



ORIGINAL ARTICLE

Well-controlled autoimmune hepatitis treatment withdrawal may be safely accomplished without liver-biopsy guidance

John Guirguis^{1,*}, Yilien Alonso², Rocio Lopez³, William Carey⁴

¹Department of Internal Medicine, Blake Medical Center, Bradenton, FL, USA, ²Department of Gastroenterology, Ochsner Health System, New Orleans, LA, USA, ³Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA and ⁴Digestive Disease Institute, Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, USA

*Corresponding author. Department of Internal Medicine, Blake Medical Center, 2020 59th St West, Bradenton, FL 34209, USA. Tel: +1-216-466-4367; Email: John_Kimy@hotmail.com

Abstract

Background: Autoimmune hepatitis may flare up after treatment withdrawal, especially in those who had not achieved histological remission but had normal liver enzymes. The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) Guidelines recommend performing liver biopsy before treatment withdrawal. The aim of the study is to define the outcome of treatment withdrawal in adults with well-controlled disease for 2 years with and without liver-biopsy guidance.

Methods: A retrospective observational study was conducted on biopsy-proven autoimmune hepatitis patients who were treated for 2 years and with persistently normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) or nearly so for 6 months prior to treatment withdrawal. Exclusions were: juvenile onset autoimmune hepatitis and prior treatment or use of agents other than corticosteroids and azathioprine. The primary endpoint was to define freedom from flare-ups for 1 year after treatment withdrawal.

Results: Thirty-four consecutive subjects meeting study criteria were identified. Treatment withdrawal was accomplished in 24 subjects without liver-biopsy guidance and 10 had pre-treatment withdrawal liver biopsy. Demographics, immunosuppressive usage, pre-treatment cirrhosis and pre-treatment liver enzymes were similar between the two groups, and 25% had an enzyme flare-up within 12 months after treatment withdrawal, which was similar in the two groups (20.8 vs 30.0%, $P = 0.57$).

Conclusions: Adults with autoimmune hepatitis and excellent response to therapy for 2 years are candidates for treatment withdrawal without the need for liver biopsy.

Key words: Autoimmune hepatitis; liver biopsy; treatment withdrawal; liver enzyme

Submitted: 22 January 2018; Revised: 26 February 2018; Accepted: 8 May 2018

© The Author(s) 2018. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-Sen University

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Introduction

Liver enzyme normalization in autoimmune hepatitis (AIH) precedes the histological resolution of inflammation. Since normal liver enzymes do not always reflect histological disease activity, liver biopsy has often been recommended before a decision to withdraw treatment is made.

The most recent American Association for the Study of Liver Disease (AASLD) guideline favors histological evidence of remission via biopsy before treatment withdrawal [1]. These recommendations are based on studies by Czaja *et al.* and Verma *et al.* [2, 3]. Liver biopsy is the most accurate diagnostic method used in patients with AIH; nevertheless, it carries significant morbidity and, to a lesser degree, mortality [4]. Others have demonstrated a close correlation between normalization of liver enzymes with the absence of interface hepatitis and residual plasma cells within the portal tract [5, 6]. Conversely, others have shown that histological resolution of features of AIH does not predict off-treatment flare-ups. Our study aims to address the question of whether persistent normalization or near normalization of the liver enzymes over 2 years will be adequate for decision-making for treatment withdrawal.

Because of the ongoing disagreement regarding the value of liver biopsy prior to treatment withdrawal, we sought to examine the experience in our large hepatology practice. We hypothesized that we could reduce cost, morbidity and mortality associated with liver biopsy without affecting patient safety using non-invasive measures to judge the timeline for treatment withdrawal in AIH patients. A retrospective observational study was conducted in our large academic practice in order to explore the adequacy of using liver tests alone as an indicator of likelihood of freedom from flare-ups after treatment withdrawal in healthy patients with well-controlled AIH. The study was performed by analysing the last 15 years of adult patients with AIH and well controlled on treatment for 2 years with a 1-year follow-up period after treatment withdrawal in our practice. We studied treatment-withdrawal outcomes of patients treated in a large hepatology practice in which treating physicians vary in reliance on liver biopsy as a tool to decide to withdraw treatment.

Materials and methods

Study design

This report describes a retrospective observational study conducted in a large academic center. After Institute Review Board (IRB) approval, records were probed for patients with the diagnosis of AIH or chronic active hepatitis from January 2000 until April 2015. The diagnosis was based on a liver-biopsy finding typical for AIH backed up with proper circulating autoantibodies (i.e. antinuclear antibody [ANA], anti-smooth muscle antibody [ASMA], anti-liver-kidney microsome [LKM] and IgG levels). A typical AIH finding upon biopsy consisted of the presence of interface hepatitis (i.e. portal and peri-portal plasma cell infiltration). All patients included in the study received standard treatment with good response to treatment initiation. Liver biopsies were conducted within 3 months of the diagnosis date.

Inclusion and exclusion criteria

Patients were included in the study if they were at least 18 years of age and experiencing their first episode of AIH. Only patients who started immunosuppressive therapy and were eligible for treatment withdrawal based on histological remission upon biopsy, persistent normalization or near normalization of their liver enzymes

were included in the analysis. Patients should have had at least 2 years of follow-up from the time of the diagnosis and at least 1 year of follow-up after treatment withdrawal. Liver enzymes, IgG levels (whenever available), ANA and ASMA were recorded for all of the included patients. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were recorded every 6 months from the time of the treatment start. Liver enzymes were followed every 6 months for at least 1 year after treatment withdrawal.

Patients were excluded if they did not have histologically demonstrated AIH or if their biopsies exhibited overlap with other liver pathologies. Patients with juvenile AIH and patients on agents other than corticosteroids or azathioprine (i.e. tacrolimus or mycophenolate mofetil) were excluded. Lastly, the presence of other diseases that require long-term immunosuppressive treatment (i.e. systemic lupus erythematosus) were excluded, but patients with other autoimmune diseases that did not require long-term immunosuppressive therapy were included (i.e. thyroiditis) in the analysis. All of the results were recorded in an Excel spreadsheet and were analysed by the Section of Biostatistics at Cleveland Clinic Foundation.

Since this study is retrospective, we aimed to decrease the incidence of bias in including or excluding patients by reviewing the reasons for inclusion or exclusion by two separate investigators, as well as having the final list be revised by the principle investigator in the study (according to Strobe checklist).

Patient stratification and endpoints

Subjects were stratified into two groups: patients were placed in the liver-biopsy positive (LB+) group if, prior to treatment withdrawal, a liver biopsy was performed and showed complete resolution of hepatocyte inflammation (Grade 0). The liver-biopsy negative (LB-) group included patients of whom the treatment-withdrawal decision was based on the persistent normalization or near normalization of liver enzymes for at least 2 years. Normalization of the liver enzymes was defined as ALT and AST less than the upper limit of normal.

Outcome measures in the two groups included recurrence rate, sustainability of remission, death and orthotopic liver transplant (OLT). The primary endpoint was a flare-free interval within 1 year of treatment withdrawal. Patients were considered to have had a flare-up if they needed to reinstitute immunosuppressive therapy based on clinician decision and increase in liver enzymes. Secondary endpoints included the likelihood of developing liver decompensation, OLT or death within the first year after treatment withdrawal. Liver decompensation was outlined as the development of coagulopathy, ascites or hepatic encephalopathy. In the LB+ group, the levels of inflammation and fibrosis before and after treatment were examined to determine whether there was a correlation between the level of inflammation or fibrosis and the incidence of flare-ups. Patients included in the study had not developed serious adverse events through the study time, with no mortality recorded in the study population at the end of the study in both groups.

Statistical analysis

Data are presented as median (25th, 75th percentiles) or frequency (percent). Univariable analysis was performed to compare subjects with and without liver biopsy prior to stopping immunosuppressive therapy. The non-parametric Kruskal-Wallis test was used for continuous and ordinal factors, and Pearson's chi-square test or Fisher's Exact test were used for categorical factors. In addition, a time-to-event analysis was conducted to assess occurrence of

flare-ups. Follow-up time was defined as months from treatment end to occurrence of flare-ups or May 2016 if there were no flare-ups and was truncated at 18 months. A Kaplan–Meier plot was constructed, and a log-rank test was used to assess differences between subjects with and without biopsy. Moreover, an invariable Cox regression analysis was performed to evaluate factors associated with risk of flare. A $P < 0.05$ was considered to be statistically significant. All analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC).

Results

We reviewed the records of 508 patients with the diagnosis of AIH or chronic active hepatitis between January 2000 and April 2015. Thirty-four patients met criteria for inclusion. Ten patients were in the LB+ group. The other 24 patients were in the LB– group. Figure 1 depicts patient stratification based on initial biopsy status and associated flare-ups.

Prior to treatment initiation

There were no significant differences between the characteristics of the two groups. The average ages were 48 years in the LB+ group and 53 years in the LB– group. The severity of the disease's effect on the liver, as demonstrated by degree of inflammation, as well as stage of fibrosis, was similar between the two groups. Biopsies pre-treatment showed significant inflammation (Stages 3 and 4) in 15 (62.5%) patients of the LB– group versus 6 (60.0%) in the LB+ group, significant fibrosis (Grade 3 and 4) in 13 (54.2%) patients of the LB– group vs 3 (30.0%) in the LB+ group. There was no difference between both groups in terms of the immunosuppression used or the duration of treatment. ALT elevation prior to treatment initiation was similar between the two groups (Table 1).

During the active treatment period

ALT and AST were checked during the 2 years of treatment and compared between the two groups. Transaminase values were analysed using a Kruskal–Wallis test, Pearson's chi-square test and Fisher's Exact test, with cutoffs being set to the upper limit of normal (ULN) and two times the upper limit of normal (2xUNL). No statistically significant differences were noted in the level of elevation of the liver enzymes during the treatment

period with a P -value of 0.39 for ULN of both ALT and AST and 0.99 for 2xUNL of ALT and AST (Table 2).

Post-treatment follow-up period

Transaminases were checked after treatment withdrawal at least every 6 months for 1 year in the LB+ and LB– groups. The median length of follow-up was 11.4 months for the LB+ group and 11.7 months for the LB– group with a P -value of 0.84. Again, no statistically significant differences were noted during the post-treatment withdrawal follow-up period in the degree of elevation of both ALT and AST between the two groups (Figure 2 and Table 3). In addition, there was no documented death or transplantation in any of the 34 subjects. The degree of fibrosis in the LB+ group showed regression post treatment in 30% of the patients (Table 4).

A time-to-event analysis was performed to assess risk of flare-ups between the groups (Figure 3). Flare-free rate at 1 year was 80% (95% confidence interval [CI]: 41–95%) for those with biopsy compared to 85% (95% CI: 60–95%) for subjects without biopsy. No other factor was observed to be associated with higher risk of flare-ups. Univariate analysis showed that 33.3% of patients on prednisone alone had flare-up with a P -value of 0.045 (Table 5). A multivariable analysis was not performed, as there were fewer than 10 patients with a flare-up.

Discussion

There is no significant difference basing the treatment-withdrawal decision on histological evidence of remission vs persistent normalization of the liver function in patients with AIH. Several studies have shown that there might be a correlation between the incidence of flare-up and IgG levels [6]. Although IgG levels were not tested in our study, we could not identify other factors that may predict the occurrence of flare-ups in either group, as shown in Table 5. Furthermore, there was no mortality difference observed between the two patient groups in our study.

Other studies have shown that histological remission might not correlate well with biochemical remission in AIH patients leading to a second biopsy prior to a treatment-withdrawal decision, similarly to the study conducted by Putra *et al.* [7], although, in that study, only 6 out of the 20 patients enrolled in the study had biopsy for the treatment-withdrawal decision, and

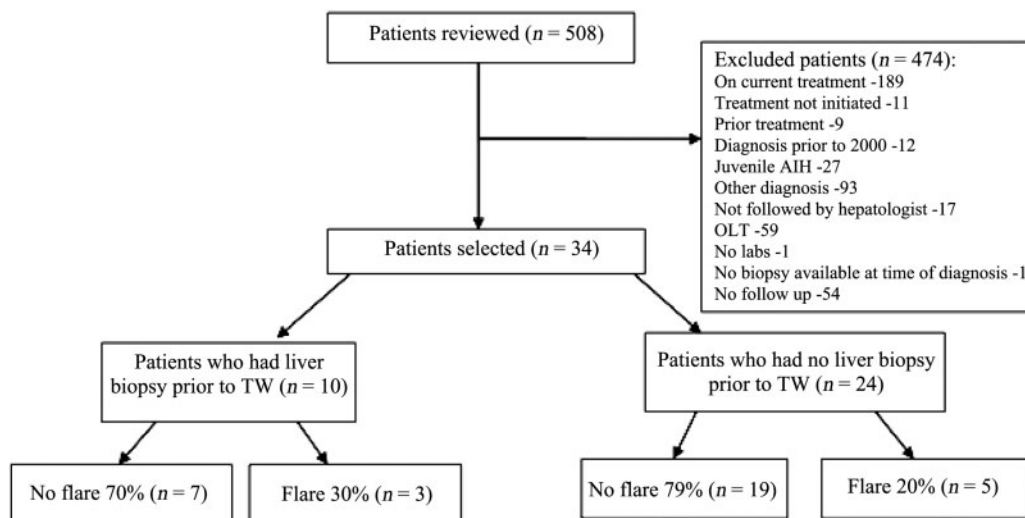


Figure 1. Patient stratification based on biopsy status and associated flare-ups. TW, treatment withdrawal; OLT, orthotopic liver transplant.

Table 1. Patient demographics and pre-treatment clinical characteristics

Factor	Total (N = 34)		No biopsy done (N = 24)		Biopsy done (N = 10)		P-value
	N	Statistics	N	Statistics	N	Statistics	
Gender	34		24		10		0.54 ^a
Male		3 (8.8)		3 (12.5)		0 (0.0)	
Female		31 (91.2)		21 (87.5)		10 (100.0)	
Age at time of diagnosis	34	54.0 [39.0, 65.0]	24	50.0 [36.5, 62.0]	10	60.5 [48.0, 65.0]	0.082 ^b
AIH duration at treatment start, months	34	0.00 [0.00, 0.62]	24	0.00 [0.00, 0.44]	10	0.00 [0.00, 0.75]	0.93 ^b
Duration of treatment, months	34	21.7 [15.6, 31.3]	24	21.7 [13.4, 31.1]	10	22.5 [17.7, 35.1]	0.73 ^b
ANA	32		22		10		0.81 ^b
Negative		13 (40.6)		10 (45.5)		3 (30.0)	
Weakly positive		10 (31.3)		5 (22.7)		5 (50.0)	
Positive		1 (3.1)		1 (4.5)		0 (0.0)	
Strongly positive		8 (25.0)		6 (27.3)		2 (20.0)	
ASMA titer	31	0.0 [0.0, 2.0]	23	0.0 [0.0, 2.0]	8	1.0 [0.0, 2.5]	0.45 ^b
Pre-treatment inflammation	34		24		10		0.53 ^b
1		7 (20.6)		5 (20.8)		2 (20.0)	
2		6 (17.6)		4 (16.7)		2 (20.0)	
3		13 (38.2)		11 (45.8)		2 (20.0)	
4		8 (23.5)		4 (16.7)		4 (40.0)	
Pre-treatment fibrosis	34		24		10		0.56 ^b
0		4 (11.8)		3 (12.5)		1 (10.0)	
1		2 (5.9)		2 (8.3)		0 (0.0)	
2		12 (35.3)		6 (25.0)		6 (60.0)	
3		13 (38.2)		11 (45.8)		2 (20.0)	
4		3 (8.8)		2 (8.3)		1 (10.0)	
Pre-treatment total bilirubin, mg/dL	34	1.50 [0.60, 3.10]	24	1.05 [0.55, 3.00]	10	2.20 [0.90, 3.70]	0.35 ^b
Pre-treatment alkaline phosphatase, U/L	33	156 [107, 270]	23	163 [109, 341]	10	134 [104, 168]	0.35 ^b
Pre-treatment ALT, U/L	34	356 [160, 949]	24	295 [159, 981]	10	503.5 [303, 910]	0.57 ^b
Pre-treatment AST, U/L	34	312.5 [136, 762]	24	280.5 [137, 698]	10	513.5 [124, 780]	0.62 ^b

Statistics presented as median [P25, P75] or N (column %).

P-values: ^a = Fisher's Exact test, ^b = Kruskal-Wallis test.

AIH, autoimmune hepatitis; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2. Labs during active treatment

Factor	Total (N = 32)*	No biopsy done (N = 22)*	Biopsy done (N = 10)	P-value
Achieved normalization of ALT anytime during treatment	28 (87.5)	18 (81.8)	10 (100.0)	0.28 ^a
Achieved normalization of AST anytime during treatment	30 (93.8)	20 (90.9)	10 (100.0)	0.99 ^a
Months from last lab during active treatment to treatment withdrawal	4.3 [1.3, 9.7]	6.0 [3.3, 11.1]	1.3 [0.3, 4.4]	0.059 ^b
Last pre-stoppage lab available				
Total bilirubin, mg/dL	0.45 [0.30, 0.70]	0.40 [0.30, 0.60]	0.60 [0.30, 0.80]	0.44 ^b
Alkaline phosphatase, U/L	71.0 [64.0, 102.0]	71.0 [66.0, 94.0]	71.5 [61.0, 110.0]	0.85 ^b
ALT, U/L	24.0 [17.5, 42.0]	26.0 [17.0, 45.0]	20.0 [18.0, 27.0]	0.25 ^b
ALT (ULN)				0.39 ^a
Normal (<45)	25 (78.1)	16 (72.7)	9 (90.0)	
Abnormal (≥45)	7 (21.9)	6 (27.3)	1 (10.0)	
ALT (2xULN)				0.99 ^a
Normal (<90)	31 (96.9)	21 (95.5)	10 (100.0)	
Abnormal (≥90)	1 (3.1)	1 (4.5)	0 (0.0)	
AST, U/L	30.5 [22.0, 36.0]	29.5 [22.0, 51.0]	31.0 [27.0, 36.0]	0.95 ^b
AST (ULN)				0.39 ^a
Normal (<40)	25 (78.1)	16 (72.7)	9 (90.0)	
Abnormal (≥40)	7 (21.9)	6 (27.3)	1 (10.0)	
AST (2xULN)				0.99 ^a
Normal (<80)	30 (93.8)	20 (90.9)	10 (100.0)	
Abnormal (≥80)	2 (6.3)	2 (9.1)	0 (0.0)	

*Two subjects without a pre-stoppage biopsy did not have a peri-treatment lab available.

Statistics presented as median [P25, P75] or N (column %).

Multivariate analysis was not performed because <10 patients had experienced a flare.

P-values: ^a = Fisher's Exact test, ^b = Kruskal-Wallis test.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

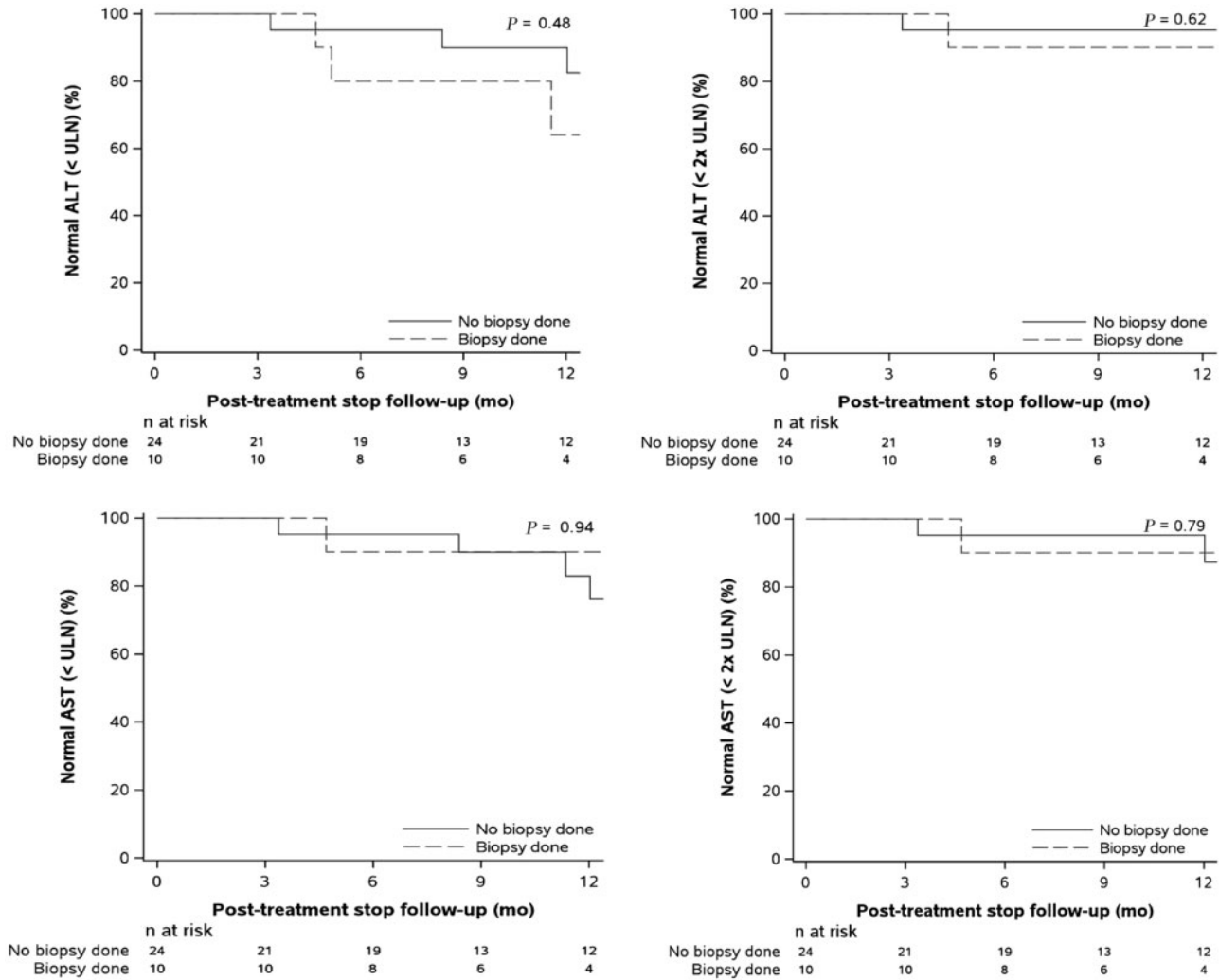


Figure 2. Actuarial curves for post-treatment lab follow-up in the two groups.

approximately 40% underwent the biopsy for elevated liver enzymes, which was different from our study population. The lag period between the biochemical and histological remission usually varies from 3 to 8 months [8]. This observation has influenced clinical practice guidelines from AASLD. Both the European Association for the Study of the Liver (EASL) and the British Society of Gastroenterology (BSG) Guidelines published in 2011 mentioned that a second biopsy should be individualized, as it facilitated documentation of inflammation resolution but did not alter the patient's ultimate outcome [9, 10]. The relevance of the short-term (3–8 months) lag between enzyme normalization and histological activity may not extend to those whose liver enzymes were normal for >12 months. Our data provide added clarity and evidence that treatment withdrawal in a selected population (i.e. patients with well-controlled disease for 2 years) can be achieved successfully without the need to repeat liver biopsy.

Our data also extend and confirm the findings of others. A prospective study by Luth *et al.* [11] including 82 patients with AIH followed using lab tests and liver biopsies revealed a close correlation between histological activity and the degree of ALT and IgG elevation. Likewise, Montano-Loza *et al.* [6] showed the importance of complete normalization of the AST as a predictor of recurrence, regardless of the complete histological remission in a prospective trial, which included 131 patients with confirmed type I AIH.

Although liver biopsies are relatively safe, they are nevertheless associated with complications. Both clinicians and patients have an aversion to biopsy, unless there is a compelling need. Indeed, in our series, the hepatologist employed liver biopsy prior to cessation of immune suppression in only 29% of the cases. Likewise, an Israeli study published in 2013, which evaluated the prevalence of AIH in the Israel population from 1995 until 2010, reported that most hepatologists enrolled in that study did not perform a liver biopsy but rather relied on the normalization of the liver enzymes as a means of follow-up [12]. Furthermore, a study from Germany looked at patient selection for treatment withdrawal. In this study, the researchers used normalization of AST and ALT for treatment-withdrawal decision in most of the recruited patients (~50%), and it showed there was no difference in the relapse rate between patients who had biopsy vs those who had treatment withdrawal without the biopsy, and also that the lower the AST and ALT prior to treatment withdrawal, the lower the chance of having a post-treatment withdrawal flare-up [13]. Finally, a study by van Gerven *et al.* [14] on the high recurrence rate among patients with AIH showed that liver biopsy confirmed histological remission before treatment withdrawal was employed in only 18% of 131 patients included in the study, and absence of liver biopsy did not influence the relapse rate.

Table 3. Post-treatment withdrawal outcomes

Factor	Total (N = 34)	No biopsy done (N = 24)	Biopsy done (N = 10)	P-value
Months from treatment stop to lab	11.5 [7.6, 12.9]	11.7 [7.9, 12.8]	11.4 [7.6, 12.9]	0.84 ^a
Post-treatment stop lab				
Total bilirubin, mg/dL	0.60 [0.40, 0.80]	0.50 [0.40, 0.75]	0.60 [0.40, 0.80]	0.66 ^a
Alkaline phosphatase, U/L	79.0 [63.0, 111.0]	79.0 [61.0, 102.5]	77.0 [65.0, 124.0]	0.66 ^a
ALT, U/L	29.0 [22.0, 41.0]	29.0 [23.0, 39.5]	29.0 [14.0, 45.0]	0.68 ^a
ALT (ULN)				0.57 ^b
Normal (<45)	26 (76.5)	19 (79.2)	7 (70.0)	
Abnormal (≥45)	8 (23.5)	5 (20.8)	3 (30.0)	
ALT (2xULN)				0.51 ^c
Normal (<90)	32 (94.1)	23 (95.8)	9 (90.0)	
Abnormal (≥90)	2 (5.9)	1 (4.2)	1 (10.0)	
AST, U/L	29.0 [21.0, 39.0]	29.0 [21.0, 39.5]	28.5 [22.0, 39.0]	0.82 ^a
AST (ULN)				0.75 ^b
Normal (<40)	26 (76.5)	18 (75.0)	8 (80.0)	
Abnormal (≥40)	8 (23.5)	6 (25.0)	2 (20.0)	
AST (2xULN)				0.99 ^c
Normal (<80)	30 (88.2)	21 (87.5)	9 (90.0)	
Abnormal (≥80)	4 (11.8)	3 (12.5)	1 (10.0)	
Post-treatment follow-up, months	12.3 [8.8, 15.3]	12.2 [8.7, 15.6]	12.8 [8.9, 15.3]	0.69 ^a
Documented flare-up	8 (23.5)	5 (20.8)	3 (30.0)	0.57 ^b
Transplantation	0 (0.0)	0 (0.0)	0 (0.0)	–
Death	0 (0.0)	0 (0.0)	0 (0.0)	–

Statistics presented as median [P25, P75] or N (column %).

P-values: ^a = Kruskal-Wallis test, ^b = Pearson's chi-square test, ^c = Fisher's Exact test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Table 4. Degree of inflammation and stages fibrosis pre and post treatment in patients with liver biopsy

Patient	Grade of inflammation		Stage of fibrosis	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
No. 1	4	2	2	2
No. 2	4	1	2	2
No. 3	4	1	2	2
No. 4	4	0	2	2
No. 5	2	2	2	2
No. 6	3	0	3	0
No. 7	1	1	0	0
No. 8	2	1	2	0
No. 9	3	0	4	0
No. 10	1	1	3	3

While sustained remission for 2 years is sufficient to safely discontinue immunosuppressive medications in patients with AIH, we were intrigued to observe that, among those who had a second biopsy, the degree of hepatic fibrosis was remarkably reduced in 30%. Equally importantly, none had more fibrosis on the second biopsy than was present in the initial biopsy. Details will be presented in a separate communication. These findings may suggest value in subjecting those with advanced fibrosis on pre-treatment liver biopsy to post-treatment non-invasive measurements of hepatic fibrosis, such as elastography. Similar regression in fibrosis in HCV (Hepatitis C virus)-treated patients has been observed [5, 15]. Further studies are required to clarify the degree of regression and its significance in patients with AIH.

Although our initial population was 508 patients, most of these patients were excluded for uncontrolled diseases, and they were either referred to transplant or were still receiving

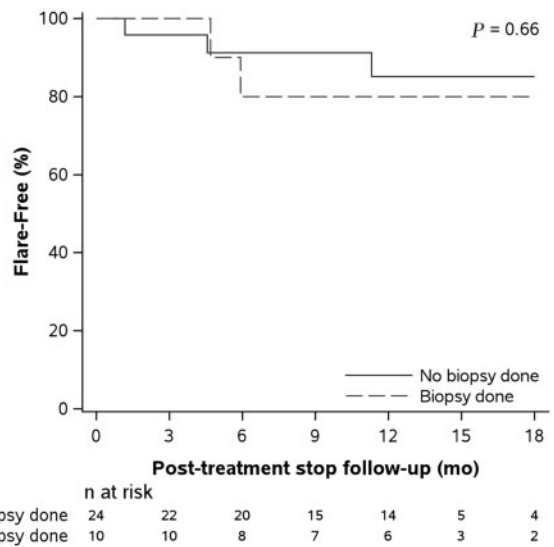


Figure 3. Kaplan-Meier plot showing risk of flare-ups between the two groups.

treatment. This finding is consistent with the data that 50–86% of patients might have flare-ups after treatment, presented by Montano-Loza et al. [6]. One limitation to our study was the small sample size, which was related to strict inclusion criteria that limited the application of the current data to all patients with AIH, and we believe it is important not to attempt treatment withdrawal, except in a highly selected patient population that has well-controlled disease over 2 years. These strict inclusion criteria led to exclusion of a large number of patients, as shown in Figure 1. We studied patients with well-controlled disease and the patients included in both groups were on a standard regime for immunotherapy, i.e. starting with 60 mg steroid as

Table 5. Univariable analysis of factors associated with occurrence of flare

Factor	Hazard ratio (95% CI)	P-value
Female vs male	1.2 (0.05–28.1)	0.92
Age (5-year increase)	0.96 (0.73–1.3)	0.8
AIH duration at treatment start (1-month increase)	1.1 (0.88–1.4)	0.41
Prednisone	0.16 (0.03–0.96)	0.045
Budesonide	3.8 (0.43–34.4)	0.23
Azathioprine	0.51 (0.09–3.1)	0.46
Duration of treatment (1-month increase)	0.96 (0.90–1.04)	0.33
ANA		
Weakly positive vs negative	0.24 (0.01–8.7)	0.44
Positive vs negative	2.1 (0.06–79.6)	0.68
Strongly positive vs negative	3.2 (0.45–22.2)	0.25
ASMA titer (1-unit increase)	1.3 (0.72–2.3)	0.41
Viral hepatitis	0.79 (0.03–19.0)	0.89
Pre-treatment inflammation	1.2 (0.49–2.7)	0.73
Pre-treatment fibrosis	0.80 (0.37–1.7)	0.56
Pre-treatment total bilirubin (0.1-mg/dL increase)	0.87 (0.61–1.3)	0.47
Alkaline phosphatase (10-U/L increase)	1.06 (1.00–1.1)	0.055
ALT (10-U/L increase)	1.01 (0.99–1.02)	0.49
AST (10-U/L increase)	1.00 (0.99–1.02)	0.43

AIH, autoimmune hepatitis; TTT, treatment; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

monotherapy and decreasing the dose weekly by 10 mg until we reached maintenance of 10–20 mg or starting with moderate-dose steroid 30 mg and azathioprine 50 mg and tapering the steroid dose 10 mg weekly until maintenance of 5–10 mg.

We believe that, due to the importance of the concept we are introducing, this study should be a pilot study to further larger double-blinded randomized trials to confirm our finding. Our report is affected by the limitations of all retrospective studies. It is gratifying that most published retrospective reports reach similar conclusions.

Current AASLD guidelines mandate a second biopsy prior to stopping the immunosuppression [1]. Our study as well as other published studies [6, 10, 11] showed that it is not mandatory to repeat the biopsy with persistent normalization of the liver enzymes. This study and the prior mentioned studies might lead to change in the current guidelines if we were able to replicate the finding in a randomized-controlled trial with a larger population size.

In conclusion, this study reveals that it is safe to withdraw treatment in patients with AIH disease without a second biopsy when they have normalized liver enzymes over 2 years. Hepatologists should be highly selective in regard to withdrawing treatment from patients with AIH.

Conflict of interest statement: none declared.

References

- Manns MP, Czaja AJ, Gorham JD et al. American association for the study of liver disease: diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;**51**:2193–213.
- Verma S, Gunuwan B, Mendler M et al. Factors predicting relapse and poor outcome in type I autoimmune hepatitis: role of cirrhosis development, patterns of transaminases during remission and plasma cell activity in the liver biopsy. *Am J Gastroenterol* 2004;**99**:1510–6.
- Czaja AJ, Menon KV, Carpenter HA. Sustained remission after corticosteroid therapy for type 1 autoimmune hepatitis: a retrospective analysis. *Hepatology* 2002;**35**:890–7.
- Filingeri V, Francioso S, Sforza D et al. A retrospective analysis of 1.011 percutaneous liver biopsies performed in patients with liver transplantation or liver disease: ultrasonography can reduce complications? *Eur Rev Med Pharmacol Sci* 2016;**20**:3609–17.
- Poynard T, Moussalli J, Munteanu M et al. Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C. *J Hepatol* 2013;**59**:675–83.
- Montano-Loza AJ, Carpenter HA, Czaja AJ. Improving the end point of corticosteroid therapy in type 1 autoimmune hepatitis to reduce the frequency of relapse. *Am J Gastroenterol* 2007;**102**:1005–12.
- Putra J, Toor A, Suriawinata AA. The utility of repeat liver biopsy in autoimmune hepatitis: a series of 20 consecutive cases. *Pathology* 2016;**48**:449–53.
- van Gerven NM, de Boer YS, Mulder CJ et al. Auto immune hepatitis. *World J Gastroenterol* 2016;**22**:4651–61.
- European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol* 2015;**63**: 971–1004.
- Gleeson D, Heneghan MA; British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* 2011;**60**:1611–29.
- Luth S, Herkel J, Kanzler S et al. Serologic markers compared with liver biopsy for monitoring disease activity in autoimmune hepatitis. *J Clin Gastroenterol* 2008;**42**:926–30.
- Delgado JS, Vodonos A, Malnick S et al. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. *J Dig Dis* 2013;**14**:611–8.
- Hartl J, Ehlken H, Weiler-Normann C et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. *J Hepatol* 2015;**62**:642–6.
- van Gerven NM, Verwer BJ, Witte BI et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *J Hepatol* 2013;**58**:141–7.
- Ellis EL, Mann DA. Clinical evidence for the regression of liver fibrosis. *J Hepatol* 2012;**56**:1171–80.