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Type 1 autoimmune hepatitis in children and adolescents: assessment of immunosuppressive treatment withdrawal

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Abstract

Objective: To assess treatment withdrawal in children and adolescents with autoimmune hepatitis, with clinical and laboratory remission for a minimum period of 24 months, determining the relapse rate after treatment withdrawal.

Method: This is a descriptive, retrospective and partially prospective study of 21 children and adolescents with type 1 autoimmune hepatitis treated at the Outpatient Division of Pediatric Hepatology, Teaching Hospital of *Universidade Federal de Minas Gerais* (UFMG), Belo Horizonte, Brazil, between January 1986 and December 2001.

Results: We assessed 54 patients and selected 21, of whom 19 were female subjects (90.5%), aged between 5.7 and 17.6 years (median = 13.8 years), with a mean follow-up of 5.1±2.4 years (median = 4.4 years) and an average clinical and laboratory remission of 4.1±1.5 years (median = 4.1 years). Out of the 21 patients studied, 10 (47.6%) manifested some inflammatory activity that prevented the discontinuation of treatment, which was withdrawn in 11 patients (52.4%). Out of these, six patients (54.5%) presented reactivation of the disease and five maintained clinical and laboratory remission with a mean follow-up of 4±1 years (median = 3.9 years). The time interval between discontinuation of treatment and reactivation of the disease ranged from 29 days to 40.3 months (median = 2.2 months).

Conclusions: We observed a high relapse rate (54.5%) in this group of patients with autoimmune hepatitis, which was more frequent within the first 12 months after treatment withdrawal, in addition to a high number of patients that presented some degree of inflammatory activity despite the long period of clinical and laboratory remission.

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Introduction

Autoimmune hepatitis (AIH) affects a group of patients with chronic hepatitis that apparently lost immune tolerance to liver-specific antigens.[1-5] In order to establish the diagnosis, it is necessary to rule out other causes of chronic liver disease. It is strongly associated with female individuals, hypergammaglobulinemia, other autoimmune disorders, with histocompatibility antigens (HLA B8, DR3, DR4) and with autoantibodies: antinuclear antibodies (ANA), anti-liver-kidney microsomal antibodies (type 1), anti-smooth muscle antibody (ASMA), antibody against soluble liver antigen, antibody against the human asialoglycoprotein receptor and antibodies against liver-specific membrane lipoprotein.[3,4] The response to immunosuppressive therapy achieved by more than two thirds of patients[5] is an important diagnostic criterion. AIH is a rare disease among children; therefore, there is a paucity of pediatric studies about it in the medical literature.[6-13]

Early discontinuation of immunosuppressive therapy, especially before histological resolution, causes relapses and increases the risk of progression to cirrhosis.[14] Relapse after treatment withdrawal occurs in 57 to 88% of adult patients,[15-18] and in 53.8 to 88.9% of children and adolescents.[8,12] By evaluating children and adolescents

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with AIH in our setting, we noted full therapeutic response in 77.8% of patients, but with complications arising from immunosuppressive therapy in 31.3% of the cases, and also height deficit indicated by the height/age z score.[19]

Due to the deleterious effects of immunosuppressants and to the paucity of literature on the discontinuation of treatment in children and adolescents with AIH,[8,12] the present study aims to assess the possibility of children and adolescents with AIH showing remission of the disease after the withdrawal of immunosuppression. Thus, the aim of this study is to assess the discontinuation of immunosuppressive therapy in children and adolescents with AIH, who had clinical and laboratory remission of the disease within at least 24 months of treatment, determining the relapse rate after treatment withdrawal and the percentage of untreated patients that maintain remission.

Patients and methods

This is a longitudinal, descriptive, retrospective and partially prospective study of children and adolescents with type 1 AIH (positive ANA and/or ASMA), treated at the Outpatient Division of Pediatric Hepatology of Hospital das Clínicas of Universidade Federal de Minas Gerais (UFMG), between January 1986 and December 2001. The treatment consisted of the combination of prednisone and azathioprine in daily doses of 1 to 2 mg/kg/day (maximum 60 mg/day) and 1.5 mg/kg/day (maximum 100 mg/day), respectively. Reassessments were made every eight weeks and the dose of prednisone was reduced to 5 mg/day, keeping the patient in clinical and laboratory remission. Azathioprine was maintained at the initial dose. For patients who presented with leukopenia and/or thrombocytopenia at the beginning of the treatment, only prednisone was maintained, whereas azathioprine was discontinued in those patients who developed leukopenia and/or thrombocytopenia during the treatment.

The following inclusion criteria were used: patients with definitive diagnosis of AIH, full response to immunosuppressive therapy according to the criteria established by the International Autoimmune Hepatitis Group,[3,4] clinical and laboratory remission (aminotransferase and gammaglobulin levels in line the reference values) of at least 24 months and negative antibody titers. A total of 54 children and adolescents with AIH were assessed, of whom 21 met the inclusion criteria, whereas 26 were excluded from the study for not having a minimum remission period of 24 months, and seven did not have full response to the therapy.

After the selection, the 21 patients were submitted to liver biopsy for assessment of inflammatory response, and medication was discontinued in patients with no inflammatory activity according to the criteria of Ishak et al.[20] The patients whose treatment was suspended were followed up in terms of their clinical and laboratory parameters every two months. Laboratory workup included the activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum protein electrophoresis and quantitative and qualitative analysis of ANA and ASMA by indirect immunofluorescence. The following signs were considered indicative of AIH resurgence: development of clinical manifestations suggestive of the disease (jaundice, adynamia, anorexia, arthralgia, myalgia), increase in aminotransferase level by more than twofold the reference value and increase in gammaglobulin fraction. Any abnormal finding concerning these parameters led to reinstitution of therapy.

In the statistical analysis, the continuous variables with normal distribution were expressed as means±standard deviation (SD) and compared using t tests and ANOVA, whereas the continuous variables without a normal distribution were expressed as medians and 25-75% interquartile range ($_{25\text{-}75\%}$IQR) and compared by the nonparametric Kruskal-Wallis test. The distribution of variables was compared by Fisher's exact test, two-tailed or chi-squared (χ^2) test with Yates' correction. The level of significance was established at 5% ($p < 0.05$). The study protocol was approved by the Ethics Committee of Universidade Federal de Minas Gerais.

Results

The patients' ages at diagnosis ranged from 1.7 to 11.6 years (mean of 8.1±2.9 SD; median of 6.6 years). Of the 21 selected patients, 19 were female (90.5%). The patients' ages on admission to the study (control liver biopsy), ranged from 5.7 to 17.6 years (mean of 13.2±3.9 SD years; median of 13.8 years). The ANA test at the time of diagnosis of AIH was positive in 12/21 patients (52.4%), with titers between 1:80 and 1:640 (median of 1:80; $_{25\text{-}75\%}$IQR - 1:40-1:160). ASMA was positive at diagnosis in 13/21 patients (57.1%), with titers between 1:80 and 1:5.120 (median of 1:480; $_{25\text{-}75\%}$IQR = 1:200-1:640), whereas the concomitant presence of positive ANA and ASMA was observed in 4/21 patients.

After a follow-up period of 2.4 to 10.6 years (median of 4.4; $_{25\text{-}75\%}$IQR = 3-6.9 years), the patients underwent a liver biopsy so that the possibility of treatment withdrawal could be analyzed. The duration of clinical and laboratory remission, up to the time of the liver biopsy, ranged from 2.2 to 7.2 years (median of 3.9; $_{25\text{-}75\%}$IQR = 2.9-5.1 years).

Of the biopsied patients, 10 showed inflammatory activity, which did not allow for treatment withdrawal (five patients with mild piecemeal necrosis, five with discrete inflammatory activity, restricted to the portal tracts; therefore, this group of patients did not benefit from the assessment of possible immunosuppressive treatment withdrawal within 24 months of clinical and laboratory remission.

The treatment was discontinued in 11 patients, who received maintenance doses of immunosuppressants for a period of 2 to 7 years (median of 3; $_{25\text{-}75\%}$IQR = 2-5.8 years). Of these 11 patients, six showed reactivation of the disease, with remission after reinstitution of the original treatment and without any side effects. The time interval between treatment withdrawal and reactivation of the disease ranged from 29 days to 40.3 months (median of 2.2;

$_{25\text{-}75\%}$IQR = 1.9-17.5 months). The relapses were characterized as follows: one patient presented with clinical manifestations (apathy, listlessness and drowsiness) with liver biopsy showing resurgence of the disease, three simply showed an elevated aminotransferase level, one patient presented with symptoms (adynamia and jaundice) associated with elevated aminotransferase levels, and another patient presented with adynamia, jaundice and positive autoantibody (ANA) results.

Only five patients still showed clinical and laboratory remission with a follow-up period of 2.6 to 5.4 years (mean of 4±1 years). No statistically significant difference was observed, when the variables listed in Tables 1 and 2 were assessed, between the group in which treatment was discontinued and the group that maintained some degree of inflammatory activity on liver biopsy (Table 1), as well as between the patients who relapsed and those who maintained remission of the disease (Table 2).

Discussion

When evaluating the possibility to discontinue immunosuppressive therapy in children and adolescents with type 1 AIH with at least 24 months of clinical and laboratory remission, we observed that out of the 21 selected patients, therapy could be discontinued in only 11, and that only five patients currently present remission of the disease for a period longer than 24 months after treatment withdrawal. The large amount of liver biopsies that still showed some degree of inflammatory activity contributed to the small number of patients who benefited from the evaluation. Despite literature reports of histopathological improvement within 18 to 20 months of clinical and laboratory remission,[16,21] 10 of the 21 selected patients still had some inflammatory activity. Such evidence corroborates the clinical and laboratory dissociation regarding the histological activity that occurs in AIH. Very likely, total resolution of the inflammatory activity will occur later on, after the 24 months proposed in this study, or will not occur completely, with only some control over the inflammatory process that prevents the progression of the disease to cirrhosis and liver failure. An increase in the length of treatment, with higher doses of immunosuppressants, may be a way to achieve complete histological normalization; however, this alternative should be weighed against the risks of side effects caused by the medication.

By taking into account only the 11 patients in whom treatment was discontinued, 45.4% benefited from this measure, with a relapse rate of 54.6%. Therefore, although the group of patients assessed in this study has a long period of clinical and laboratory remission with a constant maintenance dose of immunosuppressants, the relapse rate was similar to that found by Gregorio et al., who observed relapse in 61.5% (8/13) of the children in whom treatment was discontinued, with a 44.4% relapse rate among those patients with type 1 AIH (4/9).[12] Nevertheless, the relapse rates were lower than those found by Maggiore et al., who observed relapses in 88.9% (8/9) of the children; but it should be highlighted that five of them were anti-LKM1-positive, which does not allow for easy comparisons.[21] The relapse rate of this study is similar to that observed in adult patients, in whom it affects 57 to 88% after discontinuation of immunosuppressive therapy.[15-18,22,23]

Relapses occurred between 29 days and 40.3 months (median of 2.2; $_{25\text{-}75\%}$IQ = 1.9-17.5 months) after treatment withdrawal, a time period that is consistent with other studies, in which relapses occurred mainly in the first 12 months following the discontinuation of immunosuppressive therapy.[12,15,16,21] Even though relapses are rare 24 months after treatment withdrawal, follow-up must be done on a permanent basis, since AIH alternates inactive periods with reactivation of the disease.

The high rate of relapse and its early onset make us wonder about the actual advantage of submitting children and adolescents to a liver biopsy, with later discontinuation of the treatment, thus running the risk of reactivation of the disease, characterized by severe liver failure, as described by Hergarty et al.[15] Perhaps maintaining treatment indefinitely is an alternative in children, and Czaja described that low doses of drugs that are able to control clinical and biochemical manifestations of the disease in adults may be satisfactory,[25] especially when treatment withdrawal is not the best option. An alternative to mitigate the side effects of corticosteroids was advocated by Johnson & McFarlane in adults, in which the patient is treated only with azathioprine after the withdrawal of corticosteroids.[24]

An important factor that was not assessed in this study and that might explain the high relapse rate despite the criteria used is genetic susceptibility through HLA testing, in which there may be some variation between the several regions that may explain the different behavior regarding the response to and discontinuation of the treatment.[26-30] By studying adult patients with AIH, Kanzler et al. found a higher frequency of HLA A1; B8; DR3 (56 *versus* 29% - $p < 0.05$) in the relapse group.[17] Czaja et al. noted a higher frequency of HLA DR13 in patients with AIH in Brazil, where the onset of the disease occurs earlier, with high levels of aminotransferase and gammaglobulin, higher occurrence of ASMA and low frequency of ANA, differently from what occurs in U.S. Caucasian patients.[29]

With regard to the diagnosis of relapse after treatment withdrawal, the results obtained in this study are in agreement with the available literature, where reactivation of AIH can be safely detected through clinical evaluation (occurrence of adynamia, hyporexia, emaciation and jaundice) and laboratory assessment (aminotransferase level). Histopathological evaluation is seldom necessary, being reserved for cases in which doubt exists regarding the occurrence of relapse.[15,22] In the evaluation performed by Hergarty et al., only four of 26 patients did not show any clinical manifestation of relapse.[15] According to the study conducted by Czaja et al., fatigue (62%), arthralgia (44%), pruritus (32%), anorexia (29%), and pain in the upper right quadrant (15%) were the most important symptoms, with 24% of the patients showing just elevated levels of aminotransferases.[22]

Table 1 - Comparison of children and adolescents with autoimmune hepatitis according to the inflammatory activity found in the control liver biopsy

Variables	Without inflammatory activity	With inflammatory activity	p
Gender			
Female	10/11	9/10	0.50 *
Clínics on admission			
Acute	8/11	4/10	0.28 *
Chronic	3/11	6/10	
Age at diagnosis (years)			
Mean (standard deviation)	8.9±3.3	7.2±2.4	0.16 †
Time of clinical and laboratory remission (years)			
Median	4.7	3.6	0.96 ‡
$IQ_{25-75\%}$	2.9-6	2.8-4.3	
Gammaglobulin at diagnosis			
Median	2.6	3.2	0.62 ‡
$IQ_{25-75\%}$	2.1-3.6	2.4-3.7	
Albumine at diagnosis			
Median (standard deviation)	3.97±0.5	3.4±0.4	0.50 †
AST at diagnosis			
Median	264	463	0.33 ‡
$IQ_{25-75\%}$	177-858	227-1.734	
ALT at diagnosis			
Median	420	359	0.93 ‡
$IQ_{25-75\%}$	206-500	106-1.128	
Score of diagnostic biopsy			
Median	7	5.5	0.62 ‡
$IQ_{25-75\%}$	5-11	4-10	
Diagnostic biopsy staging			
Median	4	5	0.87 ‡
$IQ_{25-75\%}$	3-6	3-5	
Cirrhosis (number of patients)	4	3	0.83 *

AST = Aspartate aminotransferase; ALT = alanine aminotransferase.
* Fisher's exact test.
† Student's t test.
‡ Kruskal-Wallis's test.

However, it should be underscored that the size of the sample and the absence of an HLA test may limit definitive conclusions about treatment withdrawal in children and adolescents with type 1 AIH. There have been few reports in the international literature on treatment withdrawal in children and adolescents with AIH, with a smaller sample than the one used herein and with less strict selection criteria and without an HLA test.[12,21] The small patient populations are related to the rarity of the disease among pediatric patients, where only a multicenter study with a standardized treatment regimen can include a larger number of patients, allowing us to obtain adequate knowledge about relapses after treatment withdrawal. In this case, it is essential for the homogenization of groups regarding clinical and laboratory characteristics and genetic susceptibility, due to the possible variations that may occur among the different regions and that may explain the different behavior towards the response of and discontinuation of the treatment.[26-30]

Our conclusion is that the discontinuation of immunosuppressive therapy in children and adolescents coexists with a high rate of relapses, which are more frequent in the first 12 months after treatment withdrawal. Clinical manifestations and changes in the activity of aminotransferases are reliable for the diagnosis of relapses, and histopathological evaluation is reserved for the cases in which the diagnosis of recurrence cannot be established categorically. The assessment of treatment withdrawal should be made for a period longer than 24 months of disease remission, since total histopathological remission of the necroinflammatory activity has a late onset and is dissociated from clinical and laboratory remission.

Table 2 - Comparison of children and adolescents with autoimmune hepatitis submitted to treatment discontinuation with and without relapse

Variables	With relapse	Without relapse	p
Gender			
Female	6/6	4/5	0.92 *
Clinics on admission			
Acute	5/6	3/5	0.85 †
Chronic	1/6	2/5	
Age at diagnosis (years)			
Mean (standard deviation)	8.9±3.2	9.1±3.7	0.95 †
Time of clinical and laboratory remission (years)			
Median	3.5	6.2	0.96 ‡
$IQ_{25-75\%}$	2-5.7	3.8-6.3	
Gammaglobulin at diagnosis			
Median	2.5	3.1	0.58 ‡
$IQ_{25-75\%}$	1.5-3.5	2.2-3.6	
Albumine at diagnosis			
Mean (standard deviation)	4±0.6	3.9±0.5	0.71 †
AST at diagnosis			
Median	532.5	264	0.95 ‡
$IQ_{25-75\%}$	68-979	259-340	
ALT at diagnosis			
Median	410.5	420	0.72 ‡
$IQ_{25-75\%}$	55-909	317-422	
Score of diagnostic biopsy			
Median	6	9	0.52 ‡
$IQ_{25-75\%}$	2-11	7-9	
Diagnostic biopsy staging			
Median	4	4	0.97 ‡
$IQ_{25-75\%}$	3-6	4-5	
Cirrhosis (number of patients)	2	2	0.78 *

AST = Aspartate aminotransferase; ALT = alanine aminotransferase.
* Fisher's exact test.
† Student's t test.
‡ Kruskal-Wallis's test.

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