Díaz-González Á, Hernández-Guerra M, Pérez-Medrano I, et al. Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predniso(lo)ne administration. Hepatology 2023;77(4):1095–1105.

[16] Czock D, Keller F, Rasche FM, et al. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet 2005;44(1):61–98.

[17] Biewenga M, Verhelst X, Baven-Pronk M, et al. Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1. United Eur Gastroenterol J 2021;9(6):662–671.

[18] Kim WR, Brown Jr RS, Terrault NA, et al. Burden of liver disease in the United States: summary of a workshop. Hepatology 2002;36(1):227–242.

[19] Muratori P, Lalanne C, Barbato E, et al. Features and progression of asymptomatic autoimmune hepatitis in Italy. Clin Gastroenterol Hepatol 2016;14(1):139–146.

[20] Sonthalia N, Rathi PM, Jain SS, et al. Natural history and treatment outcomes of severe autoimmune hepatitis. J Clin Gastroenterol 2017;51(6):548–556.

[21] Muratori P, Granito A, Quarneti C, et al. Autoimmune hepatitis in Italy: the Bologna experience. J Hepatol 2009;50(6):1210–1218.

[22] Pape S, Gevers TJG, Vrolijk JM, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. Clin Gastroenterol Hepatol 2020;18(7):1609–1617.e4.

[23] Al-Chalabi T, Underhill JA, Portmann BC, et al. Effects of serum aspartate aminotransferase levels in patients with autoimmune hepatitis influence disease course and outcome. Clin Gastroenterol Hepatol 2008;6(12):1389–1395. quiz 287.

[24] Muratori P, Lalanne C, Bianchi G, et al. Predictive factors of poor response to therapy in Autoimmune Hepatitis. Dig Liver Dis 2016;48(9):1078–1081.

[25] **Téllez L**, **Sánchez Rodríguez E**, Rodríguez de Santiago E, et al. Early predictors of corticosteroid response in acute severe autoimmune hepatitis: a nationwide multicenter study. Aliment Pharmacol Ther 2022;56(1):131–143.

[26] Rahim MN, Liberal R, Miquel R, et al. Acute severe autoimmune hepatitis: corticosteroids or liver transplantation? Liver Transpl 2019;25(6):946–959.

[27] Feld JJ, Dinh H, Arenovich T, et al. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology 2005;42(1):53–62.

[28] Werner M, Prytz H, Ohlsson B, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008;43(10):1232–1240.

[29] Grønbæk L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol 2014;60(3):612–617.

[30] Hartl J, Miquel R, Zachou K, et al. Features and outcome of AIH patients without elevation of IgG. JHEP Rep 2020;2(3):100094.

[31] Floreani A, Niro G, Rosa Rizzotto E, et al. Type I autoimmune hepatitis: clinical course and outcome in an Italian multicentre study. Aliment Pharmacol Ther 2006;24(7):1051–1057.

[32] Triger DR, Wright R. Hyperglobulinaemia in liver disease. Lancet 1973;1(7818):1494–1496.

[33] Gordon V, Adhikary R, Appleby V, et al. Treatment and outcome of autoimmune hepatitis (AIH): audit of 28 UK centres. Liver Int 2020;42:1571–1584.

[34] Slooter CD, van den Brand FF, Lleo A, et al. Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: first report of the IAIHG retrospective registry. Hepatology 2023;79(3):538–550.

[35] **Peiseler M**, **Liebscher T**, Sebode M, et al. Efficacy and limitations of budesonide as a second-line treatment for patients with autoimmune hepatitis. Clin Gastroenterol Hepatol 2018;16(2):260–267.e1.

[36] Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010;139(4):1198–1206.

[37] Woynarowski M, Nemeth A, Baruch Y, et al. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. J Pediatr 2013;163(5):1347–13453.e1.

[38] Lohse AW, Sebode M, Jørgensen MH, et al. Second-line and third-line therapy for autoimmune hepatitis: a position statement from the European reference network on hepatological diseases and the international autoimmune hepatitis group. J Hepatol 2020;73(6):1496–1506.

[39] Snijders R, Stoelinga AEC, Gevers TJG, et al. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. J Hepatol 2024;80(4):576–585.

[40] Czaja AJ, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. Hepatology 1999;30(6):1381–1386.