Title

Normalization of serum immunoglobulin G levels is associated with improved transplant-free survival in patients with autoimmune hepatitis

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Abstract

Background: There is limited evidence linking achievement of biochemical response with outcomes in Autoimmune Hepatitis (AIH), and it is unclear whether normalization of serum immunoglobulin G (IgG) levels influences prognosis.

Aims: We aimed to investigate factors associated with death or liver transplantation in patients affected by AIH.

Methods: We undertook a retrospective analysis of all AIH patients attending a tertiary liver unit since 1980. Patients not meeting established diagnostic criteria for AIH or with a follow-up shorter than 18 months were excluded.

Results: 107 patients meeting inclusion criteria were included in the study. Mean age at diagnosis was 44 years, 29 patients (27.1%) had cirrhosis at baseline. Median follow-up was 79 months, and 70 patients (79.5%) reached biochemical response. Biochemical response was associated with reduced hazard of liver transplant or death (HR 0.07, 95% CI 0.01-0.46), whereas cirrhosis at diagnosis was an independent predictor of liver transplantation or death (Hazard ratio (HR) 11.8, 95%, confidence interval (CI) 1.18-117.4). Lack of normalization of serum IgG levels was associated with reduced 5-year transplant-free survival (95% in patients normalizing, compared to 86%, p=0.02).

Conclusion: Normalization of serum IgG levels alone translate in better transplant-free survival in patients with AIH and should be a treatment target along with transaminases.

Keywords

Risk stratification, Liver Cirrhosis, Autoimmune Liver Disease, Liver Immunology

Introduction

Autoimmune hepatitis (AIH) is an immune-mediated, chronic liver disease that can progress to cirrhosis, hepatic failure and death[1]. Whilst the underlying aetiopathogenic mechanisms are not well understood, treatment with prednisolone and azathioprine is a well-established, effective treatment approach[2–6] and the majority of treated patients achieve response with this combination. However, 10-15% of patients have inadequate responses to treatment or intolerance and require second- or third-line therapies, potentially never achieving biochemical response[6,7].

Current guidelines recommend the complete normalisation of transaminases and serum immunoglobulin G (IgG) as treatment aims in AIH[6,8], as failure to normalise serum transaminases is associated with worse clinical outcomes, including higher rates of relapse and progression to cirrhosis[6,9,10]. Amongst patients with normal transaminases and IgG, approximately half have residual inflammation evident on liver biopsy (histologic activity index (HAI) 4 or 5); nonetheless, these patients are at lower risk of progression to advanced fibrosis than patients with an HAI of 6 or more[11]. Hence, although normal transaminases and IgG do not always represent the absence of liver inflammation, they are associated with a low risk of progression. Normalisation of either traminaseses or IgG alone is not sufficient as patients normalising only one parameter may have an HAI score ≥6[11], which is an independent predictor of death[12]. Serial non-invasive measurement of liver stiffness has recently been proposed as a surrogate for histological remission in the follow-up of treated AIH patients[13]. Despite the widespread adoption of biochemical response as the primary treatment objective, evidence to support this as a surrogate endpoint is limited[13]. There is lack of data regarding the prognostic role of normalization of IgG levels alone.

We aimed to establish which clinical parameters are associated with long-term mortality and the need for liver transplantation in AIH. We performed a retrospective analysis of characteristics and clinical outcomes in a large group of patients with AIH seen at a single tertiary academic hepatology unit in the United Kingdom between 1980 and 2016.

Materials and Methods

Study population

Patients with AIH were identified retrospectively using multiple case finding strategies: all hepatology and gastroenterology department clinical notes, inpatient discharge codes, laboratory, pathology, and radiology reports were searched to identify all individuals reviewed on at least two occasions at the Royal Free Hospital between January 1980 to August 2016. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Our study did not require an written consent because of the observational and retrospective nature of the study. The diagnosis of AIH was confirmed using the revised criteria for AIH and those with a pre-treatment score >10 were included[14]. Patients with incomplete medical records preventing the calculation of diagnostic scores were excluded. Additionally, those with other concomitant hepatic disorders including viral hepatitis, biliary, metabolic, genetic or drug-induced liver diseases were excluded. The end of follow-up was determined as the time of death, liver transplantation (LT) or the last outpatient clinic attendance. The date of the diagnosis was defined as the earliest date at which a patient fulfilled diagnostic criteria for AIH (usually the date of the liver biopsy).

192 patients with AIH and no concomitant liver disease that were seen on at least two occasions were identified. Forty-five of these were excluded due to a follow-up duration of less than 18 months. This cut off was included to allow adequate time to assess biochemical response, in accordance with the established International Autoimmune Hepatitis Group (IAIHG) revised definition criteria of complete response ("Either or both of the following: marked improvement of symptoms and return of serum AST or ALT, bilirubin and immunoglobulin values completely to normal within 1 year and sustained for at least a further 6 months on maintenance therapy, or a liver biopsy specimen at some time during this period showing at most minimal activity")[14]. Forty further patients were excluded due to a revised IAIHG score <10 (six patients) or due to lacking adequate data to calculate the score (thirty-four patients). Therefore, 107 patients were included in the analysis (**Figure S-1**).

Clinical features including gender, race, mode of presentation, autoimmune comorbidities, age, and laboratory parameters and biopsy findings at diagnosis were collected for all patients. Race was recorded as that documented in the patient's demographic data in their National Health Service (NHS) records. Mode of presentation was categorised as "acute onset" referring to jaundiced hepatitis or decompensated cirrhosis, "symptomatic onset" for those reporting fatigue, malaise or any other attributable symptoms[6] or as "asymptomatic onset" (patients could therefore be either, both or neither acute or symptomatic). Pharmacological agents for induction (starting date, type of medication, dose) and maintenance (exposure to azathioprine, use of second- or third-line drugs, duration of steroid therapy) phases of treatment were recorded. Lack of compliance was defined as a documented lack of concordance with the treatment strategy discussed with the treating physician or missing more than one clinic appointment over the course of follow-up.

Treatment endpoints

Biochemical response was defined as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum IgG being all below the laboratory upper limit of normal (ULN) on at least one occasion and relapse as ALT>3 x ULN[6]. Treatment withdrawal referred to the complete cessation of immunosuppressive medication.

Statistical analysis

Analysis was performed using R (v.3.5.1, R Core Team) and a two-tailed p-value <0.05 was considered significant. Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for normally and non-normally distributed data, respectively. Categorical variables are expressed as frequencies and percentages. Log transformation of continuous variables was applied where appropriate. Chi-Square test or Fisher's exact test were used to compare frequencies of categorical variables. Parametric and non-parametric tests were used to compare

means and medians of continuous variables with normal and non-normal distribution, respectively. Cumulative incidence of normalization of transaminases was estimated using the Aalen-Johansen estimator considering death and liver transplant as competing events. Transplant-free survival was estimated using Kaplan-Meier curves. The associations between presumed risk factors and this outcome was analysed using log-rank tests and univariate and multivariate Cox proportional hazards regression. Due to the small number of events, no model selection was performed and the choice of factors to be retained in the final multivariate model was based on univariate analysis and clinical knowledge.

Results

Features of the Study Cohort

One hundred and seven patients were included, 51 (47.7%) with a definite diagnosis of AIH and 56 (52.3%) with a probable diagnosis according to IAIHG diagnostic criteria. 82 patients (76.6%) were diagnosed after 2000. Clinical features at diagnosis are outlined in **Table 1**. Twenty-six patients (24.3%) were male; the age range was 18-80 years (mean 44 years, SD 17). Median duration of follow-up was 79 months (IQR 130). Liver biopsy was performed in 104 (97.2%) patients at diagnosis, of whom 29 (29.3%) had histologically-proven cirrhosis.

Immunological investigations demonstrated positive antinuclear antibodies (ANA) in 76 (76%), anti-smooth muscle antibodies (αSMA) in 77 (74%), anti-liver kidney microsomal antibodies (αLKM) in 3 (2.9%) and anti-mitochondrial antibodies (AMA) in 5 (4.7%) patients. No features of cholestatic disease were observed on histological assessment of the patients with anti-mitochondrial antibodies. Anti-neutrophil cytoplasmic antibodies (ANCA) were tested in 44 patients and 7 (15.9%) were positive. In 36 patients tested for ANA, αLKM, αSMA, ANCA and AMA antibodies, three (8.3%) were seronegative for all autoantibodies. Five patients were tested for anti-SLA antibodies and one

resulted positive. Median serum IgG titres at diagnosis ranged from 6.5 to 66.0 g/L (median 24.5 g/L, IQR 13.9) ; nine patients (8.4%) had normal IgG levels..

Pharmacological management

Of 107 patients 102 (95.3%) received pharmacological therapy, whilst 5 did not. 101 (99%) of the treated patients received induction therapy with corticosteroids, while one patient was started directly on azathioprine (**Table 2**). The median dose of prednisolone at induction was 30mg per day, while the median starting dose of azathioprine was 50mg per day. The majority of patients (90.1%) were exposed to azathioprine over the follow-up period. Thirty patients (29.7% of the entire cohort, 1 case with missing data) were treated with a second-line drug over the course of the disease, most frequently receiving mycophenolate mofetil (11/30, 36.7%). Twenty-one subjects (21.4%, 4 cases with missing data) were non-compliant according to our definition.

Treatment Responses

Clinical outcomes are summarised in **Table 3**. Treatment response data was available for 102 patients, since 5 patients were not treated. Eighty-five patients normalized transaminases (85.9%, 3 missing data); median time (IQR) to normalisation of transaminases was 34 (64) weeks. Cumulative incidence of normalisation of transaminases at 1, 3 and 5 years was 56.6%, 80.5% and 88.6% respectively (**Figure S-2**). Seventy-five normalized IgG levels (90.4%, 10 missing data and 9 without high IgG levels at baseline). Seventy patients achieved biochemical response (79.5%, 14 missing data); 34 (50.7%, 3 missing data) relapsed whilst on maintenance treatment. Median time (IQR) to relapse "on-treatment" was 17 (67) months. Nine patients (9.5%) underwent complete treatment withdrawal and of these 5 (55.6%) relapsed, requiring the reinstitution of pharmacological therapy. Median time (IQR) to relapse off treatment was 4 (5) months.

Predictors of all-cause death or liver transplant

On univariate analysis three factors were associated with adverse prognosis: presence of cirrhosis at baseline, ALT levels at baseline and biochemical response (**Table 4**). Biopsy-proven cirrhosis at diagnosis was strongly associated with a greater hazard of dying or undergoing LT (HR 15.8, 95% CI 3.3-75.9). Conversely, higher values of ALT were associated with a lower hazard of death or LT (HR 0.52, 95% CI 0.29-0.94). The use of second-line immunosuppressive treatment was not associated with worse outcomes, whereas achieving biochemical response was strongly associated with a reduced hazard of death or LT (HR 0.04, 95% CI 0.01-0.24). Time to normalization of transaminases and starting dose of prednisolone were not associated with the risk of death or LT. Patients not compliant with treatment or follow-up were more likely to experience death or LT, even though this did not reach statistical significance (HR 3.25, 95% CI 0.87-12.2).

Gender, race, mode of onset, autoantibody status, age and serum IgG titre at diagnosis were not associated with an altered hazard of death or transplant. Similarly, the degree of hepatic dysfunction (expressed either by single laboratory parameters or by composite scores like MELD) was not associated with differences in outcome.

Variables that were associated with a different hazard of death or LT ($p < 0.05$) were entered into a multivariate Cox regression analysis, including ALT expressed as natural logarithm (LnALT), presence of cirrhosis and biochemical response (**Table 4**). We observed that cirrhosis at diagnosis and failure to achieve biochemical response were independently associated with death or LT (HR 11.8, 95% CI 1.18-117.4, $P < 0.03$ for cirrhosis and HR 0.07, 95% CI 0.01-0.46, $P < 0.006$ for achieving biochemical response). These two variables maintained their independence also when age at diagnosis and lack of compliance were added to the model (**Table S1**).

Normalization of IgG levels is associated with improved transplant-free survival

The impact of cirrhosis at diagnosis and lack of biochemical response on transplant-free survival are shown in **Figure 1A** and **1B**, respectively. The transplant-free survival of non-cirrhotic patients with

at least 18 months follow-up was 100% at 5 years from diagnosis compared to 75% (log rank test p<0.001) in patients who were cirrhotic at diagnosis. Amongst patients who achieved biochemical response, transplant-free survival was 98% at 5 years compared to 62% in those without biochemical response (log rank test p<0.001).

Splitting biochemical response into its two components, normalisation of transaminases and normalisation of serum IgG levels, revealed that each was associated with better transplant-free survival (**Figure 2A** and **2B** respectively). Transplant-free survival in those who did not normalize transaminases at 5 years was poor (47%) compared to those who did normalize (98.7%).

Transplant-free survival of patients who normalized IgG levels was 95% at 5 years, compared to 86% in those who did not normalize. We found similar rates of normalization of IgG levels between cirrhotic patients (20/23=87%) and non-cirrhotic ones (48/53=90.6%).

Discussion

Our study offers one of the first pieces of evidence that a lack of biochemical response to pharmacological therapy has a significant impact on hard clinical endpoints in treated AIH. Moreover, we provide evidence that reduction of serum IgG levels alone translates in better survival times.

These findings supports guideline recommendations that biochemical response[6,9], defined as the normalisation of both transaminases and serum IgG levels, is the treatment target for patients with AIH. The current clinical guidelines endorse the normalization of both parameters, but the evidence supporting this statement is derived from heterogenous observational studies showing that persistence of either abnormal transaminases or elevated serum IgG levels are associated with poor surrogate outcomes. Studies about persistent abnormal transaminases had often different endpoints[8,9,15,16], while studies about persistent high serum IgG levels have been scarce and unreplicated[11,17]. Our data show a significant reduction in the hazard of death or LT for patients who achieve biochemical

response, which was associated with 5-year transplant-free survival of 100%, compared to 75% in those who did not achieve biochemical response. Biochemical response has been positively associated with histological regression and a reduction in liver stiffness measurements [13]. To our knowledge, this is the first study demonstrating that reduction of serum IgG levels alone translate in improvement of hard outcome (transplant-free survival), since previous reports used only surrogate endpoints.

We have confirmed that cirrhosis at diagnosis is a strong independent predictor of poor outcome in patients with AIH. Whilst several previous studies have reported a similar association[18–22], there has been debate in the literature about the prognostic role of cirrhosis, with some conflicting reports[23–25]. Over a quarter of our cohort presented with histological signs of cirrhosis at diagnosis, in line with data from other centres[6,18–21,23,24]. The presence of cirrhosis at diagnosis may represent long standing, clinically silent disease, or potentially a group of patients with rapidly progressive disease, and the early identification of these individuals still represents a challenge..

The median time to normalize transaminases was 34 weeks, which is better than historical cohorts[26], but still unsatisfactory; we did not find an impact of time to normalization of transaminases on the outcome (**Table 4**). One could argue that longer time to remission might be due to lower dose of prednisone during induction phase, but we did not find a correlation between time these two variables (**Figure S-3**). Moreover, induction dose of steroids was not associated with likelihood of being transplanted or die (**Table 4**). To conclude, from our data we cannot infer that higher prednisolone doses might have changed the outcome of AIH patients, which is line with recent literature[27].

Our study has some limitations, the main one being its retrospective nature, with consequent missing data and selection bias. Our sample size is relatively small, even though it is larger than many other single centre reports. Our data were derived from a tertiary transplant centre where the patient population will likely differ from those in general hospitals, with a greater proportion of complex,

difficult-to-treat patients or acute onset cases and different treatment outcomes[26]. However, our data are consistent with previous reports from multiple non-transplant centres in the UK[21].

In conclusion, our data show that biochemical response to treatment is associated with improved patient outcomes in AIH and supports its validity as a surrogate endpoint. Normalization of serum IgG levels is associated with better transplant-free survival and should be achieved together with normalization of transaminases.

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Figure Legends

Figure 1. Cumulative transplant-free survival estimates according to the presence of cirrhosis at diagnosis (**A**) and according to whether patients ever achieved biochemical response (**B**).
Untreated patients were not included in the analysis for biochemical response. Legend: tick marks represent censored cases.

Figure 2. Cumulative transplant-free survival estimates according to whether patients ever achieved normalisation of transaminases **(A)** or normalisation of serum IgG levels **(B)**. IgG, Immunoglobulin G.
Untreated patients were not included in the analysis. Legend: tick marks represent censored cases.

Figure S-1. Patient inclusion and exclusion criteria.

Figure S-2. Cumulative incidence of normalization of transaminases estimated using the Aalen-Johansen estimator considering death and liver transplant as competing events.

Figure S-3. Scatter plot with smoothing line and Spearman correlation index for time to normalization of transaminases and dose of predni(so)lone at induction. Mg, milligrams.