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The Role of Pathological Staging in Selection of Appropriate Treatment Option for Autoimmune Hepatitis: Findings of a Prospective Observational Study

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Abstract

Background

This prospective study was designed to examine the role of fibrosis staging on selection and success of treatment options for autoimmune hepatitis (AIH).

Materials and Methods

The project was conducted on 110 selected AIH patients who, based on the results of liver biopsy, had been assigned into one of the three groups (mild, stages 1 and 2, moderate, stages 3 and 4, and severe, stages 5 and 6 fibrosis). The patients received prednisolone alone or in combination with azathioprine and the response to the treatment were assessed.

Results

The number of patients who were identified to have mild, moderate and severe fibrosis were 34 (31%), 35 (32%), and 41 (37%), respectively. Of 110 patients, 56 patients (51%) received prednisolone alone and 54 patients (49%) received combined drugs protocol. In total, 77 patients (70%) showed response to the treatment. The response rate for both modalities was much lower in the third group ($P<0.05$). However, compared to the prednisolone single therapy, the response rate of combination therapy was higher in this group.

Conclusion

Our results clearly showed that response to treatment in AIH patients is decreased as hepatic fibrosis becomes more severe. Our findings indicate that pathological staging could navigate the selection of appropriate therapy, i.e. prednisolone alone is used for mild and moderate fibrosis while combination therapy is reserved for severe cases.

Key Words: Autoimmune hepatitis, Liver fibrosis, Treatment regimen.

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1- INTRODUCTION

Autoimmune hepatitis (AIH) is a relatively rare, but life-threatening disease. Although it occurs in all age ranges and various societies, it is 3-4 times more common in women. Its incidence and prevalence in Sweden and New Zealand as well as Caucasian population are reported as 1-2 per 100,000 and 11-17 per 100,000, respectively (1). Similar statistics are expected for Iran (2, 3).

Diagnosis and treatment of AIH is a challenge as incorrect diagnosis of the disease and an inappropriate treatment regimen may have important consequences for the patients. The diagnosis is based on clinical manifestations, serologic tests (presence of hypergammaglobulinemia and/or autoantibodies) and liver biopsy results and it is only made after other chronic hepatic diseases are ruled out. However, in some critical forms, the treatment can be started even before the results of liver biopsy are known (4). Serum gamma globulin level and typical serum autoantibodies for example, antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), or anti-liver–kidney microsomal antibody (LKM-1) type 1 must be checked in all cases. However, serologic tests do not have high diagnostic sensitivity and specificity, because autoantibodies levels have considerable fluctuations in the course of the disease (5). On the other hand, although infiltration of plasma cells and interface hepatitis are histological characteristics of AIH, they are not very sensitive and specific (6, 7).

According to studies by Alvarez and coworkers that has been published in the American Association for the Study of Liver Diseases (AASLD) guidelines, most patients are clinically diagnosed by typical serological and histological factors. The major indication of the objective scoring system and uncommon autoantibodies is in the diagnosis of atypical cases and also in determining the prognosis of disease (8-11) and is not always mandatory for the diagnosis of AIH. AASLD guidelines have suggested two treatment regimens for AIH: prednisolone alone or in combination with azathioprine. During monotherapy, high dose prednisolone (60 mg or 1mg/kg daily) begins which then is lowered 10mg weekly within a month to reach 10-20mg daily. In combination therapy, prednisolone (30mg daily) is used with azathioprine (50 mg or 1-2 mg/kg daily) and again prednisolone is then reduced 5-10 mg weekly to reach a dose of 10mg daily (12-14).

Various studies show that fibrosis stage in liver biopsy has a negative correlation with treatment response and sustained virological response (SVR) in chronic hepatitis C (genotype 1) (15-19). Thus, determining the liver fibrosis stage of patients for treatment plan and increasing duration of treatment period are recommended for treatment of those patients (17, 18).

Despite assessment of histological characteristics of AIH in liver biopsy specimens, using fibrosis staging for the selection of the best treatment in AIH patients has not been studied yet. To this end, we aimed to study the feasibility of choosing AIH treatment regimens based on the fibrosis stage of liver biopsy and assessing the response rate accordingly.

2- MATERIALS AND METHODS

2-1. Study Design

This prospective study was conducted from Sep 2008 to Sep 2014 in the various outpatient clinics of Mashhad University of Medical Sciences, Iran. The study protocol was approved by the ethical committee of the university. The patients who had proven AIH completed a written consent form and enrolled in the study. The diagnosis was made according to the scoring system proposed by the AASLD

guidelines which bases AIH definition on clinical characteristics, positive serology and histological abnormalities. Presence of other forms of hepatitis (e.g. Wilson's disease, viral, alcoholic and/or drug hepatitis) was considered as exclusion criteria. The type of treatment regimen (prednisolone alone or in combination with azathioprine) was determined by physician according to the patient's clinical condition and AASLD's recommendations (10). Treatment in this study was performed based on routine protocol and the authors didn't interfere in treatment of patients. The authors only evaluated response rate to treatment based on stage of liver fibrosis. Liver biopsy, based on modified HAI Ishak method (19), was performed by an experienced hepatho-pathologist. Patients made two- month intervals follow up visits by a hepatologist for clinical checkups and measurement of bilirubin, gamma globulin levels and liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] in a laboratory for up to 4 years post-treatment. Non-compliance to the treatment protocol and drug discontinuation or dose reduction due to side effects was also among the exclusion criteria. The patients were divided into three groups based on the picture of their biopsy (liver fibrosis): mild or portal fibrosis (stages 1, 2), moderate or bridging fibrosis (stages 3, 4) and severe fibrosis or cirrhosis (stages 5, 6). A checklist that contained demographic data of patients, liver biopsy result, type of treatment regimen and response to the treatment was completed for all patients. Improvement of patients' clinical condition and reaching the bilirubin, gamma globulin and liver enzymes levels to normal range was defined as the positive response to the treatment regimen. Statistical analysis, using SPSS version 13.0 was used to test the significance ($P<0.05$) of any change in variables. Frequency (%) and mean (± standard deviation [SD]) were used for the description of changes and chi-squared test and ANOVA were used for inferential analytical purposes.

3- RESULTS

3-1. Patient characteristics

One hundred thirty patients enrolled in the study. 10 patients (7.7%) didn't return for follow up, 3 patients (2.3%) died due to hepatic encephalopathy before starting of treatment, 4 patients (3%) suffered to bicytopenia due to side effect of azathioprine and 3 patients (2.3%) were suspected to drug induce AIH. Finally, 110 patients completed the study. Mean duration of follow-up was 4 years (range, 3-5 years). From 110 patients, 71 (65%) were female and 39 (35%) were male. The mean (±SD) age of patients was 31 ± 10 year, ranging from 13 to 59 years, that 32 patients (29%) were under 18 years. The results of liver biopsies showed that 34 (31%) patients had mild fibrosis (stage 1 in 18 and stage 2 in 16 patients), 35 (32%) patients had moderate fibrosis (stage 3 in 20 and stage 4 in 15 patients) and 41 (37%) patients had severe fibrosis or cirrhosis (stage 5 in 18 and stage 6 in 23 patients). There was no significant difference among groups in terms of gender ($P=0.53$) and age ($P=0.91$).

3-2. Treatment regimens

Collectively, 56 patients (51%) had received prednisolone alone (single therapy) and 54 patients (49%) had received prednisolone plus azathioprine (combination therapy). There was no significant difference among groups in terms of treatment regimen ($P=0.83$) (**Table.1**).

3-3. Response to treatment

From all 110 treated patients, 77 patients (70%) showed favorable response to their treatment regimen (**Table.2**). The response rate was much lower in severe fibrosis group than in mild or moderate fibrosis

groups (P<0.001). **Table.3** demonstrates the response rate of each protocol in the three fibrosis groups. The response rate of two regimens in mild and moderate fibrosis did not significantly differ while the response rate of combination therapy was much higher than that of single therapy in the severe fibrosis group. In addition, in all patients, the response rate of combination therapy was higher than single therapy. Side effects were related to corticosteroids before dose reduction in single therapy and combination therapy respectively consisted of acne (30.7% and 30%), moon face (25.4% and 20.%), hyperglycemia (8.0% and 5.0%) and after prednisolone dose reduction (in duration of maintenance therapy) included of back pain (59.4% and 51.3%), moon face (30% and 25.3%), skin thinning (15.5% and 13.3%), striae (14.3% and 13%), hypertrichosis (7.3% and 7%), acne (3.4% and 3.0%), hyperglycemia (3.2% and 2.8%). The main side effect of azathioprine was bicytopenia (reduction in white blood cell and platelet counts). This complication occurred in 7.4% of the patients in second group (group of combination therapy).

Table-1: Treatment regimens of patients' groups

Classification	Prednisolone alone Frequency (%)	Prednisolone+ Azathioprine Frequency (%)
Mild fibrosis (stage1 or2)	18 (53%)	16 (47%)
Moderate fibrosis (stage3or 4)	18 (51%)	17(49%)
Severe fibrosis (stage5 or 6)	20 (49%)	21(51%)
Total	56 (51%)	54 (49%)

Table-2: Overall response rate to the treatment regimens in each fibrosis groups

Classification	Response Frequency (%)	No Response Frequency (%)
Mild fibrosis (stage1 or 2)	33(97%)	1 (3%)
Moderate fibrosis (stage 3 or 4)	30(86%)	5 (14%)
Severe fibrosis (stage 5 or 6)	14(34%)	27(66%)
Total	77(70%)	33(30%)

Table-3: Response rate of the treatment regimens in each fibrosis groups

Classification	Treatment Regimen	Response Frequency (%)	No Response Frequency (%)	P-value
Mild fibrosis (stage1 or 2)	Prednisolone alone	17(94%)	1 (6%)	0.529
	Prednisolone + Azathioprine	16(100%)	0 (0%)	
Moderate fibrosis (stage3 or 4)	Prednisolone alone	15(83%)	3 (17%)	0.679
	Prednisolone + Azathioprine	15(88%)	2 (12%)	
Severe fibrosis or Cirrhosis (stage5 or 6)	Prednisolonia lone	4 (20%)	16(80%)	0.006
	Prednisolone + Azathioprine	13 (62%)	8 (38%)	
Total	Prednisolone alone	36(64%)	20(36%)	0.043
	Prednisolone +Azathioprine	44(81%)	10(29%)	

4- DISCUSSION

The classification of chronic hepatitis is based on etiology and determination of disease severity (grading) and stage of progression (staging). The scoring system for histological grading and staging of liver biopsies from patients with AIH is also useful in the evaluation of new treatment regimens and in comparing pre- and post-treatment biopsies. The core of the basic therapeutic strategy for autoimmune hepatitis includes two phases of inducing and maintaining remission with steroids and azathioprine. It is important to establish the diagnosis before cirrhosis develops. Later, the avoidance of immunosuppressant side effects, non-responders to standard induction therapy, and adherence to therapy are among the greatest challenges in treating AIH. Although the clinical features of AIH have been described, the precise criteria for selecting effective and safe therapy are yet to be established. The primary objective of this research was to explore whether the severity of the disease could assist the interventionist on choosing between single or combined drug therapies.

The findings of the present study showed that more than two thirds of AIH patients responded to the prednisolone alone or in combination with azathioprine. However, the response rate in patients with severe fibrosis was dramatically low. In addition, there was no significant difference between single therapy and combination therapy in terms of response rate in mild or moderate fibrosis while the response rate in combination therapy was much higher than single therapy in severe fibrosis. Various treatment regimens for treatment of AIH have been recommended, among which the most widely accepted one is prednisolone alone or in combination with azathioprine. The success rate of these regimens is identical (80-90%) while azathioprine alone has much lower success rates (20-22).

Mieke et al. conducted a systematic review on clinical trials about AIH treatment regimens until 2009 and found that success rates of the two regimens were similar. However, because of little study in this context, they could not determine which regimen had more benefits (23). In the clinical practice, combination therapy is preferred due to fear of prednisolone complications. However, some clinicians start prednisolone alone regimen and if any complications occur or its dose reduction proves impossible, switch to the combination therapy (23, 24). On the other hand, type of treatment regimen is sometimes determined by comorbid conditions. For example, in diabetes, osteoporosis after menopause, uncontrolled hypertension, obesity, acne, and psychosis, the combination therapy is preferred due to the need for frequent dose reduction of prednisolone. However, prednisolone alone regimen is preferred in pregnancy, severe pancytopenia, fear of azathioprine drug hepatitis, congenital deficiency of thiopurine methyltransferase (TPMT) and fear of lymphoma due to azathioprine in young people with incidence rate of 3% in 10 years (7).

Malekzadeh et al. reported changing moon face as the most common side effect of prednisolone and the most common side effect of azathioprine was bicytopenia (21). In our study moon face and steroid acne were most common side effects of prednisolone before prednisolone dose reduction but back pain (59.4% and 51.3%) and moon face were most common side effects of prednisolone in maintenance therapy. The most common side effect of azathioprine was bicytopenia too. The aim of our study was to know if the severity of liver fibrosis could help us in selecting the appropriate treatment regimen for AIH. Malekzadeh et al. studied 102 AIH patients with a mean age of 29 years, which is the same as ours; they reported the severity of liver fibrosis

as follows: mild, 12.7%; and moderate, 45.1%; and severe, 41.3% (21). In our study, we had more severe forms than moderate ones. The response rate for combination therapy within 6 months in that study was 78.4% (21), which is comparable to our result (81%). In our study, the response rate to the treatment decreases with increasing pathological stage, unlike the findings of Malekzadeh et al. that is except for the platelet and prothrombin time, none of the demographic, clinical, biochemistry and pathologic stages had any effect on response rate (20, 21). In our findings, the responsiveness rates to prednisolone alone in mild and moderate fibrosis were 94% and 83% respectively, which are within acceptable range. However, in severe fibrosis the response rate of prednisolone alone was only 20% while the response rate in combination therapy was 62%.

This finding shows that in severe fibrosis, combination therapy has better treatment success than prednisolone alone. In other words, combination therapy is better than prednisolone alone therapy overall (response rates of 81% vs. 64%, respectively). Therefore, because of the capability of reduction of prednisolone dosage in 3 to 6 months in responded patients of prednisolone alone regimen and serious side effects of azathioprine (pancytopenia, drug hepatitis and increasing risk of lymphoma), we suggest that in AIH treatment the prednisolone single therapy be used for patients with mild (stages 1, 2) and moderate fibrosis (stages 3, 4), while combination therapy with prednisolone and azathioprine be reserved for patients with severe fibrosis (stages 5, 6) because of higher success rate. Although, showing the role of pathological staging in selection of better treatment option was the main point of our study, these findings must be confirmed by clinical trials with a larger sample size and longer follow-up duration.

4-1. Limitations of the study

One of the limitations in our study was small number of patients.

5. CONCLUSION

Our findings demonstrate that the response rate of AIH patients to prednisolone alone or combined with azathioprine is decreased as the pathological stage (fibrosis) of the liver is increased. Furthermore, pathological staging could navigate the selection of the more appropriate drug regimen. In the light of our studies, it can be inferred that prednisolone alone may be used for the management of mild and moderate fibrosis (stages 1-4), while combination therapy should be reserved for severe fibrosis (stages 5 and 6).

6- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So there was no conflict of interests in this article.

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