Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

# Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission

Nicole M.F. van Gerven[1,†], Bart J. Verwer[1,†], Birgit I. Witte[2,†], Bart van Hoek[3,†], Minneke J. Coenraad[3,†], Karel J. van Erpecum[4,†], Ulrich Beuers[5,†], Henk R. van Buuren[6,†], Rob A. de Man[6,†], Joost P.H. Drenth[7,†], Jannie W. den Ouden[8,†], Robert C. Verdonk[9,†], Ger H. Koek[10,†], Johannes T. Brouwer[11,†], Maureen M.J. Guichelaar[12,†], Chris J.J. Mulder[1,†], Karin M.J. van Nieuwkerk[1,†], Gerd Bouma[1,*,†]

[1]*Department of Gastroenterology and Hepatology, Vu University Medical Centre, Amsterdam, The Netherlands;* [2]*Department of Epidemiology and Biostatistics, Vu University Medical Centre, Amsterdam, The Netherlands;* [3]*Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands;* [4]*Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands;* [5]*Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands;* [6]*Department of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, The Netherlands;* [7]*Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;* [8]*Department of Gastroenterology and Hepatology, Haga Hospital, The Hague, The Netherlands;* [9]*Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;* [10]*Department of Gastroenterology and Hepatology, University Medical Center Maastricht, Maastricht, The Netherlands;* [11]*Reinier de Graaf Medical Center Delft, Delft, The Netherlands;* [12]*Department of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands*

See Editorial, pages 5–7

**Background & Aims**: Current treatment strategies in autoimmune hepatitis (AIH) include long-term treatment with corticosteroids and/or azathioprine. Here we determined the risk of relapse after drug withdrawal in patients in long-term remission and factors associated with such a relapse.

**Methods**: A total of 131 patients (out of a cohort including 844 patients) from 7 academic and 14 regional centres in the Netherlands were identified in whom treatment was tapered after at least 2 years of clinical and biochemical remission. Relapse was defined as alanine-aminotransferase levels (ALT) three times above the upper limit of normal and loss of remission as a rising ALT necessitating the reinstitution of drug treatment.

**Results**: During follow-up, 61 (47%) patients relapsed and 56 (42%) had a loss of remission. In these 117 patients, 60 patients had fully discontinued medication whereas 57 patients were still on a withdrawal scheme. One year after drug withdrawal, 59% of the patients required retreatment, increasing to 73% and 81% after 2 and 3 years, respectively. Previous combination therapy of corticosteroids and azathioprine, a concomitant autoimmune disease and younger age at time of drug withdrawal were associated with an increased risk of relapse. Subsequent attempts for discontinuation after initial failure in 32 patients inevitably resulted in a new relapse.

**Conclusions**: This retrospective analysis indicates that loss of remission or relapse occurs in virtually all patients with AIH in long-term remission when immunosuppressive therapy is discontinued. These findings indicate a reluctant attitude towards discontinuation of immunosuppressive treatment in AIH patients.

© 2012 Published by Elsevier B.V. on behalf of the European Association for the Study of the Liver.

Keywords: Autoimmune hepatitis; Relapse; Remission; Medication; Drug withdrawal; Azathioprine; Steroids.

*Received 3 April 2012; received in revised form 4 September 2012; accepted 6 September 2012; available online 16 September 2012*

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2012.10.007.

* Corresponding author. Address: Department of Gastroenterology and Hepatology, Vrije Universiteit Medical Center, De Boelelaan 1118, 1081 HV Amsterdam, The Netherlands. Tel.: +31 20 444 0613.

*E-mail address:* g.bouma@vumc.nl (G. Bouma).

† On behalf of the Dutch Auto immune hepatitis working group (see list of contributors at the end of the article).

*Abbreviations:* AIH, autoimmune hepatitis; IgG, immunoglobulin gamma G; IBD, inflammatory bowel disease; ALT, alanine-aminotransferase; ASMA, anti-smooth muscle antibodies; ANA, antinuclear antibodies; PSC, primary sclerosing cholangitis; ULN, upper limit of normal; SPSS, Statistical Package for Social Sciences; LKM, liver kidney microsomal; AST, serum-glutamic-oxaloacetic-transaminase.

## Introduction

Autoimmune hepatitis (AIH) is a relatively rare chronic inflammatory disorder of the liver of unknown aetiology, which when left untreated can lead to liver cirrhosis and hepatic failure [1–3].

The disease is characterized by elevated liver enzymes, elevated serum immunoglobulins, the presence of serum autoantibodies and characteristic findings upon liver biopsy [4]. The clinical, biochemical and histopathological findings are usually adequate to establish the diagnosis in the majority of patients. Diagnostic scoring systems have been established by an international working group that are particularly helpful in a research setting [5].

Corticosteroid therapy induces clinical, laboratory and histological improvement in 80% of the patients [6]. The combination of corticosteroids and azathioprine is associated with lower occurrence of corticosteroid-related side effects than predniso(lo)ne treatment alone, and combination treatment is the preferred therapeutic strategy for patients with active disease [7]. Remission, defined as normalization of ALT and immunoglobulin gamma G (IgG), is achieved in 65% of the patients within 18 months and in 80% of them within 3 years [8,9].

A major unresolved dilemma relates to the question as to whether treatment in patients who are in longstanding remission can be safely discontinued [9–11]. A retrospective analysis found that patients who responded to initial corticosteroid therapy can achieve a sustained remission after treatment withdrawal or, in the case of a relapse, after retreatment [12]. These findings are somewhat in contrast to older studies dating back to the 1970s and 1980s where relapse occurred in as many as 50% of the patients within 6 months after discontinuation of therapy and in 86% of the patients who had a longer follow-up [9–13].

In the current study, we assessed the frequency of relapse after drug withdrawal in a large multicenter cohort of AIH patients while being in remission for at least 2 years. We demonstrate that virtually all patients will eventually require retreatment after discontinuation of therapy and that this generally occurs within the first 2 years after drug withdrawal.

## Patients and methods

### *Patient population*

The data in this study were obtained from 7 academic medical centres and 14 general district hospitals in the Netherlands. The protocol was approved by the institutional review board of the VU medical centre and by the review boards of all participating centres. All participating patients gave written informed consent.

AIH patients were identified by treating physicians and by searching databases for ICD codes.

Patients had been diagnosed with AIH based on the combination of clinical, biochemical and histopathological criteria. The diagnosis was supported by calculating the number of points in the revised original international criteria for the diagnosis of AIH [5]. All patients had a minimal score of at least 12 points in this scoring system despite the fact that not all scoring criteria were available in some patients. Viral hepatitis (hepatitis B and C) was excluded by serological testing. Alcohol-induced and drug-related hepatitis had been excluded by clinical history and histological findings.

All patients had been evaluated (by means of serological testing and histological evaluation) for the presence of an overlap syndrome with primary sclerosing cholangitis (PSC) or primary biliary cirrosis (PBC). Three patients had an overlap with PSC whereas none of the patients in this cohort had an overlap with PBC. With regard to concomitant autoimmune diseases, the diagnosis of inflammatory bowel disease (IBD) was based on clinical, endoscopic and histopathological features, diabetes on fasting blood glucose and thyroid disease by screening for TSH, T4 and, when applicable, for thyroid antibodies. HLA typing was not available for any patient.

### *Definitions of remission, relapse and loss of remission*

Long-term clinical remission was defined as absence of symptoms and normalization of serum ALT levels for at least 2 years and, when determined, normalization of IgG levels. Histological remission was defined as the absence of histological signs of inflammation, fibrosis or cirrhosis, or, in those cases where minimal residual inflammatory activity was found, the absence of interface hepatitis as defined by Czaja *et al.* [14].

Biochemical relapse was defined according to international guidelines [4] by an increase in serum ALT levels above three times the upper limit of normal (ULN) and/or an increase in serum IgG levels to more than 2 g/dl.

A loss of remission was defined by an increase in serum ALT levels above ULN on at least two occasions with an interval of 4 weeks, with or without concomitant clinical symptoms and reinstitution of drug therapy after exclusion of other plausible causes for the elevated serum ALT. The decision of retreatment was based on the judgement of the treating physician. Retreatment schedules after relapse were individually reinstituted.

### *Treatment variety*

Medication was reduced with the aim to eventually discontinue treatment in patients who were at least 2 years in clinical and biochemical remission. ALT levels and, when available, IgG, anti-smooth muscle antibodies (ASMA) and antinuclear antibodies (ANA) were collected at the time of drug withdrawal and during follow-up.

Tapering was based on the judgement of the treating physician. Drug withdrawal schemes were individualized but in general, medication was tapered in a graduated fashion over a period of at least 6 months according to previously published guidelines [4]. In 32 patients, drug withdrawal was attempted for a second time after the first relapse.

### *Data analysis*

This retrospective analysis is mainly descriptive. Summary statistics for continuous variables are expressed as median with range (minimum–maximum). Summary statistics for categorical variables are expressed as numbers (percentages). Quantitative variables are described as means with their standard deviations or as medians with their range if not normally distributed. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS). Depending on the distribution, parametric and non-parametric tests including *t*-test, Wilcoxon signed rank test and Sign exact test were used to test for differences within and between groups. A Kaplan Meier analysis was used to determine the cumulative period until relapse and the follow-up after treatment-induced remission. The Cox regression univariate and multivariate analysis was used to test the relationship between patient characteristics and time until relapse. A *p*-value less than 0.05 was considered statistically significant.

## Results

### *Frequency of relapse and loss of remission after initial treatment*

A retrospective analysis was performed on 844 patients (186 males/658 females), who fulfilled the revised original clinical criteria for AIH as defined by Alvarez *et al.* [5]. All patients had a minimum score of 12 points for the original criteria when included. Following diagnosis, the median follow-up time of this group was 9 years (range: 0.5–45 years).

A total of 713 patients could not be included in the analysis since medication had not been discontinued as per judgement of the treating physician. In 78 patients, persistent active inflammation in a liver biopsy prohibited drug withdrawal despite complete clinical and biochemical remission for at least 2 years. A small group of patients (29 patients, 4%) had not reached long-term (i.e., >2 years) remission at the time of analysis.

In 131 patients, treatment had been tapered and/or discontinued after complete clinical remission and normalization of ALT levels for at least 2 years. This group consisted of 98 women (75%), with median age at diagnosis of 40 years (range: 4–83 years). In the 33 male patients, median age at diagnosis was 35 years (range: 9–72 years).

Download English Version:

https://daneshyari.com/en/article/6104863

Download Persian Version:

https://daneshyari.com/article/6104863

Daneshyari.com