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Original Article

Long Duration of Treatment and Sustained Biochemical Remission Increases Success Rates after Treatment Withdrawal in Patients with Autoimmune Hepatitis Admitted to a Tertiary Care Hospital in North Odisha

Pradeep Kumar Padhi*[1], Smita Patra[2]

1. Associate Professor, Department of Medicine, FakirMohan Medical College, Balasore, Odisha, India.
2. Assistant Professor, Department of Anatomy, SCB Medical College, Cuttack, Odisha, India.

***Corresponding author's E-mail:** drpkpadhy1973@gmail.com

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ABSTRACT

Background & Aims: In autoimmune hepatitis (AIH), relapse rates as high as 90% have been reported after treatment withdrawal. We therefore investigated, whether longer duration of treatment and proper patient selection could increase the long-term success rates after treatment withdrawal.

Methods: This is a single centre analysis of data acquired prospectively in a database of the Fakir Mohan Medical college, Balasore from April 2018 to May 2023. All patients with AIH and a minimum follow-up of two years were reviewed. Treatment withdrawal was considered when biochemical remission was maintained under immunosuppressive monotherapy for at least 2 years. The research protocol was approved by the local ethical committee.

Results: Out of 288 patients with well-defined AIH, 28 patients were included. Median duration of treatment was 48.5 months (range 35–179) and a sustained remission was observed for 45 months (range 24–111). All patients were in remission on immunosuppressive monotherapy for a minimum of 2 years before treatment was withdrawn. Using this strict approach, 15 patients (54%) remained in long-term remission after a median of 28 months follow-up (range 17–57) and 13 patients (46%) required reinstitution of treatment. All patients who remained in remission had ALT levels less than half the ULN and IgG levels not higher than 12 g/L at the time of treatment withdrawal.

Conclusions: Proper patient selection including a sustained complete biochemical remission on immunosuppressive monotherapy for a minimum of 2 years can markedly improve the success rates of treatment withdrawal.

Keywords: Autoimmune hepatitis (AIH); Drug withdrawal; Relapse; Remission; Loss of remission; Immunosuppressive therapy; Predictors for relapse; Treatment duration.

INTRODUCTION

Autoimmune hepatitis is a chronic necro inflammatory disorder of the liver of suspected autoimmune origin that can lead to end-stage liver disease and hepatic failure and is characterized by elevated levels of serum autoantibodies and typical histological findings, [1–3.] Immunosuppressive therapy with corticosteroids and/or azathioprine is considered the mainstay of treatment [4,5]. Treated AIH has a favourable overall survival, unless advanced cirrhosis is present at the time of diagnosis[6,7]. Despite the most excellent response to immunosuppressive therapy, the optimal duration of treatment is unclear and relapse after discontinuation of treatment remains an unsolved dilemma. In a recent Dutch multicentre study, relapse rates as high as 90% have been reported [8]. These findings are in accordance with other studies where relapse occurred in about 90% of patients after treatment cessation [9–12]. A failed attempt to withdraw treatment exposes patients to the risk of disease flares and reintroduction of steroid treatment with all its side effects.

There are limited data available on the duration, dosage and combination of immunosuppressive therapy that should be administered in patients with AIH [4,5]. A minimum treatment duration of 2 years prior to an attempt of treatment withdrawal has been proposed in the most recent AASLD practice guidelines[4]. However, our own experience suggests that an extended duration of immunosuppressive therapy is associated with lower relapse rates[13]. Also, the definition of complete biochemical remission as a surrogate for histological remission has only recently been clarified [4]. Remission is defined by repeatedly normal serum alanine-aminotransferase (ALT) and IgG levels [4,14,15]. We herein prospectively validated whether this patient selection can reduce the risk for relapse and included 28 out of 288 patients in our program who fulfilled these strict criteria.

METHODS

This is a single centre analysis of data acquired prospectively in a database of Fakir Mohan Medical college, Balasore, Odisha from April 2018 to May2023. All patients with AIH and a minimum follow-up of two years were reviewed. The research protocol was approved by the local ethical committee. Only patients in stable biochemical remission on immunosuppressive monotherapy for a minimum of 2 years were considered eligible for treatment withdrawal. Monotherapy consisted of azathioprine (n = 23), 6-mercaptopurine (n = 1), prednisolone (n = 2), or budesonide (n = 2). The end-point was defined as the requirement of retreatment after drug

withdrawal due to rising ALT- and/or IgG-levels above the upper limit of normal (ULN) or reappearance of clinical symptoms. This will be termed relapse hereafter. Remission was defined according to AASLD guidelines [4] as the normalization of serum aminotransferase and IgG levels and the absence of clinical symptom. All patients with relapses after treatment cessation were included into the analysis. The vast majority of relapses occurs within the first year after treatment withdrawal [8–12], therefore only patients with normal liver tests over a period of at least one year after drug withdrawal were considered in remission off treatment. Since this may introduce a selection bias, we performed a separate analysis including also two patients in remission but with less than 12 months of observation time after drug withdrawal. AIH was diagnosed on clinical, biochemical and histopathological findings, as suggested in the simplified diagnostic criteria by Hennes et al. [16]. All patients underwent a liver biopsy. Chronic viral hepatitis B and C had been excluded by serological testing in all patients. Drug- and alcohol-induced hepatitis had been excluded by medical history and histological examination. Based on serological testing and histological evaluation, one patient was identified who had an overlap syndrome with primary biliary cirrhosis whereas none had an overlap with primary sclerosing cholangitis. In six patients concomitant autoimmune or immune mediated disease had been diagnosed (4 Hashimotos thyroiditis, 2 diabetes mellitus type 1, 1 inflammatory bowel disease) The following biochemical and serological markers were assessed at initial presentation and follow-up: ANA, SMA, LKM, AMA, SLA/LP, IgG, c-globulin, ALT, AST, albumin, bilirubin, creatinine, and INR.

Statistical analyses:

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. Depending on the distribution, parametric and non-parametric tests including t test and Wilcoxon signed rank test were used to test for differences between groups. Cox-regression models were used to assess predictors of relapse. Hazard ratios (HR) were calculated for dichotomised personal characteristics in univariate regression models. For this purpose, all continuous exposure measures (age at initial presentation, ALT, IgG, gamma-globulins at initial presentation and at time of drug withdrawal, time to remission, fibrosis stage, ANA and SMA titre) were dichotomised into two equally sized groups. All variables with evidence of an association with relapse in univariate analyses were included in a multivariate cox regression model to adjust for potential confounding. However, to ensure validity of the multivariate models despite a low sample size, it was decided to include only variables in the multivariate models that were not correlated with each other. To assess correlation of variables the Spearman's rank correlation coefficient was calculated. Statistical analyses were performed using Stata v.12.1 (Stata Corp, Texas, USA).

RESULTS

Patient characteristics:

We reviewed the charts of 288 patients with well-defined AIH who had been regularly followed-up for at least 2 years at Fakir Mohan Medical college hospital between April 2018 and May2023. Out of these, 28 patients (10% of our patient collective) were identified in whom immunosuppressive treatment had been completely discontinued and who had been followed for at least 1 year after treatment withdrawal. In general, we discussed a trial to withdraw medication for all patients that were in stable remission on immunosuppressive monotherapy for at least 2 years, but a few patients opted against an attempt to withdraw medication, mainly because of the risk to suffer a relapse under well-tolerated maintenance treatment. Clinical characteristics of the whole group of AIH patients and those with treatment withdrawal are given in Table 1. There were no differences in baseline characteristics between the two groups. In patients who underwent treatment withdrawal, the median age at diagnosis was 33 years (range 15–65) and 68% were female. Median duration of treatment was 48.5 months (range 35–179) and median duration of complete biochemical remission prior to drug withdrawal was 45 months (range 24–111). All patients had been on immunosuppressive monotherapy for at least 2 years when medication was stopped. Treatment regimens before medication was tapered off are shown in Table 2. In patients who maintained remission, the median follow-up after discontinuation of immunosuppressive treatment was 24 months (range 17–57).

Table 1: Patients' characteristics at the time of diagnosis

Features	Whole group (n=288)	Drug withdrawal group (n=28)
Median age, years (range)	37 (11-76)	37 (12-64)
Female	81%	71%
Concomitant immune diseases	10%	21%
Cirrhosis	21%	7%
SMA	59%	54%
ANA	82%	82%
LKM	8%	8%
SLA/LP	15%	7%
Median ALT U/L (range	586 (28-2178)	713 (40-1788)
Median IgG g/L (range)	22 (9-46)	22 (12-37)
Time in remission before drug withdrawal, months (range)	--------	44 (24-111)

Table 2: Drug regimens before treatment withdrawal

	Relapse group (n-13)	Sustained remission group (n=15)
Prednisolone monotherapy, n	0	2
Median dosage (mg)	---	2.5
Azathioprine monotherapy, n	11	12
Median dosage, mg (range)	36.3 (25-50)	46.1 (25-50)
Budesonide, n	2	0
Median dosage (mg)	3	---
6-Mercaptopurine, n	0	1
Median dosage (mg)	---	25

Success rates after treatment withdrawal:

Out of 28 patients with complete drug withdrawal, 15 patients remained in remission after a minimum follow-up of 1 year after discontinuation of therapy and 13 patients (46%) required reinstitution of treatment. Relapse occurred generally shortly after drug withdrawal. Hence, treatment had to be reinstalled in eight (62%) patients within 6 months, in ten (77%) patients within one year and in 12 patients (92%) within 2 years. One patient experienced a late relapse after 4.7 years. The median ALT values at reintroduction of medication were 273 U/L (range 42–1072). No patient suffered hepatic decompensation. Treatment was usually reinstituted with a short course of dual immunosuppressive therapy, going back to azathioprine monotherapy (dosage: 1.5 mg/kg/body weight) after about 3 months. This approach led to the rapid reinduction of remission in 12 (92%) patients. In one relapsing patient retreatment failed to achieve a complete biochemical remission within 17 months. This patient had histologically proven liver cirrhosis and was positive for SLA/LP antibodies. Two patients with type I AIH and repeatedly normal liver tests after cessation of treatment but with an observation period of less than 12 months (6 and 10 months) were not included in this analysis. If we also had considered these two patients, 57% would have stayed in remission off-treatment and the relapse rate would have been 43%. Both patients were in stable remission on azathioprine for more than 2 years (3 and 7 years) when medication was tapered off.

Predictors of relapse:

Aminotransferase (ALT), IgG and c-globulin levels were normal in all patients prior to treatment withdrawal. However, there were variations within the normal range with higher levels in patients who subsequently required retreatment (ALT: 20.2 vs. 14.7 U/l; IgG: 12.7 vs. 10.3 g/L; ¥-globulin: 16.7 vs. 12.9%). All patients in the sustained remission group had ALT levels not higher than half the ULN and an IgG not higher than 12 g/L, whereas only three patients (23%) in the relapse group fulfilled these criteria. In univariate cox regression analysis, higher levels of ALT (HR 5.95, CI 1.59–22.28, p = 0.008), IgG (HR 4.9; 1.32–18.27; p = 0.002) and ¥-globulin levels (HR 46.03; CI 1.29–28.06; p = 0.02) were associated with the time to relapse. IgG and c-globulin levels were highly correlated (Spearman's correlation coefficient: 0.53, p = 0.01). Based on the a priori decision to include only variables that were not correlated, it was decided to include only IgG in the multivariate model. The multivariate regression analysis, including ALT and IgG, revealed good evidence for an association between higher levels of ALT (HR 4.35; CI = 1.10–17.07; p = 0.04) and risk of relapse. Serum IgG levels were not significantly associated with relapse in the multivariate analysis (HR = 3.05; CI 0.79–11.85; p = 0.1). This indicates, that levels of aminotransferase and IgG within the normal range could provide additional information on the degree of remission and the durability of immunological tolerance. There was no significant difference in the time to achieve the initial remission between those patients who sustained their remission after withdrawal of treatment and those who suffered a relapse (2.7 vs. 5.3 months; HR 2.18; CI 0.69–6.84; p = 0.18). There was no evidence for an association between gender, age, IgG levels, ANA or SMA antibody titres at the time of primary diagnosis and risk of relapse. Concomitant autoimmune or immune mediated diseases were diagnosed in six (21%) patients and were not associated with the risk for relapse. Patients' characteristics before drug withdrawal are displayed in Table 3. The results of statistical analyses to assess the relationship of patients' characteristics with the risk for relapse are shown in Table 4

Table 3: Patients' characteristics before treatment withdrawal

Features	Relapse group (n=13)	Sustained remission group (n=15)
Median age at drug withdrawal years (range)	39 (18-73)	41(20-64)
Female, n	9 (69%)	11 (73%)
Concomitant autoimmune disease, n	3 (23%)	3 (20%)
Cirrhosis, n	2 (15%)	0
SMA n	7 (54%)	10 (67%)
ANA, n	12 (92%)	12 (80%)
LKM, n	2 (15%)	0
SLA/LA, n	2 (15%)	0
Biopsy prior to withdrawal, n	5 (38%)	6 (40%)
Time to achieve initial remission, months (range)	5.3 (2-13)	2.7 (1-5)
Median ALT U/L (range)	20.1 (14-34)	14.7 (8-17)
Median IgG g/L (range)	12.7 (9.6-17)	10.3 (5.2-12)
γ-Globulin (range)	16.9% (14-20)	12.9% (7.8-18)

Liver histology prior to treatment withdrawal

Only 13 out of 30 patients opted for liver biopsy prior to a trial of drug withdrawal. In two patients liver biopsy revealed inflammatory activity (mHAI >3/18 points) despite normal biochemical markers and therefore therapy was not stopped. In 11 patients (85%) liver biopsy confirmed the absence of active inflammation (mHAI 63/18 points) and medication was withdrawn. Five (46%) of the 11 patients with a normal liver histology required retreatment.

Table 4: Predictors of relapse: Crude and adjusted Cox-regression analysis

Characteristics	Crude analysis			Adjusted Analysis[1]		
	HR	95% CI	p value	HR	95% CI	p value
ALT at withdrawal	5.9	1.59-22.28	0.008	4.35	1.10-17.07	0.04
IgG at withdrawal	4.9	1.32-18.27	0.02	3.05	0.79-11.85	0.11
γ-Globulin at withdrawal	6.03	1.32-18.27	0.02			
Time to remission	2.18	0.69-6.84	0.18			

[1]Adjusted for other variable in the model. All variables with p<.1 in crude analysis were included except for ¥-globulines. This is due to the high number of missing values in the category (4 missings) and a high correlation with IgG (Spearmans correlation coefficient: 0.53, p = 0.01)

DISCUSSION

Autoimmune hepatitis is a chronic and life-long disease in the vast majority of patients[17]. On the other hand, continuous immunosuppressive treatment has potential side effects, such as the risk of infection and malignancy, and especially younger patients are reluctant to accept this life-long treatment without having tried to discontinue their medication. A clear recommendation when to offer treatment withdrawal is lacking. In clinical practice, relapse rates as high as 90% have been reported after drug withdrawal [8–12]. Relapse exposes patients to the risk of higher dose of immunosuppressive treatment and disease progression [4,18]. We conducted this single centre study in order to determine whether proper patient selection can reduce the risk of relapse and increase the chance of a sustained remission after complete drug withdrawal in patients with AIH. The clinical data of our patients were acquired prospectively according to a treatment protocol that had been developed in our hospital for treatment of AIH. Out of 288 patients with AIH, 28 patients with complete drug withdrawal were included. Using the described patient selection and duration of treatment, 54% of patients maintained a long-term remission without treatment, one of the highest rates reported. Most physicians consider drug withdrawal after about 2 years of treatment, and some even earlier if patients enter remission quickly. There is considerable uncertainty with regard to the optimal drug regimen, treatment duration and necessity of prior liver biopsy to prove histological remission and only few data are available addressing these issues. Current guidelines recommend a minimum treatment duration of about 2 years before offering treatment withdrawal in case of biochemical remission [4]. The relapse rate after treatment cessation may depend on prior treatment duration with a higher chance of sustained remission if treatment was maintained for at least four years[13]. We here prospectively validated this approach and our patients were treated for a median time of 48 months with 45 months in complete biochemical remission under medication, before treatment cessation was discussed with the patient. Importantly and in contrast to former studies, complete biochemical remission was defined as recommended in the recent AASLD guidelines[4] with repeatedly normal serum aminotransferase levels as well as normal IgG levels. The value of complete biochemical remission for the prognosis of the disease has been shown [19]. This may be underlined by the recent Dutch multicentre study, in which only 50% of patients had serum IgG levels measured and relapse rates were 90% [8]. The other important point of the approach validated here is that remission must be maintained under immunosuppressive monotherapy, mostly using low dose azathioprine, for a minimum of 2 years. This strategy is in accordance with the study by van Gerven et al. where treatment withdrawal under dual therapy ended in relapse in the vast majority of cases [8]. It has become clear that better predictors for relapse have to be identified. From other liver diseases we know that variations within the normal range of biochemical values may point to differences in disease severity [20]. In the treatment of AIH one can often observe that serum IgG can be significantly reduced within the normal range under immunosuppressive treatment. Although all patients in this study had normal ALT and IgG levels when medication was stopped, there were variations within the normal range with higher ALT and IgG levels in patients who required reinstitution of therapy. In particular, all patients in the sustained remission group had IgG levels not higher than 12 g/L and ALT levels less than half of the upper limit of normal when medication was stopped, whereas only three patients in the relapse group fulfilled both of these criteria. Statistical analysis revealed good evidence that the level of ALT within the normal range is

associated with risk of relapse after drug withdrawal and that the level of IgG is possibly associated with the time to relapse. These results are in accordance with a previous report [14] and indicate that the interpretation of biochemical values within the normal range could give valuable information on the degree of remission and the durability of immunological tolerance after cessation of therapy. However, these findings have to be interpreted with caution as we could only include 28 patients in our study, reflected by the large confidence intervals given. Therefore, further studies are warranted to validate our findings and to create robust data on predictors of relapse. A previous study[21] suggested that a rapid treatment response indicates a higher probability to maintain immunological tolerance without treatment. Patients who remained treatment-free tended to achieve initial remission more rapidly than those who required retreatment (2.7 vs. 5.3 months). However, this difference failed to reach statistical significance in our study and the cox regression model did not show evidence for an association between time to remission and risk of relapse. If biochemical remission is used as a surrogate of histological remission, around 20% of patients will still have histologically active disease at the time of treatment cessation [22]. Patients with active AIH proven histologically will almost inevitably relapse after treatment withdrawal [23]. Therefore, also in our study, two of 13 biopsied patients in biochemical remission (15%) were excluded from treatment withdrawal due to histological activity. Previously, histology was offered to all patients before treatment withdrawal but many patients opt for a trial of treatment withdrawal without biopsy. The value of liver histology for predicting clinical relapse is unclear & current recommendations diverge [4,5]. Of note, the relapse rate in the 11 patients with prior liver biopsy and proven histological remission in the study reported here was not different to the failure rate of the whole group of 28 patients (each 46%). However, the number of patients having received prior liver biopsy was too small to derive management recommendations on this issue Two patients had established cirrhosis at the time of diagnosis and two had already undergone a failed attempt of drug withdrawal before. All four patients had a relapse within 6 months. Although the number of patients is too small to draw general conclusions, it has to be taken into account that patients who suffer multiple relapses are more likely to develop cirrhosis and even hepatic failure, especially when cirrhosis is pre-existing [4]. There is ongoing discussion on the best maintenance dose of azathioprine that should be administered after relapse and doses as high as 2 mg/kg/body weight have been suggested[24]. Our institutional approach is to reinstitute immunosuppression with a short course of dual therapy, going back to azathioprine monotherapy usually within 3 months and to keep patients on the lowest effective dose. This approach succeeded to reinduce remission in 12 (92%) patients with an azathioprine maintenance dose of 1–1.5 mg/kg/body weight within 12 months. Proper patient selection cannot increase the overall number of patients maintaining remission without treatment, but it can reduce the rate of futile attempts to withdraw treatment. In the recent large Dutch study, only 1.7% of the whole group of patients remained in remission off treatment [8]. Of the entire patient cohort described here, only 28 (10%) out of 288 patients qualified for a trial of drug withdrawal and only 5% reached a sustained remission without treatment. This underlines, that AIH generally is a chronic disease, requiring life-long treatment in the vast majority of patients.

CONCLUSION

An extended duration of therapy with a stable remission on immunosuppressive monotherapy for at least 2 years can lead to acceptable rates (54%) of sustained remission off treatment. The interpretation of biochemical markers (IgG and ALT) within the normal range at the time of drug withdrawal could aid in predicting the chance to maintain a sustained biochemical remission after drug withdrawal, whereby ALT levels should preferably be less than half the ULN and IgG levels not higher than 12 g/L. Further studies are necessary to substantiate these findings and to identify predictors for relapse.

Late relapses may occur in single patients[25], therefore patients maintaining biochemical remission for more than 1 year should still be followed-up at regular intervals.

Conflict of interest:

Both authors who have taken part in this study declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this article.

Authors' contributions:

Both authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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