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Predictive factors of poor response to therapy in Autoimmune Hepatitis

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ABSTRACT

Aim: To evaluate "ex ante" the predictive factors of incomplete/absent response to the standard therapy in a well characterized series of Autoimmune Hepatitis (AIH) patients from Italy.
Methods: Of 282 AIH patients screened from our database 166 (59%) had a sustained response and 116 (41%) had an incomplete/absent response to the therapy; all patients were analyzed for the clinical, serological and histological parameters at diagnosis.
Results: The patients with incomplete/absent response were characterized by significantly younger age (30 aa vs 42 aa $p = 0.001$) and a significantly higher frequency of cirrhosis at diagnosis than patients who had a complete response to therapy (26% vs 3% $p < 0.0001$); furthermore, patients with incomplete/absent response were distinguished from those with a complete response for significantly lower serum levels of both AST (7.9 × upper normal limit [unl] vs 13 × unl $p < 0.005$) and ALT (10.9 × unl vs 18 × unl $p = 0.002$) at diagnosis, and by an increase in IgG serum levels (1.43 × unl vs 1.27 × unl $p = 0.009$). After stepwise logistic regression, cirrhosis at diagnosis ($p = 0.003$, OR 0.12, 95% CI 0.03–0.49) and younger age ($p = 0.001$, OR 1.03, 95% CI 1.01–1.05) represent two independent variables of incomplete/absent response.
Conclusions: Younger age and cirrhosis are predictive of lack of response to the standard therapy in AIH patients.

1. Introduction

Autoimmune Hepatitis (AIH) is a chronic progressive liver disease characterized by interface hepatitis, hypergammaglobulinemia and circulating autoantibdies [1], that, if untreated, can progress to the end stage liver disease.

Since the first controlled trials with the steroids in the seventies [2–5], the response to immunosuppressive therapy was so good that even today the steroid is the cornerstone of treatment of Autoimmune Hepatitis. On the other hand, over the years, the perception on therapeutic goals to be achieved is changed; the maintenance of transaminases below the value of 2× now is no longer considered a therapeutic success, on the contrary a failure, or at least an incomplete response to therapy [6]. Unfortunately, there is a rate of patients who does not get or maintain remission with the conventional therapy represented by steroids and azathioprina. Alternative immunosuppressive drugs such as cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, everolimus, sirolimus and rituximab have been reported for this difficult to treat patients with promising but inconclusive results [7–10]. The aim of the present study was to evaluate "ex ante", before starting therapy, the predictive factors of incomplete/absent response to the standard therapy in a well characterized series of AIH Italian patients. The importance to identify risk factors predicting the response to the standard therapy reside in the opportunity to be more aggressive in the first line therapy and/or start immediately with an alternative drug and to strictly monitor this group of patients

2. Patients and methods

For the selection of patients with AIH, we took advantage from our database collecting cases of ALD during the last twenty years. All patients were negative for the known hepatotropic viruses

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and other causes of chronic liver disease, in particular we have excluded from our study all the cases of overlap syndrome between HCV and AIH, between primary biliary cholangitis and AIH and between primary sclerosing cholangitis and AIH. The drug history was negative for all potential hepatotoxic drugs. The diagnosis of Autoimmune Hepatitis was based on the score of 1999 of the International Autoimmune Hepatitis Group [11], and all patients reaching this diagnosis have been treated. In terms of clinical presentation AIH has been called "acute" when there was evidence of jaundiced acute hepatitis, "chronic" when symptoms not directly related to liver disease were chronically observed (fatigue, weight loss, fever, sickness, loss of appetite) and "asymptomatic" when, during screening tests, abnormalities in serum transaminases and bilirubin level were found without any symptom [12–14]. Patients were monitored over the years through outpatient check-ups/hospitalization at rates quarterly/half-yearly/yearly depending on the clinical needing. Laboratory tests such as ALT, AST, and bilirubin were regularly monitorated in order to evaluate the efficacy of the therapy.

2.1. Histology

Liver biopsy was available in 232 of 282 (82%) of patients; all patients had the presence of interface hepatitis and linphoplasmocytic infiltrate, while the presence of hepatocytic rosettes and regenerative nodules were representative of a severe histological activity [11]. All the patients who did not perform a liver biopsy however reached a score of AIH "probable" at the score of 1999 [11].

3. Serological tests

Smooth muscle antibodies (SMA), antinuclear antibodies (ANA), liver kidney microsome type 1 (LKM1), and liver cytosol type 1 (LC1) were evaluated by indirect immunofluorescence on rat tissues as reported earlier [15]. A dilution of 1:40 in adults and 1:20 in child was considered significant. Anti soluble liver antigen (anti-SLA) was detected by ELISA kit in according with the manufacturer's instructions (Euroimmun, Lubeck, Germany).

4. Treatment

All patients received conventional treatment with corticosteroids and azathioprine, starting with methyl-prednisolone 1–2 mg/kg body weight and then adding azathioprine [6]. Clinically we considered "responders" all patients normalized transaminases, while we considered patients with an incomplete/absent response those patients despite high doses of steroid therapy maintained transaminases altered under 2× (incomplete response) or more than value of 2× (no response) [12].

5. Statistical analysis

Categorical variables were compared using chi-square and Fisher' s exact test when applicable. Comparison of continuous variables between the different groups was performed using the Mann–Whitney test. Stepwise multiple regression analysis was performed with incomplete absent response as dependent variable. Clinical and/or laboratory parameters were considered as independent variables. A p value less than 0.05 was considered significant. Statistical analysis was performed using both GraphPad InStat 3.0a for Macintosh (GraphPad Software, San Diego, CA) and SPSS for Windows 10.0.07 (SPSS Inc., Chicago, IL).

6. Results

The group of patients who had an incomplete/absent response to standard therapy was characterized by significantly younger age (30 aa vs 42 aa $p = 0.001$), higher frequency of cirrhosis at diagnosis (26% vs 3% $p < 0.0001$) and higher serum levels of IgG (× 1.43 unl vs × 1.27 unl $p = 0.009$) than patients with a complete response; furthermore, patients achieving a complete remission were distinguished from patients who had an incomplete/absent response to therapy for significantly higher serum levels of both AST (13 × unl vs 7.9 × unl $p < 0.005$) and ALT (18 × unl vs 10.9 × unl $p = 0.002$) at diagnosis. Under clinical and biochemical point of view no other significant differences between the two groups have been observed, and also the rate of relapse during the tapering of steroid therapy was similar (73% vs 68%). Under serological profile the two groups were distinguished by a higher frequency of seropositivity for SMA (59% vs 46% $p = 0.03$) and LC1 (18% vs 4%, $p = 0.001$) in patients with incomplete/absent response while shared similar frequencies of detection for antinuclear antibody, anti ds DNA, LKM1, and SLA. All the reported data are summarized in Tables 1–3.

After the stepwise logistic regression using incomplete/absent response as dependent variable we observed that cirrhosis at diagnosis ($p = 0.003$, OR 0.12, 95% CI 0.03–0.49) and younger age ($p = 0.001$, OR 1.03, 95% CI 1.01–1.05) represents the two independent variables of incomplete/absent response to therapy.

7. Discussion

To date immunosuppressive therapy with steroids and azathioprine is the conventional therapy for AIH; it is now accepted that maintaining the transaminases between 1 and 2 × upper normal limits (incomplete response) should not be considered as endpoint because relapse after termination of therapy in those patients is common [6]. The design of our study was to identify "ex ante" patients that partially respond or do not respond to standard immunosuppressive therapy to get to them a more aggressive therapeutic approach.

In our study we found a low rate of complete remission among patients with cirrhosis at diagnosis and cirrhosis appear to be a independent variable of lack of response to therapy; our observation is in according with some other experiences from the literature; for example Feld et al. [16] identified the presence of cirrhosis at diagnosis as predictive of poor prognosis in a Canadian AIH population, while Kirkstein et al. [17] described cirrhosis at diagnosis, together with younger age and anti SLA positivity, as risk factor for a poor short and long term outcome, so these patients should be strictly monitored. In contrast to these data, there are other reports from Japan [18] and New Zealand [19] which does not confer any negative prognostic significance to the cirrhosis at diagnosis. Given the same therapeutical approach it is difficult to identify the reasons of these discrepancies; one of them could reside in the differences in geographical, ethnic and genetic background of the studied populations.

In according with Kirkstein et al. we also found the younger age as independent factor of incomplete/absent response to therapy and we cannot rule out that a low compliance to therapy over all in young female patients could account, at least in part, for this result; on the other hand it is right to underscore how AIH in elderly patients is often mild and well controlled by the therapy [13]. With respect to the gender, at variance with other autoimmune disorder such as early rheumatoid arthritis, where women showed a considerably lower remission rate than men [20], in our series of AIH patients treatment response does not appear to be affected by sex.

With regard to the other results, the observation of lower serum levels of transaminases within the group of patients with an