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COMPARISON OF PREDNISOLONE ALONE AND IN COMBINATION WITH AZATHIOPRINE REGIMENS IN TREATMENT OF AUTOIMMUNE HEPATITIS: A PROSPECTIVE STUDY

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- **ABSTRACT**

Background: Side effects of steroid therapy of autoimmune hepatitis are seen more frequently with prednisolone only regimen. However, the question of efficacy restrains the broad use of prednisolone in combination with azathioprine.
Objective: To compare biochemical responses to the two standard immunosuppressive drug regimens (prednisolone alone and prednisolone in combination with azathioprine) in children with autoimmune hepatitis.
Methods: The study was performed on 42 children with autoimmune hepatitis. Patients were attributed to two groups,with group A receiving prednisolone alone and group B receiving prednisolone in combination with azathioprine, using simple random attribution unless there was a contraindication to azathioprine. The patients were evaluated for treatment response on three occasions: short term (one month after starting therapy), intermediate term (four to six month after starting therapy), and long term (one year after starting therapy). Chemical response was defined as decrease in aminotransferases to a level below two times the normal values and gamma globulin to lower than 2.8 g/dL. Clinical response was defined as improvement in the initial clinical signs and symptoms (jaundice, hepatomegaly, splenomegaly, fever, and edema/ascites).
Results: There were no differences in chemical and clinical response rates between the two groups. Both clinical and chemical response rates in intermediate term were significantly higher than short term. However, clinical and chemical response rates in long term did not significantly differ from intermediate term.
Conclusion: The study shows that some patients need time to respond to therapy. Nonetheless, it seems that whenever there is no improvement after six months of therapy, it is prudent to change the treatment regimen rather than waiting for response. With the same efficacy and less side effects, the combination regimen must be preferred as the standard regimen, unless there is a contraindication to azathioprine.

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Key Words • Hepatitis, autoimmune • drug therapy • prednisolone • azathioprine

Introduction

Autoimmune hepatitis is a hepatocellular inflammation of unknown cause, characterized by hypergammaglobulinemia, serum liver-associated autoantibodies, and periportal hepatitis on histologic examination[1]. Early diagnosis and treatment of this condition is essential to improve survival, quality of life, and defer liver failure requiring transplantation[2].

Different drug regimens are used, to induce remission through immunosuppression in patients with autoimmune hepatitis. Prednisolone alone and prednisolone (half does) in combination with azathioprine are the standard regimens[1,3,4]. Other treatments regimens include cyclosporine[5,6,7], methotrexate[8], tacrolimus[9], budesonide[10], or ursodeoxycholic acid (UDCA)[11,12]. These latter regimens are alternatives to the first two regimens, administered when the first two regimens show failure. Intravenous immunoglobulin has also been successfully used in one patient, but more investigation is needed before giving value to this treatment regimen.[13]

Since higher doses of prednisolone is needed, side effects of steroid therapy are seen more frequently with prednisolone only regimen. However, the question of efficacy restrains the broad use of prednisolone in combination with azathioprine. This is especially true in developing countries such as

Iran where delays in the diagnosis and treatment prevent the physician to accept any further risk of indefinite efficacy.

The aim of this prospective study was to compare responses to the two standard immunosuppressive drug regimens (prednisolone alone and prednisolone in combination with azathioprine) in children in Iran.

Patients and Methods

The study was performed using 42 children with autoimmune hepatitis attending Shiraz University of Medical Sciences Pediatric Clinics and Tehran Pediatrics Center, from September 1995 to September 1999. Diagnosis of autoimmune hepatitis was based on the followings: 1- Elevated serum aminotransferases and gamma globulin. 2- Normal serum α 1-antitrypsin and ceruloplasmin. 3- Seronegativity for HBsAg and anti-HCV. 4- Negative past history of parenteral blood exposure. 5- No recent use of drugs with known hepatotoxicity.[14]

After confirmation of the diagnosis, the patients were divided to two groups each receiving one of the two standard regimens. Group A received prednisolone alone on the following schedule: 60 mg/1.73 m^2 surface area (SA) for one week, then 40 mg/1.73 m^2 SA for one week, then 30 mg/1.73 m^2 SA for two weeks, and finally 20 mg/1.73 m^2 SA for one year. Group B received prednisolone on the same schedule of group A but with half those amounts, plus one mg/Kg azathioprine. Patients were attributed to the groups using simple random attribution unless there was a contraindication to azathioprine (thrombocytopenia and/or leukopenia). The drugs used were obtained from Iranian generic drug market.

The patients were evaluated for treatment response on three occasions: Short term (one month after starting therapy), intermediate term (four to six months after starting therapy), and long term (one year after starting therapy). Chemical response was defined as decrease in aminotransferases to a level below two times the normal values and gamma globulin to lower than 2.8 g/dL. Clinical response was defined as improvement in the initial clinical signs and symptoms (jaundice, hepatomegaly, splenomegaly, fever, and edema/ascites) evaluated by the physician. Since most of the patients (67%) refused the second liver biopsy one year after the initiation of therapy, histologic response was not assessed.

Two-tailed *t*-test, GLM-repeated measures, Chi-square, and Fisher's exact test were statistical tests used for data analysis.

Results

The patients were consisted of 27 girls (64.3%) and 15 boys (35.7%). The female/male ratio was 1.8 (95% confidence interval (CI) = 1.4 – 2.5). Mean ? standard deviation (SD) of age at the onset of disease was 6.9 ? 3.8 years (95 % CI= 5.7 – 8.1). Mean age at the onset of disease was 6.8 ? 3.7 years for girls and 7.2 ? 3.9 years in boys showing no significant difference. Mean ? SD for the time interval between the onset of symptoms to the initiation of therapy was 7.0 ? 13.5 months. The most common clinical finding (Table 1) was hepatomegaly (88%), followed by jaundice (71%) and splenomegaly (64%). There were no patients with arthritis.

There were 29 patients in group A and 13 patients in group B. Before starting therapy, Mean ? SD for serum SGOT was 923 ? 900 U/ml for group A and 435 ? 439 U/ml for group B, with a significant statistical difference (P=0.02, two-tailed *t*-test). At the same time, Mean ? SD for serum SGPT was

707 ? 747 U/ml for group A and 247 ? 199 U/ml for group B, with a significant statistical difference (P=0.004, two tailed *t*-test). Mean ? SD for serum albumin was 3.6 ? 0.65 g/100ml for group A and 2.9 ? 0.86 g/100ml for group B, with no significant statistical difference at the onset of therapy. Mean ? SD for serum globulin was 3.76 ? 1.16 g/100ml for group A and 4.6 ? 2.1 g/100ml for group B, with no significant statistical difference (Table 2).

Thirty seven patients returned for short-term clinical examinations. Clinical response was seen in six (16.2%). This was the same for group A with clinical response in four (16%) of 25 and group B with clinical response in two (16.7%) of 12 (p=0.88, Fisher's exact test). Thirty-five patients returned for intermediate term clinical examinations. Clinical response was seen in 16 (45.7%). This was the same for group A with clinical response in 10 (43.5%) of 23 and group B with clinical response in six (50.0%) of 12 (p=0.71, Chi-square test). Thirty-one patients returned for long term clinical examinations. Clinical response was seen in 12 (41.9%). This was the same for group A with clinical response in 10 (41.6%) of 24 and group B with clinical response in three (42.9%) of seven (p=0.64, Fisher's exact test). Table 3 summarizes these data.

There were significant decreases in serum SGOT, SGPT, and globulin and increase in serum albumin with time in both groups ($p < 0.001$ for all tests, GLM–repeated measures). There were no significant differences in SGPT and SGOT, albumin, and globulin between groups at any time (Table 2). In short term chemical response was seen in five (14.3%) of 35. This was statistically the same for group A with chemical response in four (16.6%) of 24 and group B with chemical response in one (9.1%) of 11 (p=0.49, Fisher's exact test). Laboratory data was available for thirty-three patients at intermediate term. Chemical response was seen in 12 (36.4%). This was the same for group A with chemical response in eight(36.4%) of 22 and group B with chemical response in four (36.4%) of 11 (p=0.65, Fisher's exact test). Laboratory data was available for twenty-five patients at long term. Chemical response was seen in nine (36%). This was the same for group A with chemical response in seven (36.8%) of 19 and group B with chemical response in two (33.3%) of six (p=0.63, Fisher's exact test). Table 3 summarizes these data. Both clinical and chemical responses in intermediate term were significantly higher than short term (P =0.03 and P= 0.006, Chi square test). However, clinical and chemical responses in long term did not significantly differ from intermediate term.

Side effects of steroid therapy were seen more frequently in group A (79.3%) than group B (23.1%). This was statistically significant (p = 0.001, Fisher's exact test).

Discussion

Higher prevalence of the disease in girls is in accordance with previous studies indicating female preponderance in all ages and all types of autoimmune hepatitis[1]. Mean age of the patients was 6.9 years Since the study sample was drawn from a pediatric clinic (i.e. population with age less than 16 years), this does not show the age distribution of the disease. There was a one-month-old neonate in the study group, a very rare event.

Mean time interval between the onset of symptoms and therapy was seven months. This shows delay in referral and/or diagnosis in our health care system. Since delayed diagnosis and treatment leads to lower response rate and higher progression toward cirrhosis,[15] solving this problem is necessary for our health care system.

There were similar treatment responses in the two groups. This similarity was seen in both clinical and chemical responses. The equal effectiveness of prednisolone alone and in combination with azathioprine

is supported with previous findings.[3]

Response rates in intermediate term were higher than short term. This shows that some patients need time to respond to therapy. Nonetheless, there was no significant increase in the response rate after intermediate term. In other words, there is little hope to achieve response to therapy after intermediate term, if it is not done yet. Cyclosporine and methotrexate have shown promise in treatment of patients with steroid resistant autoimmune hepatitis.[7,8] It seems that whenever there is no improvement after six months of therapy, it is prudent to change the treatment regimen to these drugs rather than waiting for response. A longer prospective study is also required to judge more precisely about this. Since higher

doses of prednisolone is needed, side effects of steroid therapy are seen more frequently in prednisolone only group. With the same efficacy and less side effects, the combination regimen must be preferred as the standard regimen, unless there is a contraindication to azathioprine.

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