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Rapid Response to Treatment of Autoimmune Hepatitis Associated With Remission at 6 and 12 Months

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BACKGROUND & AIMS: **Changes in serum levels of transaminases immediately after initiation of treatment for autoimmune hepatitis (AIH) might be associated with biochemical markers of remission and liver-related events. We assessed the outcomes of patients with vs without rapid response to treatment of AIH in a large international cohort.**

METHODS: **We performed a retrospective cohort study, collecting data from 2 independent cohorts of adults with AIH from 12 centers in 7 countries in Europe. We collected information on patient demographics; serologic, histologic, and biochemical analyses; and treatment. We used a receiver operating characteristic curve and Youden index to calculate the optimal percentage decrease in level of aspartate aminotransferase (AST) after 8 weeks of treatment that associated with normalization of transaminase levels after 26 weeks of treatment with predniso(lo)ne (primary outcome) in the first (discovery) cohort (n = 370). We evaluated the results in the second (validation) cohort (n = 370). Secondary outcomes were liver-related death or transplantation. We performed univariate and multivariable logistic and Cox regression with correction for confounders.**

RESULTS: **A significant decrease in level of AST after 8 weeks of treatment was significantly associated with normalization of transaminase levels at 26 and 52 weeks ($P < .001$); a decrease of more than 80% in level of AST was associated with optimal normalization. In both cohorts, rapid responders (≥80% decrease in level of AST after 8 weeks) were more likely to achieve normalization of transaminases at 26 and 52 weeks when compared to non-rapid responders. Rapid responders in the discovery cohort had lower risk of liver-related death or transplantation (adjusted hazard ratio 0.18; 95% CI 0.05–0.63; $P = .007$), although this was not**

[a]Member of the European Reference Network RARE-LIVER.

Abbreviations used in this paper: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; OR, odds ratio; ULN, upper limit of normal.

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confirmed in the validation cohort. Results from measurement of alanine aminotransferase did not differ significantly from those of AST for the primary outcome. Slow responders (without normalization of transaminases after 1 year) had the highest risk of liver transplantation or liver-related death.

CONCLUSIONS: **In a retrospective study of patients with AIH, we found that a rapid response to treatment, based on level of AST after 8 weeks, associates with normalization of transaminase levels in the following year. Patients with a rapid response also have a lower risk of liver-related death or transplantation than patients without this rapid response.**

Keywords: Induction Therapy; Prognostic Factor; Liver Enzyme; Steroid.

Autoimmune hepatitis (AIH) is a rare, chronic liver disease that is characterized by elevated serum transaminases and IgG, inflammatory liver histology, and presence of circulating autoantibodies.[1,2] Treatment consists of induction therapy with corticosteroids followed by maintenance therapy with azathioprine.[3] Biochemical remission is defined as normalization of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and IgG below the upper limit of normal (ULN). This endpoint is associated with low histologic disease activity and regression of fibrosis.[4]

Reports on the relationship between elevation and dynamics of transaminases and relevant outcomes are limited. Cases with AST levels greater than 10 times ULN at presentation have a lower risk of developing cirrhosis and had a better long-term outcome.[5] Patients who do not achieve at least a 50% decrease of transaminases within 6 months run an increased risk for liver transplantation.[6]

A large proportion of patients with AIH have a rapid decline of serum transaminases in the first weeks after initiation of steroids, persisting throughout treatment. The exact relationship between the rapidity of decline in transaminases during treatment and long-term clinical events, such as liver transplantation and liver-related mortality, is unknown. We hypothesized that patients with a rapid decrease in transaminases have a higher probability to achieve biochemical remission and a lower risk for liver-related morbidity later in time. Therefore, we used data from 2 independent cohorts of patients with AIH to investigate the relationship between early treatment response and the effect on biochemical remission, liver-related mortality, and liver transplantation.

Methods

Study Design

We performed a retrospective cohort study, establishing 2 independent cohorts of patients with AIH from 12 centers across 7 countries in Europe. We included patients with a probable or definite AIH diagnosis according to the simplified International Autoimmune Hepatitis Group score.[7–9] When patients scored as "no AIH" by the simplified criteria, but were treated by their physicians as patients with AIH, the revised score was used to calculate a score per patient. Only patients with a pretreatment score >10 were classified as AIH and were included in our study. Only patients who were ≥18 years old at time of diagnosis were included. We excluded patients who had variant syndromes with primary biliary cholangitis; primary sclerosing cholangitis; or other forms of liver disease, such as viral hepatitis and nonalcoholic steatohepatitis. Ethics approval was waived after review by local institutional review board.

Data Collection

Patient data were retrieved from patient records and local databases. We collected demographics variables, serologic, histologic, biochemical, and treatment variables. The original pathology report was used to classify a patient as cirrhotic. Additionally, data on mortality and liver transplantation were collected. Laboratory values were collected at baseline and after 8, 26, and 52 weeks of therapy.

Outcomes

Primary outcomes were normalization of transaminases after 26 and 52 weeks of treatment. The gender-specific ULN for ALT and AST of each center was used. Secondary endpoints included biochemical remission, defined as normalization of transaminases and normal serum IgG after 26 and 52 weeks of treatment, liver-related mortality or liver transplantation, all-cause mortality, and development of hepatocellular carcinoma. In case of missing ALT or AST values at the 26- or 52-week time point, we used last observation carried forward to account for missing values.

Analysis

We randomly generated a discovery and validation cohort with stratification for baseline predniso(lo)ne dose. First, we analyzed the correlation between percentage decrease of AST after 8 weeks and normalization of transaminases after 26 weeks in the discovery cohort

(n = 370) using a receiver operating characteristic curve analysis. The Youden index was calculated to generate a cutoff level of percentage of AST decrease after 8 weeks.

Second, patients from the discovery cohort were divided into 2 groups based on the cutoff, generated from the first analysis. Patients with a percentage fall of AST after 8 weeks above the cutoff were classified as "rapid responders" and were compared with patients with a fall of AST below the cutoff. Univariate comparisons between the 2 groups were made with the chi-square test, Mann-Whitney *U* test, or Student *t* test as appropriate. We applied logistic regression to determine endpoints in the 2 groups of patients. The final regression model included institute, cirrhosis, acute-severe AIH (AS-AIH defined as a presentation with an international normalized ratio ≥1.5 without evidence of cirrhosis[10]), predniso(lo)ne dose, use of maintenance therapy, AST at baseline, and bilirubin at baseline. Results of the multivariable logistic regression are presented as odds ratio (OR) and 95% confidence interval (CI). We used Kaplan-Meier curves with log-rank testing and Cox regression with adjustment for confounders for the composite endpoint of liver-related mortality and transplantation. Results of the Cox regression analysis are presented as hazard ratio (HR) with 95% CI.

Third, the cutoff generated from the discovery cohort was used to determine outcomes in the validation cohort (n = 370). We performed similar univariate and multivariable analyses as in the discovery cohort. Fourth, we performed a subgroup analysis in both cohorts combined on patients with cirrhosis at presentation. Additionally, we performed exploratory analyses targeting slow responders who achieved normalization of transaminases at Week 52. Analysis for the primary and secondary outcomes was also performed with percentage ALT decrease as the independent variable in both cohorts. $P < .05$ was considered statistically significant. Statistical analysis was performed using SPSS version 25 (IBM Corporation, Armonk, NY).

What You Need to Know

Background

Changes in serum levels of transaminases immediately after initiation of treatment for autoimmune hepatitis (AIH) might be associated with biochemical markers of remission and liver-related events.

Findings

In a retrospective study of patients with AIH, we found that a rapid response to treatment, based on level of aspartate aminotransferase after 8 weeks, associates with normalization of transaminase levels at 26 and 52 weeks. Patients with a rapid response also have a lower risk of liver-related death or transplantation than patients without this rapid response. Patients with a slow response and without normalization of transaminases after one year had the highest chance of liver transplantation or liver related death.

Implications for patient care

Levels of aminotransferases to should monitored immediate after patients with AIH begin treatment with steroids, to identify those likely to respond.

Results

Population

Both the discovery and validation cohort consisted of 370 patients. Most patients were female (74.5%). Patients in the validation cohort were slightly older at time of diagnosis compared with patients in the discovery cohort (49.58 years vs 47.09 years; $P = .04$). Other baseline and treatment characteristics were comparable between the cohorts (Supplementary Table 1).

Receiver Operating Characteristic Analysis

Percentage decrease of AST after 8 weeks of treatment was significantly associated with normalization of transaminases at 26 weeks of treatment in receiver operating characteristic analysis (area under the curve, 0.65; 95% CI, 0.59–0.71; $P < .001$). The highest Youden index was 0.274, which corresponded with an AST decrease of 80%. This percentage was used as cutoff to determine patients with a rapid treatment response. Corresponding sensitivity, specificity, and positive predictive value were 64.6%, 62.8%, and 77.3%, respectively.

Discovery Cohort: Baseline Characteristics

Of all patients in the discovery cohort, 60.8% (225/370) of patients were scored as rapid treatment responders (≥80% AST decrease after 8 weeks). Rapid responders had significantly higher transaminases (ALT × ULN 21.34 vs 3.27; $P < .001$; AST × ULN 19.29 vs 2.61; $P < .001$) and total bilirubin (107 vs 21 μmol/L; $P < .001$) levels at baseline when compared with patients without a rapid treatment response (Table 1). Rapid responders were less likely to have cirrhosis at baseline when compared with slow responders (13.8% vs 24.1%; $P = .01$) and were more likely to have AS-AIH (21.8% vs 6.9%; $P < .001$). Patients with a rapid treatment response were treated with higher initial predniso(lo)ne dosages (0.73 mg/kg/day vs 0.50 mg/kg/day; $P < .001$).

Discovery Cohort: Outcomes

Rapid responders had higher rates of normalization of transaminases at 26 weeks compared with patients

Table 1. Baseline and Treatment Characteristics of the Discovery Cohort

	<80% AST decrease at week 8 (n = 145)	≥80% AST decrease at week 8 (n = 225)	*P* value
Female sex, n (%)	105 (72.4)	171 (76)	.44
Age at diagnosis, *y* (SD)	48.08 (16.39)	46.46 (16.07)	.35
Probable AIH diagnosis, n (%)	66 (45.5)	100 (44.4)	.84
Definite AIH diagnosis, n (%)	79 (54.4)	125 (55.6)	.84
ALT × ULN, median (IQR)	3.27 (5.59)	21.34 (28.31)	< .001
AST × ULN, median (IQR)	2.61 (4.16)	19.29 (22.70)	< .001
Bilirubin (*μmol/L*), median (IQR)	21 (37.5)	107 (207.1)	< .001
INR, median (IQR)[a]	1.10 (0.29)	1.25 (0.54)	< .001
IgG (*g/L*), median (IQR)	17.73 (13.2)	20.0 (11.7)	.07
Cirrhosis, n (%)	35 (24.1)	31 (13.8)	.01
AS-AIH, n (%)	10 (6.9)	49 (21.8)	< .001
Treatment characteristics			
Prednisone dose at start (*mg/kg*), median (IQR)	0.50 (0.44)	0.73 (0.81)	< .001
Predniso(lo)ne dose at start (*mg/d*), median (IQR)	40 (40)	50 (68)	< .001
On predniso(lo)ne at 26 wk, n (%)	96 (96.0)	149 (94.3)	.54
Predniso(lo)ne dose at 26 wk (*mg/d*), median (IQR)	7.5 (10.0)	7.5 (5.0)	.04
On predniso(lo)ne at 52 wk, n (%)	62 (82.7)	113 (82.5)	.97
Predniso(lo)ne dose at 52 wk (*mg/d*), median (IQR)	5.0 (7.5)	5.0 (5.0)	.46
Use of maintenance therapy at wk 26, n (%)	105 (72.4)	173 (76.9)	.33
AZA	86 (59.3)	148 (65.8)	.21
MMF	4 (2.8)	6 (2.7)	.96
TAC	1 (0.7)	2 (0.9)	.84
6-MP	7 (4.8)	8 (3.6)	.55
6-TG	0	1 (0.4)	.42
CsA	3 (2.1)	4 (1.8)	.84
Other	1 (0.7)	3 (1.3)	.56

NOTE. Patients are divided into 2 groups based on their treatment response.
6-MP, 6-mercaptopurine; 6-TG, 6-tioguanine; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; AZA, azathioprine; CsA, cyclosporine; IAIHG, International Autoimmune Hepatitis Group; INR, international normalized ratio; IQR, interquartile range; MMF, mycophenolate mofetil; SD, standard deviation; TAC, tacrolimus; ULN, upper limit of normal.
[a]Available for 291 patients.

with a slower treatment response: 77.3% vs 57.2% ($P <$ .001). This difference persisted after 52 weeks of treatment: 86.7% of rapid responders had normalization of transaminases versus 64.8% of nonrapid responders ($P <$ .001). In a subgroup of patients with available IgG (n = 227 for 26 weeks, n = 210 for 52 weeks), we found that biochemical remission rates were higher in the rapid responders when compared with nonrapid responders: 77.1% versus 52.9% ($P <$ .001) and 79.7% versus 61.2% ($P =$ .004) or 26 and 52 weeks, respectively (Table 2).

Multivariable logistic regression showed that rapid responders had a higher probability to reach normalization of transaminases after 26 weeks (OR, 3.63; 95% CI, 1.94–6.79; $P <$ .001) and 52 weeks (OR, 4.99; 95% CI, 2.44–10.24; $P <$.001) of treatment. The same results were observed for biochemical remission in patients with available IgG: ORs were 4.51 (95% CI, 2.05–9.92; $P <$.001) and 2.77 (95% CI, 1.18–6.47; $P =$ .02) for 26 and 52 weeks, respectively (Table 3). In a sensitivity analysis in a dataset without imputed AST and ALT values we found similar significant results ($P <$ .001 for normalization of transaminases at both 26 and 52 weeks).

To exclude the presence of cirrhosis as a confounder, we performed a sensitivity analysis in patients without cirrhosis at time of diagnosis in the discovery cohort, which demonstrated consistency with our primary analysis. Rapid responders without cirrhosis had a higher chance of normalization of transaminases at 26 and 52 weeks of treatment when compared with those without cirrhosis who responded slower (OR, 3.62; 95% CI, 1.81–7.26; $P <$ .001 and OR, 4.18; 95% CI, 1.87–9.36; $P =$ .001 for Week 26 and 52, respectively).

During a median follow-up of 6.2 years, liver-related death or liver transplantation, as a composite endpoint, occurred less frequently in rapid responders: 3.1% versus 15.9% (log-rank $P <$ .001) (Figure 1). This also held for all-cause mortality, which occurred in 4.9% of rapid responders versus 13.9% in slow responders (log-rank $P =$ .001). Multivariable Cox regression showed that rapid responders were at a lower risk of liver-related death or transplantation (adjusted HR, 0.18; 95% CI, 0.05–0.63; $P =$ .007) and for all-cause mortality (adjusted HR, 0.26; 95% CI, 0.09–0.75; $P =$ .01). Development of hepatocellular carcinoma occurred only in the slow responder group (2.8% vs 0%; $P =$ .01).

Slow responders in the discovery cohort who did not achieve normalization of transaminases after 52 weeks of treatment had higher rates of liver-related death or liver transplantation when compared with slow responders that did achieve normalization of transaminases after

Table 2. Outcomes in the Discovery Cohort: Patients With a Rapid Treatment Response (>80% AST Decrease After 8 Weeks of Treatment) Versus Patients Without a Rapid Treatment Response

	<80% AST decrease at week 8 (n = 145)	≥80% AST decrease at week 8 (n = 225)	*P* value
Normal transaminases at 26 wk, n (%)	83 (57.2)	174 (77.3)	< .001
Biochemical remission at 26 wk, n (%)[a]	46 (52.9)	108 (77.1)	< .001
Predniso(lo)ne dose ≤10 mg at 26 wk, n (%)	32 (22.1)	77 (34.2)	.01
Normal transaminases at 52 wk, n (%)	94 (64.8)	195 (86.7)	< .001
Biochemical remission at 52 wk, n (%)[b]	41 (61.2)	114 (79.7)	.004
Predniso(lo)ne dose ≤10 mg at 52 wk, n (%)	65 (44.8)	125 (55.6)	.04
Liver-related death or LTx, n (%)	23 (15.9)	7 (3.1)	< .001
All-cause mortality, n (%)	20 (13.9)	11 (4.9)	.002
HCC development, n (%)	4 (2.8)	0	.01

NOTE. Primary outcome was normalization of transaminases after 26 and 52 weeks of treatment. For patients with available IgG, we performed a subgroup analysis for biochemical remission.
AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; LTx, liver transplantation.
[a]Data available for 227 patients.
[b]Data available for 210 patients.

52 weeks: 35.3% versus 5.3% ($P < .001$). This difference remained significant after multivariable Cox regression (adjusted HR, 0.13; 95% CI, 0.03–0.52; $P = .004$). Slow responders who did not have normal transaminases after 52 weeks had higher pretreatment transaminases and bilirubin and were more frequently cirrhotic (Supplementary Table 2). Similar observations were made in the validation cohort: slow responders that did not reach normal transaminases after 52 weeks had numerically higher rates of liver-related death or liver transplantation, although this did not reach statistical significance: 16.0% versus 8.4% ($P = .17$). However, when corrected for confounders in the multivariate Cox regression, reaching normal transaminases at Week 52 predicted a lower chance of liver-related death or transplantation (adjusted HR, 0.27; 95% CI, 0.08–0.84; $P = .02$).

Validation Cohort: Baseline Characteristics

In the validation cohort, 60.8% (225/370) of patients were assigned to the rapid responder group. We observed similar differences in baseline characteristics as in the discovery cohort: rapid responders had higher ALT, AST, bilirubin, and IgG at baseline (Supplementary Table 3). Cirrhosis was unevenly but not significantly distributed among rapid and slow responders (14.7% vs 20.7%; $P = .13$). AS-AIH occurred in rapid responders (13.7%) and slow responders (8.3%; $P = .11$). Rapid responders were treated with significantly higher prednisolone dosages when compared with slow responders (0.71 mg/kg/day vs 0.51 mg/kg/day; $P < .001$), whereas use of maintenance therapy at Week 26 did not differ (73.3% vs 69.0%; $P = .36$).

Validation Cohort: Outcomes

Consistent with the results in the discovery cohort, we found that rapid responders were more likely to achieve normalization of transaminases after 26 and 52 weeks of treatment (73.3% vs 51.7%; $P < .001$ and 83.6% vs 65.5%; $P < .001$). The observation was made in patients with available IgG for biochemical remission after 26 and 52 weeks (72.8% vs 42.0%; $P < .001$ and 84.4% vs 56.8%; $P < .001$) (Table 4).

Multivariable logistic regression showed a significant advantage for rapid responders for normalization of transaminases after 26 and 52 weeks (OR, 2.97; 95% CI, 1.66–5.33; $P < .001$ and OR, 2.45; 95% CI, 1.28–4.69; $P = .007$), or for biochemical remission at the same time

Table 3. Results of the Discovery Cohort After Multivariable Logistic Regression and Cox Regression for Patients With a ≥80% AST Decrease After 8 Weeks of Treatment

Logistic regression	Uncorrected OR	*P* value	Corrected OR	*P* value
Normal transaminases at 26 wk	2.55 (1.62–4.01)	< .001	3.63 (1.94–6.79)	< .001
Biochemical remission at 26 wk	3.01 (1.69–5.36)	< .001	4.51 (2.05–9.92)	< .001
Normal transaminases at 52 wk	3.53 (2.11–5.90)	< .001	4.99 (2.44–10.24)	< .001
Biochemical remission at 52 wk	2.49 (1.32–4.72)	.005	2.77 (1.18–6.47)	.02
Cox regression	**Uncorrected HR**	***P* value**	**Corrected HR**	***P* value**
Liver-related death or LTx	0.18 (0.08–0.43)	< .001	0.18 (0.05–0.63)	.007
All-cause mortality	0.32 (0.15–0.67)	.002	0.26 (0.09–0.75)	.01

NOTE. In all multivariable analyses we adjusted for institute, cirrhosis, AS-AIH, predniso(lo)ne dose, use of maintenance therapy, AST at baseline, and bilirubin at baseline.
AS-AIH, acute-severe AIH; AST, aspartate aminotransferase; HR, hazard ratio; OR, odds ratio; LTx, liver transplantation.

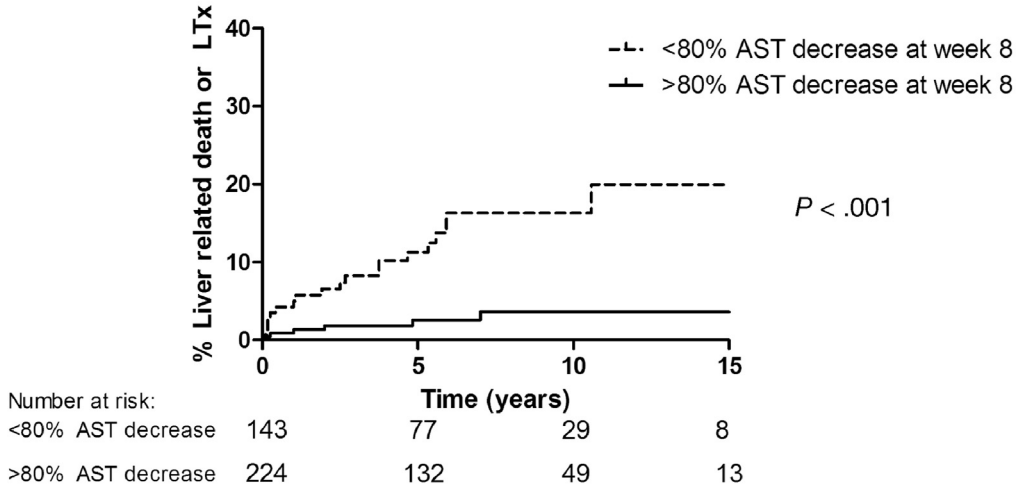

Figure 1. Kaplan-Meier curve of liver-related death or transplantation over time in the discovery cohort. Patients with an AST decrease of ≥80% are compared with patients with an AST decrease <80% (log-rank $P < .001$). LTx, liver transplantation.

points (OR, 3.62; 95% CI, 1.68–7.82; $P = .001$ and OR, 4.34; 95% CI, 1.77–10.65; $P = .001$) (Table 5).

During a median follow-up of 6.2 years, liver-related death or liver transplantation occurred more frequently in slow responders: 11.0% versus 3.6% (log-rank p = .006) (Supplementary Figure 1). A multivariable Cox regression failed to assign statistical significance (adjusted HR, 0.47; 95% CI, 0.16–1.39; $P = .17$). Similar results were seen for all-cause mortality (9.0% vs 4.9%; log rank p = .14; adjusted HR, 0.68; 95% CI, 0.26–1.79; $P = .15$).

Table 4. Outcomes in the Validation Cohort: Patients With a Rapid Treatment Response (>80% AST Decrease After 8 Weeks of Treatment) Versus Patients Without a Rapid Treatment Response

	<80% AST decrease at week 8 (n = 145)	≥80% AST decrease at week 8 (n = 225)	*P* value
Normal transaminases at 26 wk, n (%)	75 (51.7)	165 (73.3)	< .001
Biochemical remission at 26 wk, n (%)[a]	34 (42.0)	99 (72.8)	< .001
Predniso(lo)ne dose ≤10 mg at 26 wk, n (%)	33 (22.8)	71 (31.6)	.07
Normal transaminases at 52 wk, n (%)	95 (65.5)	188 (83.6)	< .001
Biochemical remission at 52 wk, n (%)[b]	50 (56.8)	114 (84.4)	< .001
Predniso(lo)ne dose ≤10 mg at 52 wk, n (%)	67 (46.2)	135 (60.0)	.009
Liver-related death or LTx, n (%)	16 (11.0)	8 (3.6)	.004
All-cause mortality, n (%)	13 (9.0)	11 (4.9)	.12
HCC development, n (%)	0	0	—

NOTE. Primary outcome was normalization of transaminases after 26 and 52 weeks of treatment. For patients with available IgG, we performed a subgroup analysis for biochemical remission.

AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; LTx, liver transplantation.

[a]Data available for 217 patients.

[b]Data available for 229 patients.

Sensitivity Analysis With Alanine Aminotransferase

We performed a sensitivity analysis in patients with available ALT at Week 8 in the discovery cohort (n = 326) and the validation cohort (n = 337). In both cohorts we found that rapid responders based on ALT had a higher likelihood for normalization of transaminases and biochemical remission when compared with slow responders. The composite endpoint of liver transplantation and liver-related death was significant in the discovery cohort, but not in the validation cohort after Cox regression (Supplementary Tables 4 and 5).

Subgroup Analysis in Patients With Cirrhosis

We performed a subgroup analysis in patients from both cohorts combined who had cirrhosis at presentation (Supplementary Table 6). Sixty-four (49.6%) were rapid responders. In rapid responding patients with cirrhosis, rates of normalization of transaminases were higher than in those with a slow response: 73.4% versus 44.6% ($P = .001$) and 79.7% versus 47.7% ($P < .001$) for 26 weeks and 52 weeks, respectively, which remained significant in the multivariable analysis (OR, 8.93; 95% CI, 2.69–29.69; $P < .001$; OR, 5.95; 95% CI, 1.92–18.50; $P = .002$). Rates of biochemical remission were also higher in the univariate analysis in rapid responding patients with cirrhosis: 70% versus 40% ($P = .009$) and 77.5% versus 48.5% ($P = .01$) for 26 weeks and 52 weeks, respectively. Only the 26-week time point remained significant in the multivariable analysis ($P = .04$ and $P = .42$ for Week 26 and 52, respectively). The composite endpoint of liver-related death or transplantation occurred less often in rapid responding patients with cirrhosis: 6.3% versus 27.7% ($P = .001$), although there was no significant difference in the multivariable analysis ($P = .13$).

Table 5. Results of the Validation Cohort After Multivariable Logistic Regression and Cox Regression for Patients With a ≥80% AST Decrease After 8 Weeks of Treatment

Logistic regression	Uncorrected OR	*P* value	Corrected OR	*P* value
Normal transaminases at 26 wk	2.57 (1.65–3.98)	< .001	2.97 (1.66–5.33)	< .001
Biochemical remission at 26 wk	3.70 (2.07–6.61)	< .001	3.62 (1.68–7.82)	.001
Normal transaminases at 52 wk	2.67 (1.64–4.37)	< .001	2.45 (1.28–4.69)	.007
Biochemical remission at 52 wk	4.11 (2.21–7.64)	< .001	4.34 (1.77–10.65)	.001
Cox regression	**Uncorrected HR**	***P* value**	**Corrected HR**	***P* value**
Liver-related death or LTx	0.33 (0.14–0.77)	.01	0.47 (0.16–1.39)	.17
All-cause mortality	0.55 (0.25–1.14)	.15	0.68 (0.26–1.79)	.43

Note. In all multivariable analyses we adjusted for institute, cirrhosis, AS-AIH, predniso(lo)ne dose, use of maintenance therapy, AST at baseline, and bilirubin at baseline.
AS-AIH, acute-severe AIH; AST, aspartate aminotransferase; HR, hazard ratio; OR, odds ratio; LTx, liver transplantation.

Discussion

We show that patients with AIH with a substantial decrease (≥80%) of transaminases in the first 8 weeks of treatment have a high chance of normalization of transaminases and biochemical remission after 26 and 52 weeks of treatment. A rapid treatment response was independently associated with a lower risk of liver-related death or liver transplantation, although only in the discovery cohort. The clinical consequence of these observations is that ≥80% decrease in transaminase levels within 8 weeks of treatment initiation may serve as a predictor of long-term disease course and serves as a clinical tool for patient stratification. Additionally, we found that patients with AIH with a slow treatment response who failed to reach normalization of transaminases after 1 year of treatment were at the highest risk for development of liver-related mortality or transplantation.

High transaminases were associated with a rapid response and it is possible these patients with acute AIH are more susceptible to immunosuppressive treatment. Lower baseline transaminases in the slow responders might suggest a subclinical or protracted disease course in the months/years preceding diagnosis, leading to a delay in initiation of effective therapy, and poorer response rates.[11] Theoretically, a rapid and intense suppression of the inflammatory response may lead to hepatic stellate cell deactivation, cease proliferation of myelofibroblasts, and prevent fibrosis development.[12]

Earlier studies on predictors of treatment response showed that a diagnosis <18 years old, histologic cirrhosis, and positive soluble liver antigen/liver pancreas antigen were associated with poor short- and long-term outcome.[13] However, the concept of rapidity of treatment response and its consequences has been largely unexplored. Results of our study accord with those of The King's College group who described an association between baseline AST levels and cirrhosis development and long-term outcome.[5] Patients with AST levels at diagnosis less than 10 times ULN had a higher risk on liver transplantation or death. Similarly, patients had higher bilirubin levels and less cirrhosis at time of diagnosis. Our study provides new and important clinical information because we show that transaminase dynamics surpass a single AST measurement as a predictor for outcomes in AIH. To further illustrate this, we stratified patients from both cohorts combined according to their initial AST elevation, which shows that a rapid response has predictive value, regardless of baseline AST level (Supplementary Table 7). Our data accord with another, much smaller study that demonstrated that a rapid treatment response (defined as a response within 6 months after treatment initiation) mitigated the risk for the development of cirrhosis and need for liver transplantation.[14]

We found that there is a wide phenotypical heterogeneity of AIH, in terms of variation of transaminases at presentation. Both slow responders and AIH cirrhotics have lower transaminases on presentation.[15,16] However, our sensitivity analysis in patients without cirrhosis gave similar results, excluding cirrhosis as a confounding factor. Moreover, a rapid treatment response after 8 weeks of treatment is associated with improved outcomes regardless of presence of cirrhosis. These findings indicate that even in in patients with cirrhosis, rapidity of treatment response acts as a prognostic factor, although the statistical power precludes us to confirm the benefit for our composite outcome of liver-related death or transplantation.

Our study comes with limitations. First, because of its retrospective design, it carries selection bias. Only patients who had available serum transaminases in the first weeks of treatment were included in this study. However, the large number of participating centers allows us to collect a large AIH cohort that reflects real-world practice. Second, rapid responders were treated with higher predniso(lo)ne dosages, suggesting that steroid dose might act as a confounder. Indeed, we noticed that in a subgroup of patients with available data, cumulative steroid dosages in the first year of treatment were slightly lower in slow responders, although this was not statistically significant. However, we have shown

previously that initial steroid dose is independent from the likelihood of biochemical remission.[17,18] We adjusted for steroid dose in the logistic regression model, which gave similar results to the univariate analysis. Third, we used normalization of transaminases as our primary endpoint, which contrasts international guidelines that state that complete biochemical remission, including normalization of IgG, should be the desired endpoint in AIH.[3,19] We found that IgG levels were not as frequently measured as guidelines stipulate. This suggests decision making in routine care is based on transaminases alone. Therefore, we chose to incorporate biochemical remission as a secondary endpoint for patients with an available IgG at the time points of interest, which yield similar results as our primary analysis.

Fourth, we do not provide data on histologic disease activity at diagnosis or follow-up. Very few centers use the hepatitis activity index in their histology reports. Practical and logistic hurdles hampered us from revising all the biopsy samples from the patients in our cohort. Although older studies questioned the relationship between normalization of serum markers and complete histologic remission,[20,21] a recent study confirmed that biochemical remission is associated with histologic disease activity and regression of fibrosis.[4] Fifth, the concept of rapid treatment response described in this study is only applicable to patients that reach the 8-week time point. Our model is of little value for patients with AIH who present with acute liver failure that warrants immediate escalation of therapy or transplantation because they were excluded from our study. Sixth, we included patients with AS-AIH in both our cohorts and included them in our primary analysis. Although a subgroup analysis without AS-AIH showed similar results (data not shown), one could consider to exclude patients with AS-AIH in future studies, given the differences in presentation, kinetics, and prognosis. Lastly, missing data points hampered us from investigating other predictive models that had a slightly better performance than a model with AST only. Additionally, we were unable to analyze various factors that might have played a role in treatment outcomes, such as compliance to therapy, flares of AIH, and drug levels. Future studies should prospectively validate models that include a combination of ALT, AST, and bilirubin after 8 weeks of treatment.

The results of our study underline that a rapid and substantial amelioration of biochemical inflammatory activity is an important prognostic factor for remission of AIH. The absence of such a response after 8 weeks might be used to identify patients that might benefit from intensified monitoring and escalation of treatment, although this hypothesis needs future prospective research. Because we observed that a large proportion of patients without a rapid response ultimately achieved biochemical remission, clinicians should be encouraged to continue adequate immunosuppression with the goal of later remission. In clinical practice, patients with AIH should be monitored intensively during the first weeks after initiation of treatment, to obtain a clear picture of dynamics of transaminases.

To conclude, patients with AIH with a rapid treatment response after 8 weeks of treatment have a favorable disease course with a high likelihood of biochemical remission and possibly a reduced risk for liver-related mortality and liver transplantation. Moreover, these results suggest that stratification according to early treatment response may also identify patients at greatest risk and need for treatment intensification.

Supplementary Material

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.2019.11.013.

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The authors disclose no conflicts.

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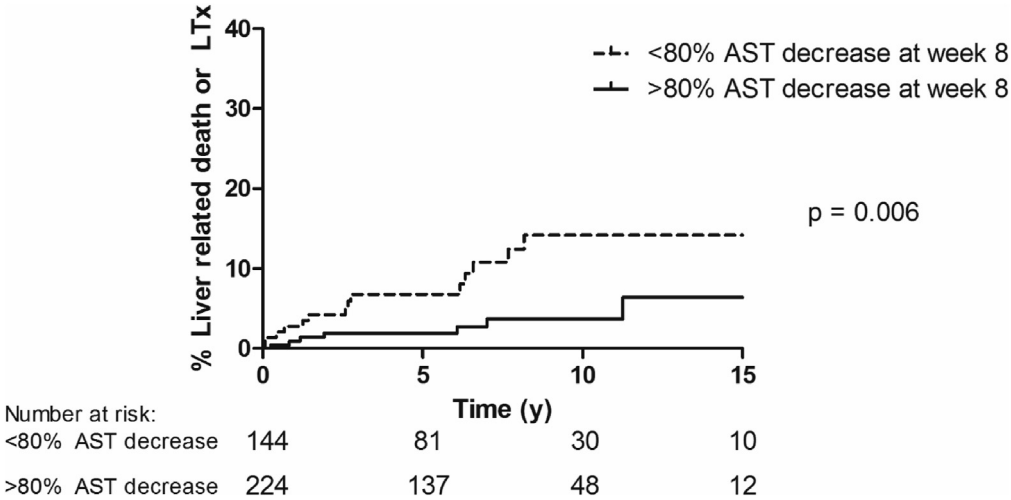

Supplementary Figure 1. Kaplan-Meier curve of liver-related death or transplantation over time in the validation cohort. Patients with an AST decrease of ≥80% are compared with patients with an AST decrease <80% (log-rank $P = .006$). LTx, liver transplantation.

Supplementary Table 1. Baseline and Treatment Characteristics of the Discovery and Validation Cohort

	Discovery cohort (n = 370)	Validation cohort (n = 370)	*P* value
Female sex, n (%)	276 (74.6)	275 (74.3)	.93
Age at diagnosis, *y* (SD)	47.09 (16.19)	49.58 (16.49)	.04
Probable AIH diagnosis, n (%)	166 (44.9)	151 (40.8)	.27
Definite AIH diagnosis, n (%)	204 (55.1)	219 (59.2)	.27
ALT × ULN, median (IQR)	11.3 (23.04)	9.81 (21.84)	.88
AST × ULN, median (IQR)	10.13 (19.52)	10.45 (22.19)	.80
Bilirubin (*μmol/L*), median (IQR)	40 (145.2)	42.5 (152.3)	.41
INR, median (IQR)[a]	1.10 (0.30)	1.20 (0.34)	< .001
IgG (*g/L*), median (IQR)	21.1 (11.2)	18.4 (12.2)	.06
Cirrhosis, n (%)	66 (17.8)	63 (17.0)	.77
AS-AIH, n (%)	59 (15.9)	43 (11.6)	.09
Treatment characteristics			
Prednisone dose at start (*mg/kg*), median (IQR)	0.62 (0.59)	0.63 (0.57)	.83
Predniso(lo)ne dose at start (*mg/d*), median (IQR)	40 (45)	40 (46)	.87
On predniso(lo)ne at 26 wk, n (%)	245 (95.0)	243 (94.2)	.70
Predniso(lo)ne dose at 26 wk (*mg/d*), median (IQR)	7.5 (5.0)	7.5 (5.0)	.42
On predniso(lo)ne at 52 wk, n (%)	175 (82.5)	184 (82.1)	.91
Predniso(lo)ne dose at 52 wk (*mg/d*), median (IQR)	5.0 (5.0)	5.0 (5.0)	.81
Use of maintenance therapy at wk 26, n (%)	278 (75.1)	265 (71.6)	.28
AZA	234 (63.2)	224 (60.5)	.45
MMF	10 (2.7)	7 (1.9)	.46
TAC	3 (0.8)	7 (1.9)	.20
6-MP	15 (4.1)	11 (3.0)	.43
6-TG	1 (0.3)	3 (0.8)	.32
CsA	7 (1.9)	8 (2.2)	.79
Other	8 (2.2)	5 (1.4)	.40

6-MP, 6-mercaptopurine; 6-TG, 6-tioguanine; ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; AZA, azathioprine, CsA, cyclosporine; IAIHG, International Autoimmune Hepatitis Group; INR, international normalized ratio; IQR, interquartile range; MMF, mycophenolate mofetil; SD, standard deviation; TAC, tacrolimus; ULN, upper limit of normal.

[a]Available for 288 patients.

Supplementary Table 2. Baseline Comparison of Slow Responders in the Discovery Cohort

Slow responders (n = 145) in discovery cohort	Abnormal transaminases at week 52 (n = 51)	Normal transaminases at week 52 (n = 94)	*P* value
Female sex, n (%)	34 (66.7)	71 (75.5)	.25
Age at diagnosis, *y* (SD)	50.31 (16.06)	46.86 (16.53)	.23
Probable AIH diagnosis, n (%)	22 (43.1)	44 (46.8)	.67
Definite AIH diagnosis, n (%)	29 (56.9)	50 (53.2)	.67
ALT × ULN, median (IQR)	4.25 (10.34)	2.67 (3.93)	< .001
AST × ULN, median (IQR)	3.78 (4.81)	2.10 (3.43)	< .001
Bilirubin (*μmol/L*), median (IQR)	36.0 (44.0)	14.68 (25.9)	< .001
INR, median (IQR)	1.2 (0.36)	1.1 (0.19)	< .001
IgG (*g/L*), median (IQR)	23.2 (13.4)	17.1 (8.8)	.01
Cirrhosis, n (%)	20 (39.2)	15 (16.0)	.002
AS-AIH, n (%)	6 (11.8)	4 (4.3)	.09

NOTE. Slow responders in the discovery cohort who did not achieve normalization of transaminases at Week 52 had higher baseline ALT, AST, and bilirubin and were more frequently cirrhotic.
ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

Supplementary Table 3. Baseline and Treatment Characteristics of the Validation Cohort

	<80% AST decrease at week 8 (n = 145)	≥80% AST decrease at week 8 (n = 225)	*P* value
Female sex, n (%)	104 (71.7)	171 (76.0)	.36
Age at diagnosis, *y* (SD)	50.08 (15.74)	49.26 (16.92)	.64
Probable AIH diagnosis, n (%)	52 (35.9)	99 (44.0)	.12
Definite AIH diagnosis, n (%)	93 (64.1)	126 (56.0)	.12
ALT × ULN, median (IQR)	3.5 (4.83)	22.89 (26.48)	< .001
AST × ULN, median (IQR)	2.87 (4.38)	22.39 (23.24)	< .001
Bilirubin (*μmol/L*), median (IQR)	17 (26.5)	85.5 (171.1)	< .001
INR, median (IQR)[a]	1.18 (0.45)	1.18 (0.35)	.82
IgG (*g/L*), median (IQR)	19.6 (9.5)	21.8 (12.0)	.02
Cirrhosis, n (%)	30 (20.7)	33 (14.7)	.13
AS-AIH, n (%)	12 (8.3)	31 (13.8)	.11
Treatment characteristics			
Prednisone dose at start (*mg/kg*), median (IQR)	0.53 (0.51)	0.71 (0.72)	< .001
Predniso(lo)ne dose at start (*mg/d*), median (IQR)	40 (35)	40 (60)	< .001
On predniso(lo)ne at 26 wk, n (%)	97 (96.0)	146 (93.0)	.31
Predniso(lo)ne dose at 26 wk (*mg/d*), median (IQR)	7.5 (5.0)	7.5 (5.0)	.08
On predniso(lo)ne at 52 wk, n (%)	67 (84.8)	117 (80.7)	.44
Predniso(lo)ne dose at 52 wk (*mg/day*), median (IQR)	5.0 (7.0)	5.0 (5.0)	.02
Use of maintenance therapy at wk 26, n (%)	100 (69.0)	165 (73.3)	.36
AZA	82 (56.6)	143 (63.1)	.21
MMF	3 (2.1)	4 (1.8)	.84
TAC	4 (2.8)	3 (1.3)	.33
6-MP	2 (1.4)	9 (4.0)	.15
6-TG	1 (0.7)	2 (0.9)	.84
CsA	5 (3.4)	3 (1.3)	.17
Other	2 (1.4)	0	.08

NOTE. Patients are divided into 2 groups based on their treatment response.
6-MP, 6-mercaptopurine; 6-TG, 6-tioguanine; ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; AZA, azathioprine; CsA, cyclosporine; IAIHG, International Autoimmune Hepatitis Group; INR, international normalized ratio; IQR, interquartile range; MMF, mycophenolate mofetil; SD, standard deviation; TAC, tacrolimus; ULN, upper limit of normal.
[a]Available for 579 patients.

Supplementary Table 4. Outcomes in the Discovery Cohort: Sensitivity Analysis in Patients With a Rapid Treatment Response Based on ALT Instead of AST (>80% ALT Decrease After 8 Weeks of Treatment

	<80% ALT decrease at week 8 (n = 145)	≥80% ALT decrease at week 8 (n = 182)	*P* value
Normal transaminases at 26 wk, n (%)	79 (54.5)	142 (78.0)	< .001
Biochemical remission at 26 wk, n (%)[a]	45 (53.6)	87 (77.0)	.001
Normal transaminases at 52 wk, n (%)	93 (64.1)	157 (86.3)	< .001
Biochemical remission at 52 wk, n (%)[b]	42 (60.0)	93 (83.8)	< .001
Liver-related death or LTx, n (%)	21 (14.5)	7 (3.8)	.001
All-cause mortality, n (%)	19 (13.2)	10 (5.5)	.02
Logistic regression	**Uncorrected OR**	***P* value**	**Corrected OR**	***P* value**
Normal transaminases 26 wk	2.97 (1.84–4.79)	< .001	5.53 (2.83–1 .80)	< .001
Biochemical remission 26 wk	2.90 (1.57–5.35)	.001	4.76 (2.11–1 .70)	< .001
Normal transaminases 52 wk	3.51 (2.04–6.04)	< .001	6.58 (3.08–14.06)	< .001
Biochemical remission 52 wk	3.44 (1.72–6.90)	< .001	5.15 (2.05–12.95)	< .001
Cox regression	**Uncorrected HR**	***P* value**	**Corrected HR**	***P* value**
Liver-related death or LTx	0.21 (0.09–0.51)	.001	.28 (.09– .93)	.04
All-cause mortality	0.36 (0.17–0.77)	.009	.51 (.18–1.44)	.20

ALT, alanine aminotransferase; HR, hazard ratio; LTx, liver transplantation; OR, odds ratio.
[a]Data available for 197 patients.
[b]Data available for 181 patients.

Supplementary Table 5. Outcomes in the Validation Cohort: Sensitivity Analysis in Patients With a Rapid Treatment Response Based on ALT Instead of AST (>80% ALT Decrease After 8 Weeks of Treatment

	<80% ALT decrease at week 8 (n = 143)	≥80% ALT decrease at week 8 (n = 194)	*P* value
Normal transaminases at 26 wk, n (%)	73 (51.0)	140 (72.2)	< .001
Biochemical remission at 26 wk, n (%)[a]	35 (44.3)	80 (72.1)	< .001
Normal transaminases at 52 wk, n (%)	94 (65.7)	157 (80.9)	.002
Biochemical remission at 52 wk, n (%)[b]	50 (57.5)	94 (83.2)	< .001
Liver-related death or LTx, n (%)	15 (10.5)	9 (4.6)	.04
All-cause mortality, n (%)	13 (9.1)	10 (5.2)	.16
Logistic regression	**Uncorrected OR**	***P* value**	**Corrected OR**	***P* value**
Normal transaminases 26 wk	2.49 (1.58–3.91)	< .001	2.88 (1.57–5.28)	.001
Biochemical remission 26 wk	3.24 (1.77–5.96)	< .001	3.76 (1.65–8.59)	.002
Normal transaminases 52 wk	2.21 (1.35–3.64)	.002	2.00 (1.04–3.86)	.04
Biochemical remission 52 wk	3.36 (1.90–7.02)	< .001	3.42 (1.36–8.56)	.01
Cox regression	**Uncorrected HR**	***P* value**	**Corrected HR**	***P* value**
Liver-related death or LTx	0.47 (0.21–1.08)	.08	.83 (.29–2.42)	.74
All-cause mortality	0.65 (0.28–1.49)	.31	.91 (.32–2.57)	.85

ALT, alanine aminotransferase; HR, hazard ratio; LTx, liver transplantation; OR, odds ratio.
[a]Data available for 190 patients.
[b]Data available for 200 patients.

Supplementary Table 6. Baseline Characteristics and Outcomes of Patients With Cirrhosis at Presentation

Baseline	<80% AST decrease at week 8 (n = 65)	≥80% AST decrease at week 8 (n = 64)	*P* value
Female sex, n (%)	47 (72.3)	44 (68.8)	.66
Age at diagnosis, *y* (SD)	49.45 (16.85)	51.64 (16.07)	.45
Prednisone dose at start (*mg/kg*), median (IQR)	0.51 (0.48)	0.62 (2.01)	.02
ALT × ULN, median (IQR)	3.09 (5.30)	16.20 (21.12)	< .001
AST × ULN, median (IQR)	3.03 (4.12)	17.71 (20.66)	< .001
Bilirubin (*μmol/L*), median (IQR)	27.0 (38.6)	83 (234)	< .001
IgG (*g/L*), median (IQR)	19.1 (16.1)	20.7 (15.6)	.35
Outcomes, n (%)			
Normal transaminases at 26 wk	29 (44.6)	47 (73.4)	.001
Biochemical remission at 26 wk[a]	14 (40)	28 (70.0)	.009
Predniso(lo)ne dose ≤10 mg at 26 wk	16 (24.6)	23 (35.9)	.16
Normal transaminases at 52 wk	31 (47.7)	51 (79.7)	< .001
Biochemical remission at 52 wk[b]	16 (48.5)	31 (77.5)	.01
Predniso(lo)ne dose ≤10 mg at 52 wk	26 (40)	35 (54.7)	.10
Liver-related death or LTx	18 (27.7)	4 (6.3)	.001
All-cause mortality	15 (23.1)	7 (10.6)	.07
HCC development	2 (3.1)	0	.16

ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; IQR, interquartile range; LTx, liver transplantation.
[a]Data available for 75 patients.
[b]Data available for 73 patients.

Supplementary Table 7. Rates of Normalization of Transaminases in Both Cohorts Combined

	<80% AST decrease at week 8	>80% AST decrease at week 8	*P* value
AST at baseline 0.28–4.81 × ULN			
Normal transaminases at week 26, n (%)	136 (66.3)	35 (87.5)	.008
AST baseline 4.82–19.31 × ULN			
Normal transaminases at week 26, n (%)	16 (22.2)	128 (74.4)	< .001
AST baseline 19.32–140 × ULN			
Normal transaminases at week 26, n (%)	3 (30.0)	173 (74.2)	.002

NOTE. Patients are stratified according to their AST elevation at baseline. Patients with low AST at baseline but a rapid AST response demonstrate higher rates of normalization of transaminases compared with patients without such a response, even compared when patients have initial high AST. AST, aspartate aminotransferase; ULN, upper limit of normal.