Aminotransferases During Treatment Predict Long-Term Survival in Patients With Autoimmune Hepatitis Type 1: A Landmark Analysis

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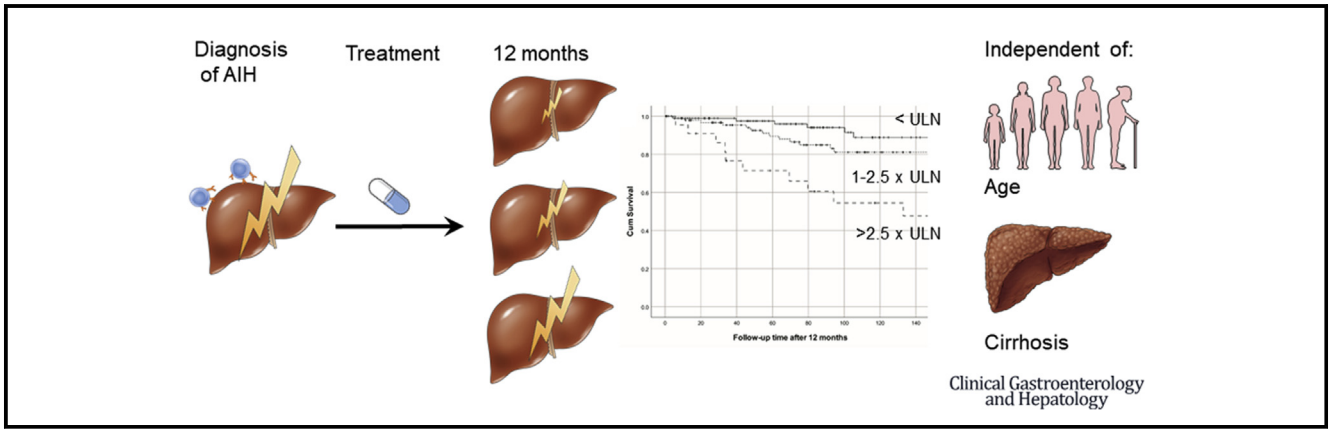

BACKGROUND & AIMS: **Biochemical remission, important treatment goal in autoimmune hepatitis (AIH), has been associated with better long-term survival. The aim of this study was to determine the independent prognostic value of aminotransferases and immunoglobulin G (IgG) during treatment on long-term transplant-free survival in AIH.**

METHODS: **In a multicenter cohort alanine aminotransferase, aspartate aminotransferase (AST), and IgG were collected at diagnosis and 6, 12, 24, and 36 months after start of therapy and related to long-term outcome using Kaplan-Meier survival and Cox regression analysis with landmark analysis at these time points, excluding patients with follow-up ending before each landmark.**

RESULTS: **A total of 301 AIH patients with a median follow-up of 99 (range, 7–438) months were included. During follow-up, 15 patients required liver transplantation and 33 patients died. Higher AST at 12 months was associated with worse survival (hazard ratio [HR], 1.86; $P < .001$), while IgG was**

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AIH, autoimmune hepatitis; HR, hazard ratio; IgG, immunoglobulin G; ULN, upper limit of normal.

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not associated with survival (HR, 1.30; $P = .53$). In multivariate analysis AST at 12 months (HR, 2.13; $P < .001$) was predictive for survival independent of age, AST at diagnosis and cirrhosis. Multivariate analysis for AST yielded similar results at 6 months (HR, 2.61; $P = .001$), 24 months (HR, 2.93; $P = .003$), and 36 months (HR, 3.03; $P = .010$). There was a trend toward a worse survival in patients with mildly elevated aminotransferases (1–1.5× upper limit of normal) compared with patients with normal aminotransferases ($P = .097$).

CONCLUSIONS: **Low aminotransferases during treatment are associated with a better long-term survival in autoimmune hepatitis. IgG was not associated with survival in first 12 months of treatment. Normalization of aminotransferases should be the treatment goal for autoimmune hepatitis to improve long-term survival.**

Keywords: Long Term Survival; Biochemical Remission; Treatment Response; Immunoglobulin G.

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver, commonly treated with a combination of glucocorticoids and thiopurines.[1] With treatment, 10-year survival is between 80% and 96%.[2–5] Noncirrhotic patients have a similar life expectancy as the general population.[6]

The primary aim of treatment is to reach complete biochemical remission, which likely prevents further development of cirrhosis, disease progression, and death.[7] Complete biochemical remission has been defined as normalization of aminotransferases and immunoglobulin G (IgG) and is reached in approximately 80%–90% of patients during follow-up.[7] In patients with partial biochemical remission, second-line therapy with mycophenolate mofetil or tacrolimus can be considered.[8] Discontinuation of treatment leads to relapse or loss of remission in the majority of patients.[9] Usually, lifelong treatment with thiopurines and in some patients glucocorticoids is needed to retain remission. Generally, thiopurines are preferred for maintenance, as long-term treatment with (low-dose) glucocorticoids increases risk of diabetes mellitus, fractures, and cataract.[10]

Side effects of treatment should be balanced against the benefit of biochemical remission on disease progression and survival. Several studies report that partial treatment response and recurrent relapses in comparison to sustained complete remission are associated with worse survival,[6,11–16] although some studies did not find such a difference.[17,18] A weakness in all of these studies is that treatment response, which occurs during follow-up, was used as a baseline variable. This leads to immortal time bias, which exaggerates the presumed effect of complete biochemical remission as compared with partial remission.[19] To prevent this immortal time bias and definitely assess whether prognosis is different for complete vs partial remission, landmark analysis, in which follow-up starts at different predefined time points, should be used.[19]

The aim of this study was therefore to evaluate the association of aminotransferases and IgG during treatment with long-term transplant-free survival after correction for known risk factors and using landmark analysis at different time points.

Materials and Methods

All patients with probable or definite AIH type 1, according to the revised pretreatment International AIH Group criteria, from 4 academic centers and 4 general hospitals in the Netherlands and Belgium were eligible for inclusion. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of latest revision of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. All data were obtained from chart review. All patients with AIH type 2, defined by the presence of anti LKM-1 antibodies, and patients with AIH–primary biliary cirrhosis and AIH–primary sclerosing cholangitis variant syndromes were excluded.

Treatment response was evaluated using alanine aminotransferase (ALT), aspartate aminotransferase (AST), and IgG serum levels at 6, 12, 24, and 36 months after therapy. A 6-week range was used. Patients with no ALT, AST, or IgG values during follow-up were excluded.

Response to treatment was defined according to the European Association for the Study of the Liver guidelines: complete biochemical remission was defined as normalization of aminotransferases and IgG and partial remission as improvement of aminotransferases and IgG without normalization.[7]

Follow-up time was defined as the time from diagnosis until last visit to the outpatient clinic, liver transplantation, or death. Transplant-free survival was defined as survival free of liver transplantation and death. Liver-related death was defined as death related to acute liver failure, decompensated cirrhosis, or hepatocellular carcinoma.

Statistical Analysis

Statistical analysis was performed in IBM SPSS 25.0 (IBM, Armonk, NY). Analysis of variance, Fisher's exact test, chi-square test, Mann-Whitney *U* test, and independent samples *t* test were used where appropriate. For related variables, the Wilcoxon signed rank test was used. Missing data were imputed in the derivation cohort using fully conditional specification, creating 10 imputed datasets.

Imputation was used for continous biochemical variables and outcomes were included in the imputation model.

Biochemical parameters with different upper limit of normal (ULN) or lower limit of normal in the participating centers were corrected according to the ULN or lower limit of normal. Logarithmic transformation was used in case of not normal distribution.

In order to prevent immortal time bias landmark analysis was used at 6, 12, 24, and 36 months during follow-up.[19] Treatment response was determined at the landmark and follow-up started at the landmark. Patients with a follow-up shorter than the landmark were excluded from this analysis. Predictors of survival were analyzed by Kaplan-Meier survival analysis with log-rank test and univariate and multivariate Cox regression analysis. As collinearity was expected between ALT and AST, the variable most significant in univariate analysis was entered in multivariate analysis. To evaluate if effects were similar in cirrhotic and noncirrhotic patients, interaction analysis was performed. A P value $<.05$ was considered significant.

What You Need to Know

Background

Previous studies suggest that biochemical remission is associated with better long term survival in autoimmune hepatitis. However, the prognostic value of aminotransferases and immunoglobulin G (IgG) are still unknown.

Findings

Higher AST during treatment was independently from age, AST at diagnosis and liver cirrhosis associated with worse survival. IgG at 6 or 12 months was not associated with survival

Implications for patient care

Aminotransferases below the upper limit of normal should be the treatment aim to improve long term survival. Isolated elevated IgG can be permitted as it does not influence survival.

Results

In total, 301 patients with AIH type 1 were included. Survival of patients with follow-up shorter than the used landmark is shown in Supplementary Figure 1. Mean age at diagnosis was 51 (range, 6–84) years. Cirrhosis was present in 85 (28%) patients. Baseline characteristics are shown in Table 1.

Treatment Response

Laboratory values at diagnosis and during first years of treatment are also shown in Table 1. Aminotransferases were normal at 6 months in 97 (38%) of the 255 patients. Median ALT decreased from 11.2× ULN (range, 0.35–146) at diagnosis to 1.0× ULN (range, 0.22–25.8; $P < .001$) (Table 1) at 6 months and was below the reference limit in 136 (53%) of the 260 patients at 6 months. Median IgG decreased from 1.34× ULN (range, 0.42–4.69) at diagnosis to 0.78 (range, 0.29–2.31; $P < .001$) at 6 months. At 6 months of treatment, 44 (34%) of the 131 patients with IgG available were in complete remission.

At 12 months aminotransferases were below the reference limit in 96 (43%) of the 222 patients. Of the 145 (41%) patients with IgG available at 12 months, 60 (41%) patients were in complete biochemical remission at 12 months. At 12 months, median ALT was 0.89× ULN (range, 0.23–14.6) and median AST was 1.03× ULN (range, 0.39–38) (Table 1). IgG was 0.78× ULN (range, 0.36–2.1) at 12 months. ALT, AST, and IgG values at 24 months and 36 months are shown in Table 1.

Survival

Median follow-up was 99 (range, 7–438) months. During follow-up, 15 patients received a liver transplantation and 33 patients died in median 81 (range, 8–251) months. In 14 patients, death was liver related. The Kaplan-Meier transplant-free survival estimate was 83.2% (95% confidence interval, 78.0%–88.4%) after 10 years of follow-up. In univariate Cox regression analysis with a landmark at 12 months, ALT (hazard ratio [HR], 0.56; $P < .001$) and AST (HR, 0.70; $P = .005$) at diagnosis were significantly associated with lower risk of mortality or liver transplantation (Table 2). In contrast to ALT and AST at diagnosis, ALT and AST at 12 months were associated with higher risk of mortality or liver transplantation (for ALT: HR, 1.56; $P = .020$; for AST: HR, 1.86; $P < .001$). Patients with AST and ALT below the ULN at 12 months had lower risk of mortality or liver transplantation compared with patients with AST and ALT 1–2.5× or more than 2.5× ULN ($P < .001$ for AST; $P = .02$ for ALT) (Figure 1). IgG at diagnosis or at 12 months was not associated with mortality or liver transplantation (HR, 0.92; $P = .67$; and HR, 1.30; $P = .53$). Non-Caucasian ethnicity was associated with a higher risk of mortality or liver transplantation (HR, 2.80; $P = .002$). Complete biochemical remission at 12 months (HR, 0.58; $P = .14$) was also not associated with mortality or liver transplantation, while normalization of both aminotransferases (HR, 0.53; $P = .071$) at 12 months tended to be associated with lower risk of mortality or liver transplantation.

Using interaction analysis, effects of AST ($P = .86$ at diagnosis and $P = .083$ at 12 months), ALT ($P = .55$ at diagnosis and $P = .16$ at 12 months), and IgG ($P = .17$ at diagnosis and $P = .57$ at 12 months) were similar between patients with and without cirrhosis.

Univariate Cox regression with a landmark at 6, 24, and 36 months yielded similar results (Supplementary

Table 1. Baseline Characteristics and Laboratory Values at Diagnosis and During First Years of Treatment

	Data	N
Female	225 (75%)	301
Age at diagnosis, y	51 (6–84)	297
Caucasian	270 (90%)	301
Cirrhosis	85 (28%)	293
Laboratory values		
Bilirubin, μmol/L	29 (3–596)	273
ALT × ULN	11.2 (0.35–146)	292
AST × ULN	11.0 (0.61–161)	277
AP × ULN	1.45 (0.23–19.1)	288
GGT × ULN	3.64 (0.05–24.0)	189
IgG × ULN	1.34 (0.42–4.69)	281
6 mo		
Bilirubin, μmol/L	11 (2–89)	243
ALT × ULN	1.00 (0.22–25.8)	260
AST × ULN	1.13 (0.35–25.8)	251
AP × ULN	0.67 (0.08–9.54)	240
GGT × ULN	1.45 (0.21–55.7)	241
IgG × ULN	0.78 (0.29–2.31)	131
12 mo		
Bilirubin, μmol/L	11 (2–325)	192
ALT × ULN	0.88 (0.23–14.6)	222
AST × ULN	1.03 (0.39–38.0)	219
AP × ULN	0.77 (0.22–9.26)	207
GGT × ULN	1.11 (0.26–13.7)	133
IgG × ULN	0.78 (0.36–2.09)	145
24 mo		
ALT × ULN	0.79 (0.18–9.38)	108
AST × ULN	0.94 (0.39–13.6)	109
AP × ULN	0.70 (0.20–3.57)	100
GGT × ULN	0.84 (0.18–27.0)	100
IgG × ULN	0.78 (0.31–3.18)	67
36 mo		
ALT × ULN	0.87 (0.16–6.88)	110
AST × ULN	1.03 (0.29–7.00)	107
AP × ULN	0.72 (0.20–3.31)	99
GGT × ULN	0.84 (0.13–12.1)	99
IgG × ULN	0.83 (0.38–2.00)	65

Values are n (%) or median (range).
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT γ-glutamyltransferase; IgG, immunoglobulin G; ULN, upper limit of normal.

Table 1). In contrast to 6 and 12 months, in which IgG was not associated with mortality or liver transplantation, IgG levels at 24 months (HR, 2.29; $P = .032$) and 36 months (HR, 4.17; $P = .031$) were significantly associated with higher risk of mortality or liver transplantation.

Exclusion of the 27 patients with pediatric onset yielded similar results. Complete biochemical remission and normalization of aminotransferases were associated with lower risk of mortality or liver transplantation (HR, 0.42; $P = .037$ and HR, 0.41; $P = .019$) (Supplementary Tables 2 and 3).

Multivariate Analysis

As AST at 12 months was more significant than ALT in univariate analysis, AST was included in multivariate analysis. AST at 12 months was corrected for age, cirrhosis at diagnosis, and AST at diagnosis. Owing to limited number of events and a higher estimated effect of age and cirrhosis, ethnicity was not entered in multivariate analysis. In multivariate analysis, AST at 12 months (HR, 2.11; $P < .001$) was a significant predictor for mortality or liver transplantation (Table 3). Corrected for age, cirrhosis, and AST at diagnosis, a doubling of AST at 12 months results in a 69% increase in hazard for liver transplantation or mortality. In addition, AST was also independently associated with mortality or liver transplantation at 6 months (HR, 2.61; $P = .001$), 24 months (HR, 2.93; $P = .003$), and 36 months (HR, 3.03; $P = .010$) (Table 3).

Multivariate analysis with ALT yielded similar results (Supplementary Table 4).

Risk of Mildly Raised Aminotransferases

At 12 months, 89 patients had mildly raised aminotransferases, defined as AST or ALT between 1 and 1.5× ULN, and 80 patients had AST and ALT below the ULN. There was a trend toward lower risk of mortality or liver transplantation in patients with AST and ALT < ULN compared with patients with mildly raised aminotransferases ($P = .097$) (Figure 2).

Risk Factors for Patients With Normal AST

As increase in AST was related to worse outcome, a subgroup analysis was performed in 101 patients with normal AST at 12 months to analyze if aminotransferase in this group also correlated to outcome. In these patients, ALT and AST at 12 months were not significantly associated with mortality or liver transplantation (for ALT: HR, 1.25; range, 0.27–5.91; $P = .78$; for AST: HR, 7.81; range, 0.44–140; $P = .16$).

Besides aminotransferases, the other component of biochemical remission, IgG was analyzed. Median IgG was 0.71× ULN (range, 0.36–1.36), and in 11 (11%)

Table 2. Univariate Cox Regression With a Landmark at 12 Months for Predictors of Mortality or Liver Transplantation

	Hazard Ratio (95% CI)	*P* Value
Baseline		
Female	1.06 (0.54–2.09)	.87
Non-Caucasian	2.80 (1.47–5.34)	.002
Cirrhosis	2.98 (1.67–5.31)	<.001
Bilirubin, μmol/L	1.00 (0.99–1.00)	.200
Ln ALT × ULN	0.56 (0.44–0.72)	<.001
Ln AST × ULN	0.70 (0.55–0.90)	.005
Ln AP × ULN	1.08 (0.69–1.69)	.75
Ln GGT × ULN	1.33 (0.94–1.89)	.11
IgG × ULN	0.92 (0.63–1.34)	.67
12 mo		
Age	1.02 (1.00–1.04)	.011
Ln ALT × ULN	1.56 (1.07–2.28)	.020
Ln AST × ULN	1.86 (1.39–2.51)	<.001
Ln AP × ULN	1.61 (1.04–2.49)	.032
Ln GGT × ULN	2.06 (1.49–2.85)	<.001
IgG × ULN	1.30 (0.57–2.97)	.53
Complete biochemical remission	0.58 (0.28–1.19)	.14
Normalization ALT and AST	0.53 (0.27–1.06)	.071

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; GGT γ-glutamyltransferase; IgG, immunoglobulin G; ULN, upper limit of normal.

patients IgG was elevated while AST was normal. In patients with normal AST at 12 months, IgG was not significantly associated with mortality or liver transplantation (HR, 0.87; range, 0.081–9.35; $P = .91$).

Discussion

In this multicenter cohort study, it was shown that higher aminotransferases during treatment were independent of baseline risk factors associated with liver transplantation–free survival in patients with AIH type 1. To prevent immortal time bias, a landmark analysis was used at 6, 12, 24, and 36 months in which all patients with liver transplantation or mortality before the landmark were excluded. The hazard ratio of AST level was in the same range at 6, 12, 24, and 36 months, suggesting that the effect of AST level during treatment on mortality or liver transplantation remains similar at least during the first 3 years of therapy. This is consistent with a previous study that reported that a rapid reduction of AST in the first months of treatment predicts normalization of aminotransferases at 12 months and was predictive for long-term survival.[20]

Increase in the level of serum AST at 12 months was correlated to worse long-term transplant-free survival: a doubling of AST resulted in a 69% increase in HR. Transplant-free survival was poorer for patients with AST >2.5× ULN compared with patients with AST 1–2.5× ULN or < ULN. For patients with mildly raised aminotransferases (1–1.5× ULN) compared with patients with normal aminotransferases the difference in transplant-free survival became smaller, but a similar trend was present. In patients with normal AST at 12 months, aminotransferases were not correlated with transplant-free survival. This suggests that the benefit

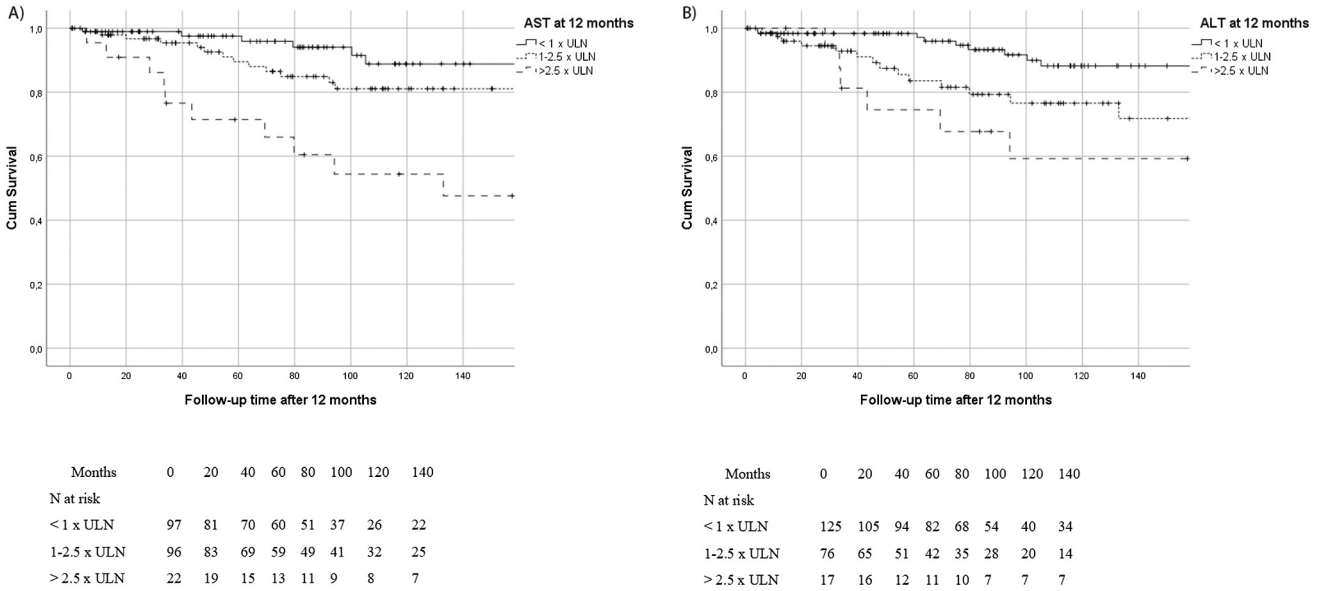


Figure 1. Transplant-free survival of patients with (*A*) AST and (*B*) ALT at 12 months >2.5× ULN compared with 1–2.5× ULN and below the ULN ($P < .001$ for AST and $P = .017$ for ALT). As follow-up starts at 12 months after diagnosis, 0 months at the x-axis is 12 months after diagnosis.

Table 3. Multivariate Cox Regression With Landmark at 6, 12, 24, and 36 Months for Mortality or Liver Transplantation

	Hazard Ratio (95% CI)	*P* Value
6 mo		
Age	1.04 (1.02–1.05)	<.001
Cirrhosis at diagnosis	3.09 (1.62–5.89)	.001
Ln AST × ULN at diagnosis	0.66 (0.48–0.90)	.010
Ln AST × ULN at 6 mo	2.61 (1.47–4.61)	.001
12 mo		
Age	1.03 (1.02–1.05)	<.001
Cirrhosis at diagnosis	2.42 (1.21–4.87)	.013
Ln AST × ULN at diagnosis	0.64 (0.47–0.86)	.004
Ln AST × ULN at 12 mo	2.13 (1.46–3.11)	<.001
24 mo		
Age	1.05 (1.02–1.07)	<.001
Cirrhosis at diagnosis	2.83 (1.33–6.05)	.007
Ln AST × ULN at diagnosis	0.67 (0.48–0.95)	.024
Ln AST × ULN at 24 mo	2.93 (1.48–5.80)	.003
36 mo		
Age	1.04 (1.02–1.06)	<.001
Cirrhosis at diagnosis	2.71 (1.34–5.46)	.005
Ln AST × ULN at diagnosis	0.67 (0.48–0.93)	.017
Ln AST × ULN at 36 mo	3.03 (1.33–6.86)	.010

AST, aspartate aminotransferase; CI, confidence interval; ULN, upper limit of normal.

for long-term transplant-free survival of having very low normal aminotransferases (eg, <0.5× ULN) is limited. However, the number of patients in this subanalysis is not large enough to strongly state that there is no benefit of having a very low ALT compared with levels in the upper reference range. Having low aminotransferases and low IgG have previously been associated with a higher rate of successful treatment withdrawal.[21] Patients with histological remission had lower ALT than patients with biochemical remission without histological remission.[22] These data suggest a long-term benefit of very low ALT, but this requires further confirmation.

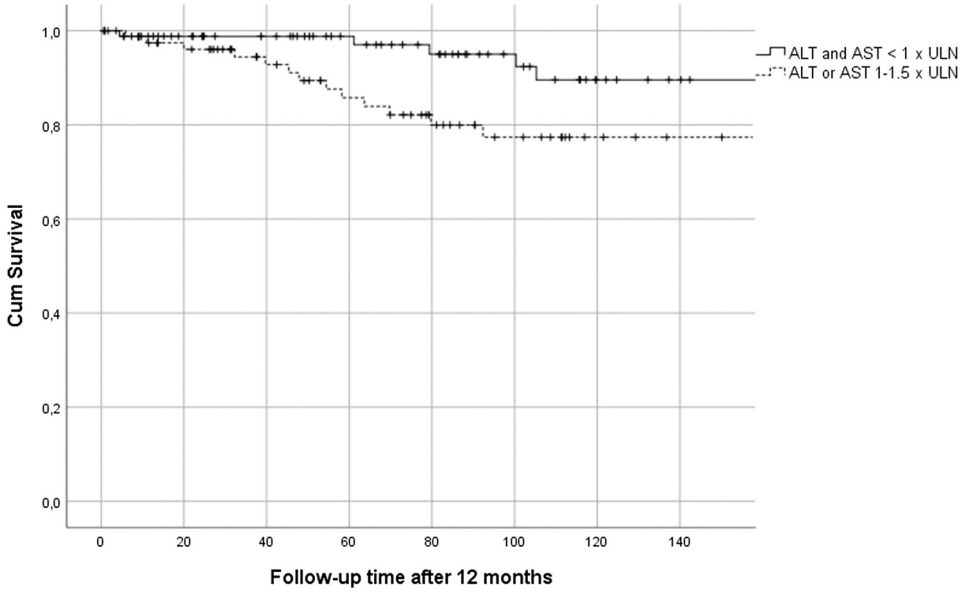
Besides aminotransferases, IgG is also a component of the current definition of complete biochemical remission.[7] In this study, IgG level at 6 and 12 months was not associated with long-term transplant-free survival. Also in patients with normal ALT at 12 months, IgG was not associated with transplant-free survival. In contrast to this, in univariate analysis at 24 and 36 months elevated IgG was associated with a worse long-term transplant-free survival in a limited number of patients. Recently, it was reported that IgG at diagnosis is not related to therapy response or outcome.[23] Several studies have been published on the effect of IgG during treatment. Raised IgG levels were reported to correlate to histological activity of AIH, progression of fibrosis on liver elastography, and increased risk of relapse after treatment withdrawal.[24–26] Patients with normal aminotransferases but elevated IgG had a higher risk of liver-related adverse events.[16] Patients without normalization of IgG had a decreased transplant-free survival, but no landmark analysis was used.[27] In contrast to these studies, in our study IgG in the first year was not a risk factor for long-term outcome. However, univariate analysis suggested that IgG becomes a more important factor after the first year of treatment, which fits with the previous mentioned studies on the role of IgG during treatment. Possibly improvement in immunological activity and hepatic inflammation do not necessarily coincide in time. More research on the value of IgG and other markers that reflect immunological activity during treatment is needed.

Surprisingly, complete biochemical remission and normalization of both aminotransferases at exactly 12 months were not significantly associated with better transplant-free survival, despite a trend for the latter. A possible explanation is that gradual tapering of glucocorticoids leads to loss of remission at 12 months in some patients. After increase of glucocorticoid dose, remission can often be regained in these patients.

In several studies, partial biochemical remission has been associated with worse survival compared with complete remission,[6,11–16] but not in all studies.[17,18] One study even showed reduced survival in patients with complete biochemical remission without histological remission compared with patients with both biochemical and histological remission.[22] Unfortunately, all of those studies were flawed, using follow-up variables as baseline variables, which can lead to immortal time bias. Immortal time bias means that patients who reached remission would be "immortal" until they reach remission, while those with death or liver transplantation before reaching remission would be in the group with partial remission. Landmark analysis, as used by the current study, avoids overestimation of the effect of remission by immortal time bias.[19]

Multiple relapses during treatment have also been associated with a worse survival in AIH.[11,15] In our study patients with higher AST at 12 months had a worse transplant-free survival. This AST level could be a relapse after remission or a partial primary treatment response. Relapses and loss of remission that occurred after the landmark could not be included in this study, as this would introduce a new immortal time bias, but they could be an additional risk factor.

Aminotransferases during treatment were corrected for previously reported risk factors, including age, aminotransferases at diagnosis, and liver cirrhosis at diagnosis. Higher aminotransferases at diagnosis have previously been reported to be associated with a better



Months	0	20	40	60	80	100	120	140
N at risk								
ALT and AST < 1 x ULN	89	73	65	55	47	36	26	21
ALT or AST 1-1.5 x ULN	80	70	56	47	37	29	21	18

Figure 2. Transplant-free survival of patients with AST or ALT between 1 and 1.5× ULN compared with patients with AST and ALT below the ULN ($P = .097$). As follow-up starts at 12 months after diagnosis, 0 months at the x-axis is 12 months after diagnosis.

long term survival.[18,28] In the current study a doubling of AST at diagnosis resulted in 27% decrease in HR. Patients with high levels of aminotransferases at diagnosis more often have symptoms and less often have decompensated cirrhosis.[28] The increased rate of symptoms could lead to earlier diagnosis and treatment. Better treatment response in patients with high aminotransferases at diagnosis was previously suggested by another study.[18] As aminotransferases at diagnosis was a predictor that was independent from aminotransferases during treatment, better treatment response will not completely explain this finding.

This study has some limitations. Owing to the landmark analysis, we excluded all patients with liver transplantation or mortality before the landmark. This means that study conclusions are only generalizable to subjects who have survived until the landmark time. Especially patients with acute (on chronic) liver failure needing urgent transplantation within 6 months are therefore not included in this study. For such patients, the 2-week response of international normalized ratio and bilirubin indicates short-term prognosis.[29]

Values at especially 24 and 36 months were available in a smaller number of patients. Owing to the relatively good prognosis of AIH with treatment, only a limited number of events occurred, which limits the number of variables that could be included in multivariate analysis.

As patients with AST < ULN at 12 months had the best long-term prognosis, this should be the first treatment aim. After this maintenance of normal AST should be the second aim. The benefit of treatment response should be balanced against the side effects of treatment: in individual patients who experience a high burden of side effects despite adjusting immunosuppression, accepting mildly elevated aminotransferases up to 1.5× ULN could be considered, as the relationship of mildly elevated aminotransferases with long-term survival was limited.

In conclusion, aminotransferases during treatment were significantly associated with long-term transplant-free survival, independent of age, aminotransferases at diagnosis, and cirrhosis. Elevated IgG was not predictive for long-term transplant-free survival in the first year of treatment. Normalization of aminotransferases in the first year should be the first treatment aim in AIH, although the benefit in transplant-free survival should be balanced against the side effects in individual patients.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.05.024.

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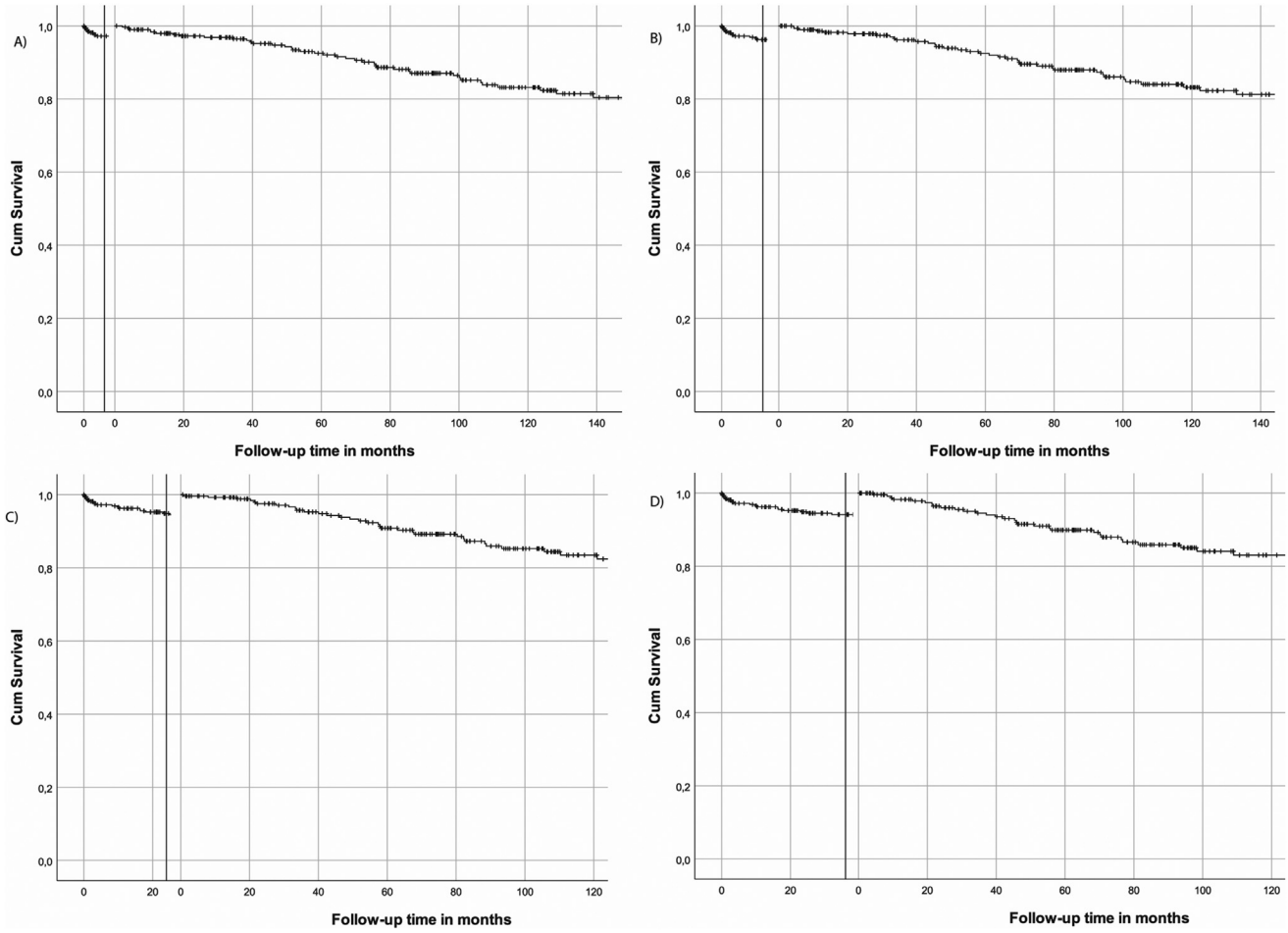

Supplementary Figure 1. The relation between the used landmark analysis at (*A*) 6 months, (*B*) 12 months, (*C*) 24 months, and (*D*) 36 months and transplant-free survival. The black vertical line represents the landmark.

Supplementary Table 1. Univariate Cox Regression With a Landmark at 6, 24, and 36 Months for Predictors of Liver Transplant–Free Survival

	Hazard Ratio (95% CI)	*P* Value
6 mo		
Age	1.02 (1.01–1.04)	.007
Ln ALT × ULN	1.28 (0.89–1.83)	.19
Ln AST × ULN	2.29 (1.43–3.66)	.001
Ln AP × ULN	1.64 (1.14–2.38)	.008
Ln GGT × ULN	1.79 (1.29–2.49)	.001
IgG × ULN	1.53 (0.73–3.21)	.26
24 mo		
Age	1.03 (1.01–1.05)	.004
Ln ALT × ULN	1.63 (0.88–3.05)	.12
Ln AST × ULN	2.29 (1.41–3.72)	.001
Ln AP × ULN	1.72 (0.91–3.25)	.096
Ln GGT × ULN	2.57 (1.89–3.50)	.001
IgG × ULN	2.29 (1.07–4.89)	.032
36 mo		
Age	1.03 (1.01–1.05)	.005
Ln ALT × ULN	1.32 (0.84–2.06)	.25
Ln AST × ULN	3.03 (1.37–6.72)	.008
Ln AP × ULN	2.06 (0.93–4.57)	.076
Ln GGT × ULN	2.33 (1.44–3.79)	.001
IgG × ULN	4.17 (1.14–15.3)	.031

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; IgG, immunoglobulin G; ULN, upper limit of normal.

Supplementary Table 2. Baseline Characteristics of Patients With Pediatric Onset and Adult Onset

	Median (Range)	Pediatric	Adult	*P* Value
N		27	270	
Female	225 (75)	17 (63)	204 (76)	.153
Age at diagnosis, y	51 (6–84)	14 (6–17)	53 (18–84)	<.001
Caucasian	270 (90)	19 (70)	247 (91)	.003
Cirrhosis	85 (28)	11 (41)	72 (27)	.143
Laboratory values				
Bilirubin, μmol/L	29 (3–596)	41 (7–486)	26 (3–596)	.322
ALT × ULN	11.2 (0.35–146)	16 (0.35–79.5)	10 (0.75–146)	.228
AST × ULN	11.0 (0.61–161)	21 (0.74–104)	10 (0.65–161)	.028
AP × ULN	1.45 (0.23–19.1)	2.62 (0.91–6.0)	1.39 (0.23–19.1)	<.001
GGT × ULN	3.64 (0.05–24.0)	2.23 (0.78–5.78)	3.92 (0.05–24.0)	.008
IgG × ULN	1.34 (0.42–4.69)	2.00 (0.98–4.69)	1.3 (0.42–4.25)	.001
6 mo				
Bilirubin, μmol/L	11 (2–89)	10 (5–89)	11 (8–88)	.987
ALT × ULN	1.00 (0.22–25.8)	1.20 (0.33–6.03)	1.00 (0.22–25.8)	.475
AST × ULN	1.13 (0.35–25.8)	1.38 (0.58–4.19)	1.10 (0.35–25.8)	.182
AP × ULN	0.67 (0.08–9.54)	1.02 (0.09–4.23)	0.66 (0.08–9.54)	.013
GGT × ULN	1.45 (0.21–55.7)	1.39 (0.31–6.05)	1.43 (0.21–55.7)	.730
IgG × ULN	0.78 (0.29–2.31)	0.75 (0.52–2.29)	0.78 (0.29–2.31)	.606
12 mo				
Bilirubin, μmol/L	11 (2–325)	15 (6.8–325)	11 (2–138)	.050
ALT × ULN	0.88 (0.23–14.6)	1.03 (0.45–9.93)	0.87 (0.23–14.6)	.117
AST × ULN	1.03 (0.39–38.0)	1.35 (0.58–38.0)	1.00 (0.39–11.1)	.043
AP × ULN	0.77 (0.22–9.26)	1.27 (0.47–9.26)	0.73 (0.22–3.23)	<.001
GGT × ULN	1.11 (0.26–13.7)	0.96 (0.29–7.21)	1.11 (0.26–13.7)	.531
IgG × ULN	0.78 (0.36–2.09)	0.79 (0.56–2.08)	0.78 (0.36–2.09)	.579
24 mo				
ALT × ULN	0.79 (0.18–9.38)	1.29 (0.36–8.79)	0.76 (0.18–9.38)	.058
AST × ULN	0.94 (0.39–13.6)	1.35 (0.46–13.6)	0.94 (0.39–8.86)	.160
AP × ULN	0.70 (0.20–3.57)	1.16 (0.50–3.57)	0.69 (0.20–3.41)	.017
GGT × ULN	0.84 (0.18–27.0)	1.20 (0.34–5.33)	0.84 (0.18–27.0)	.507
IgG × ULN	0.78 (0.31–3.18)	0.92 (0.31–3.18)	0.74 (0.36–2.09)	.092
36 mo				
ALT × ULN	0.87 (0.16–6.88)	1.12 (0.27–2.22)	0.85 (0.16–6.88)	.731
AST × ULN	1.03 (0.29–7.00)	1.16 (0.29–1.94)	1.03 (0.42–7.00)	.985
AP × ULN	0.72 (0.20–3.31)	0.80 (0.47–2.71)	0.72 (0.20–3.31)	.462
GGT × ULN	0.84 (0.13–12.1)	0.51 (0.18–12.1)	0.87 (0.13–8.16)	.049
IgG × ULN	0.83 (0.38–2.00)	0.81 (0.39–1.36)	0.83 (0.38–2.00)	.548

Values are n (%) or median (range).
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT γ-glutamyltransferase; IgG, immunoglobulin G; ULN, upper limit of normal.

Supplementary Table 3. Univariate Cox Regression of Patients With an Adult Onset of AIH

	Hazard Ratio (CI)	P-Value
Baseline		
Female	0.87 (0.43–1.78)	.71
Non-Caucasian	2.73 (1.30–5.74)	.008
Cirrhosis	3.24 (1.75–5.99)	<.001
Ln ALT × ULN	0.55 (0.42–0.72)	<.001
Ln AST × ULN	0.71 (0.54–0.92)	.009
Ln AP × ULN	1.20 (0.75–1.94)	.446
Ln GGT × ULN	1.32 (0.91–1.90)	.139
IgG × ULN	1.08 (0.67–1.72)	.753
12 mo		
Age	1.03 (1.00–1.05)	.013
Ln ALT × ULN	1.76 (1.19–2.61)	.005
Ln AST × ULN	2.97 (1.89–4.66)	<.001
Ln AP × ULN	2.19 (1.26–3.81)	.006
Ln GGT × ULN	2.16 (1.51–3.08)	<.001
IgG × ULN	1.63 (0.64–4.18)	.306
Complete biochemical remission	0.42 (0.19–0.95)	.037
Normalization ALT and AST	0.41 (0.20–0.86)	.019

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT γ-glutamyltransferase; IgG, immunoglobulin G; ULN, upper limit of normal.

Supplementary Table 4. Multivariate Cox Regression With Landmark at 6, 12, 24, and 36 Months for Liver Transplant–Free Survival

	Hazard Ratio (95% CI)	*P* Value
6 mo		
Age	1.04 (1.02–1.05)	<.001
Cirrhosis at diagnosis	2.95 (1.55–5.62)	.001
Ln ALT × ULN at diagnosis	0.57 (0.41–0.78)	<.001
Ln ALT × ULN at 6 mo	1.68 (1.06–2.67)	.028
12 mo		
Age	1.03 (1.01–1.04)	.001
Cirrhosis at diagnosis	2.15 (1.16–3.99)	.016
Ln ALT × ULN at diagnosis	0.56 (0.42–0.75)	<.001
Ln ALT × ULN at 12 mo	1.97 (1.26–3.09)	.003
24 mo		
Age	1.04 (1.02–1.07)	<.001
Cirrhosis at diagnosis	2.71 (1.32–5.56)	.007
Ln ALT × ULN at diagnosis	0.61 (0.44–0.83)	.002
Ln ALT × ULN at 24 mo	1.97 (0.99–3.92)	.053
36 mo		
Age	1.04 (1.02–1.06)	<.001
Cirrhosis at diagnosis	2.76 (1.37–5.60)	.005
Ln ALT × ULN at diagnosis	0.60 (0.43–0.82)	.002
Ln ALT × ULN at 36 mo	2.76 (1.37–5.60)	.075

ALT, alanine aminotransferase; CI, confidence interval; ULN, upper limit of normal.