Budesonide versus Prednisone with Azathioprine for the Treatment of Autoimmune Hepatitis in Children and Adolescents

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Objective To compare the effect of budesonide vs prednisone therapy both in combination with azathioprine in pediatric patients with autoimmune hepatitis (AIH).

Study design Forty-six patients with AIH (11 males and 35 females) aged 9-17 years were enrolled in a 6-month, prospective, double-blind, randomized, active-controlled, multicenter phase IIb study evaluating budesonide (n = 19; 3 mg twice or 3 times daily) vs prednisone (n = 27; 40 mg/day tapered to 10 mg/day), both with azathioprine (1-2 mg/kg/day), followed by a further 6 months of open-label budesonide therapy. The primary efficacy endpoint was complete biochemical remission (normal serum alanine aminotransferase and aspartate aminotransferase levels) without predefined steroid-specific side effects.

Results We observed no statistically significant difference in the percentage of patients who met the primary endpoint between the budesonide (3 of 19; 16%) and prednisone groups (4 of 27; 15%) after 6 months, nor in the percentage of patients who experienced biochemical remission (budesonide, 6 of 19 [32%]; prednisone, 9 of 27 [33%]), lack of steroid-specific side effects (budesonide, 10 of 19 [53%]; prednisone, 10 of 27 [37%]). The mean weight gain was 1.2 ± 3.5 kg in the budesonide group and 5.1 ± 4.9 kg in the prednisone group (P = .006). A total of 42 patients received open-label budesonide treatment for another 6 months. After 12 months, 46% of these patients achieved complete remission.

Conclusion Oral budesonide with azathioprine can induce and maintain remission in pediatric patients with AIH and may be considered an alternative therapy to prednisone. The treatment causes fewer side effects and does not lead to weight gain; however, it may be less effective than prednisone in inducing remission. *(J Pediatr 2013;163:1347-53)*.

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Autoimmune hepatitis (AIH) is a chronic progressive liver disease associated with significant morbidity and mortality.[1] It occurs at all ages and affects predominately females, and is particularly aggressive in children and adolescents.[2,3] Untreated, the prognosis for active AIH is poor, with 5- and 10-year survival rates between 50% and 10%, respectively.[4]

The estimated prevalence of AIH per 1 million population is 107 in Sweden,[5] 170 in Norway,[6] and 189 in New Zealand.[7] In Poland, the estimated prevalence is ~40 cases per 1 million pediatric patients,[8] hindering the ability to perform controlled, randomized, and adequately powered trials in patients with AIH.

Therapy with corticosteroids alone or in combination with azathioprine has been shown to induce remission and improve survival[9]; 20% of children with AIH type 1 can successfully discontinue treatment.[2,10] Steroid therapy does not cure the disease, however, and relapses are common after discontinuation.[11,12] Thus, many children continue remission maintenance therapy with azathioprine.[13] Consequently, patients with AIH require long-term treatment and are at risk for side effects of steroids or, less frequently, azathioprine.

Experience with other immunosuppressive therapy in children with AIH is limited, and no controlled, randomized trials have been reported. Cyclosporine A was found to induce biochemical remission in treatment-naïve children[14,15]; however, another study showed that despite biochemical improvement, none of the patients fulfilled the criteria for discontinuing therapy.[16] Tacrolimus has had limited efficacy in children with AIH and is probably insufficient to achieve complete remission.[17] Mycofenolate mofetil may be considered as rescue therapy

AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
NS	Not significant

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in children resistant to standard immunosuppression.[18] Treatment with these medications may be accompanied by significant unwanted effects, and thus they are used in treatment-resistant patients, not as first-line therapy.[19]

A potential alternative to standard prednisone therapy for AIH is the use of topical steroids such as budesonide, which has a 90% first-pass effect in the noncirrhotic liver.[20] The experience with budesonide in patients with AIH is limited. Two studies concluded that budesonide is effective and has a low rate of side effects,[21,22] whereas another study reported lack of efficacy in inducing remission and a high rate of side effects.[23] However, Czaja and Lindor[23] explored budesonide in difficult-to-treat patients with AIH in whom previous therapy with standard of care had failed. These 3 studies were open-label, not randomized, and included low numbers of patients. The first large, multicenter, randomized trial comparing budesonide with prednisone, both in combination with azathioprine demonstrated that oral budesonide in combination with azathioprine effectively achieves and maintains remission in 60% of noncirrhotic patients with AIH in conjunction with a low rate of steroid-specific side effects.[24] The population studied by Manns et al[24] included 208 adult and pediatric patients with a first diagnosis of acute AIH or a relapse of therapy following previously diagnosed disease and no cirrhosis present. The aim of this study was to compare oral budesonide with oral prednisone in combination with azathioprine after 6 months in a double-blind treatment period and to describe the outcome after a subsequent 6 months of budesonide open-label treatment in children and adolescents with AIH.

Methods

Patients with AIH aged 9-17 years were included in this analysis. The diagnosis of AIH was established according to the criteria of the International Autoimmune Hepatitis Group.[25] Patients enrolled in the study had either a first diagnosis of acute AIH or had experienced a relapse of previously diagnosed AIH based on liver biopsy analysis performed within 12 months before screening. Patients had serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) levels at least twice the upper limit of normal, along with elevated levels of gammaglobulins and IgG. All patients exhibited normal thiopurinemethyltransferase activity, normal levels of adrenocorticotrophic hormone, α1-antitrypsin, ceruloplasmin, and serum copper.

The Institutional Review Boards of each participating center approved the study protocol. Legal representatives of minor patients and parents whenever required by local regulations provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. An external data and safety monitoring board reviewed the results of the 2 interim analyses and made recommendations to the sponsor.

Exclusion criteria included the presence of hepatitis A, B, C, D, E, or G virus infection; primary biliary cirrhosis; primary sclerosing cholangitis; Wilson disease; hemochromatosis; cirrhosis; fulminant liver failure; recent treatment with drugs with known liver toxicity; and parenteral administration of blood or blood products within 6 months before screening.

This study is a subanalysis of the large multicenter randomized trial comparing budesonide with prednisone, both in combination with azathioprine.[24] It was a 6-month double-blind, double-dummy controlled study (segment A) with a further 6-month open-label phase (segment B) (**Figure 1**; available at www.jpeds.com). Sequential randomization to 1 of 2 possible treatment arms was 1:1. During segment A, patients were randomly assigned to receive either budesonide (3 mg 3 times daily or 3 mg twice daily after biochemical remission) or prednisone (starting dose 40 mg/day, tapered to 10 mg/day according to a fixed high-dose or a low-dose regimen for early treatment responders) (**Figure 1**). Patients who experienced biochemical remission after 3 months in segment A (ie, normal ALT and AST values after 3 months of therapy) were eligible to enter segment B. Patients without biochemical remission at month 6 also could proceed to segment B at the investigator's discretion. During segment B, all patients were treated with budesonide (3 mg 2 or 3 times daily). Azathioprine was administered at a dose of 1-2 mg/kg/day throughout both segments A and B.

Safety variables, including adverse events, predefined steroid-specific side effects (moon face, acne, buffalo hump, hirsutism, striae, diabetes, glaucoma, and elevated intraocular pressure), laboratory values, vital signs, and complete physical examination results, were assessed throughout the study.

Study Endpoints

The primary efficacy endpoint was complete response to therapy, defined as complete biochemical remission at the patient's last visit in segment A and the absence of predefined steroid-specific side effects throughout segment A. Secondary endpoints included complete biochemical remission and the occurrence or absence of steroid-specific side effects. In addition, complete response, biochemical response, and the absence of steroid-specific side effects were described at month 12 of the study in all patients receiving both budesonide and azathioprine and in patients who had switched from prednisone to budesonide after month 6.

Changes in body weight between baseline and the month 6 visit and between the month 6 and month 12 visits were documented in patients receiving budesonide and in those who had switched from prednisone to budesonide.

Statistical Analyses

The study power was first calculated for the core study including all patients, adult and pediatric. We anticipated complete response rates of 35% in the budesonide group and 17.5% in the prednisone group. With 102 evaluable patients per treatment group, a 1-sided χ^2 test at an α-level of 2.5 % had a power of ~80% to detect a difference as assumed.[24]