CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Budesonide Induces Remission More Effectively Than Prednisone in a Controlled Trial of Patients With Autoimmune Hepatitis

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BACKGROUND & AIMS: Autoimmune hepatitis (AIH) is a chronic liver disease associated with cirrhosis and liver failure. Corticosteroid therapy induces long-term remission but has many side effects. We compared the effects of budesonide (a steroid that is rapidly metabolized, with low systemic exposure) and prednisone, both in combination with azathioprine. **METHODS:** We performed a 6-month, prospective, double-blind, randomized, active-controlled, multicenter, phase IIb trial of patients with AIH without evidence of cirrhosis who were given budesonide (3 mg, three times daily or twice daily) or prednisone (40 mg/d, tapered to 10 mg/d); patients also received azathioprine (1–2 mg/kg/d). Treatment was followed by a 6-month, open-label phase during which all patients received budesonide in addition to azathioprine. The primary end point was complete biochemical remission, defined as normal serum levels of aspartate aminotransferase and alanine aminotransferase, without predefined steroid-specific side effects, at 6 months. **RESULTS:** The primary end point was achieved in 47/100 patients given budesonide (47.0%) and in 19/103 patients given prednisone (18.4%) ($P < .001$; 97.5% 1-side confidence interval [CI] = 16.2). At 6 months, complete biochemical remission occurred in 60% of the patients given budesonide versus 38.8% of those given prednisone ($P = .001$; CI: 7.7); 72.0% of those in the budesonide group did not develop steroid-specific side effects versus 46.6% in the prednisone group ($P < .001$; CI = 12.3). Among 87 patients who were initially given prednisone and then received budesonide after 6 months, steroid-specific side effects decreased from 44.8% to 26.4% at month 12 ($P < .002$). **CONCLUSIONS: Oral budesonide, in combination with azathioprine, induces and maintains remission in patients with non-cirrhotic AIH, with a low rate of steroid-specific side effects.**

Keywords: Autoimmune Hepatitis; Steroid Side Effects; Remission; Budesonide, Prednisone, and Azathioprine.

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Autoimmune hepatitis (AIH), represents a disease entity within the heterogeneous spectrum of chronic hepatitis[1] that has a significant potential for morbidity and mortality. It has been characterized as a disease with hypergammaglobulinemia (mainly immunoglobulin G [IgG]), is associated with extrahepatic autoimmune syndromes and high necroinflammatory activity, frequently accompanied by histologic signs of chronic hepatitis. AIH responds favorably to steroid treatment and has become the first liver disease for which medical therapy has been shown to improve survival. Current management of AIH constitutes of prednisone alone or in combination with azathioprine,[2–7] which induces remission in approximately 80% of patients. Other immunosuppressive drugs such as mycophenolate mofetil,[8,9] cyclosporine A,[10] or tacrolimus[11] have shown only modest success but have been associated with significant un-

Abbreviations used in this paper: ACTH, adrenocorticotrophic hormone; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HLA, human leukocyte antigen; IgG, immunoglobulin G; ITT, intention to treat; LKM-1, liver-kidney microsomal type 1; PP, per protocol; SLA/LP, soluble liver antigen/liver pancreas; ULN, upper limit of normal.

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wanted effects. Withdrawal of therapy after 2 years leads to relapse in 85% of cases, but long-term therapy carries the risk of significant steroid-specific side effects and azathioprine-related adverse effects such as jaundice, leucopenia, and anemia. In clinical practice these adverse events are a major problem for young as well as for middle-aged women.

One alternative is the use of "topical" steroids with low systemic side effects such as budesonide.[12] Budesonide has a 90% first-pass effect in the liver and has been reported to improve liver function in patients with AIH.[13] In a small study of 10 patients with AIH who had not responded to previous standard therapy the effect of budesonide was reported to be modest,[14] but in 2005 a pilot study showed budesonide monotherapy to be effective in 12 previously untreated patients with AIH.[15]

We report here the results of the largest prospective, randomized, multicenter trial published to date for the treatment of AIH, in which the efficacy and safety of budesonide was compared with standard prednisone therapy, both administered in combination with azathioprine.

Materials and Methods

Setting and Participants

Patients 10–70 years of age were eligible for the study if they had (1) either a first diagnosis of acute AIH based on liver biopsy results obtained ≤3 months before screening or were experiencing relapse after a previous diagnosis of AIH based on histology findings ≤12 months before screening, according to the criteria of the International Autoimmune Hepatitis Group[16]; (2) thiopurine methyltransferase activity and adrenocorticotrophic hormone (ACTH) levels in the normal range; (3) serum alanine aminotransferase (ALT) levels or serum aspartate aminotransferase (AST) levels ≥2 times higher than the upper limit of normal (ULN), (4) normal levels of α1-antitrypsin, serum copper, and ceruloplasmin; and (5) elevated levels of γ-globulins or IgG. Exclusion criteria included the presence of hepatitis A, B, C, D, or E virus infection; primary biliary cirrhosis; primary sclerosing cholangitis; Wilson disease or hemochromatosis; liver cirrhosis; fulminant liver failure; recent treatment with drugs having known liver toxicity; and parenteral administration of blood or blood products within 6 months before screening.

Design Overview

This was a 6-month double-blind, double-dummy, controlled study (segment A) with a further 6-month open-label phase (segment B) (Figure 1*A*). During segment A, patients were randomly assigned to receive budesonide (3 mg three times daily, or 3 mg twice daily, after biochemical remission) or prednisone (starting dose 40 mg/d tapered to 10 mg/d). Patients who already showed biochemical remission after 3 months in segment A were eligible to enter segment B. Patients without biochemical remission at month 6 could also proceed to segment B at the investigator's discretion. During segment B, all patients were treated with budesonide (3 mg three times daily or twice daily). Azathioprine was administered at a dose of 1–2 mg/kg/d, according to clinical judgment, throughout both segments A and B.

Baseline findings on liver biopsy were scored by local pathologists with the use of the Knodell score[17] to exclude cirrhosis. Patients with biopsy-proven liver cirrhosis were excluded, because first-pass hepatic extraction of budesonide may be reduced because of shunting of portal venous blood. Safety variables were assessed throughout the study, including adverse events, steroid-specific side effects, laboratory variables, vital signs, and complete physical examination.

Study End Points

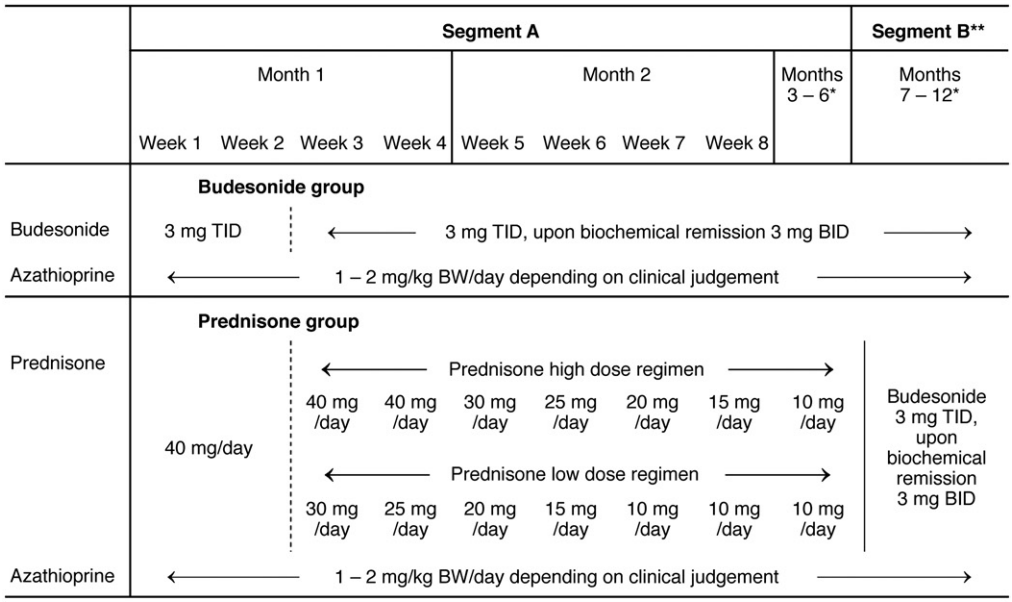
The primary efficacy end point was complete response to therapy, defined as complete biochemical remission (ie, serum AST and ALT within normal range determined by a central laboratory) at the patient's last visit of segment A, and the absence of predefined steroid-specific side effects (ie, moon face, acne, buffalo hump, hirsutism, striae, diabetes, glaucoma, and increased intraocular pressure) throughout segment A. Secondary end points included complete biochemical remission and the occurrence or absence of steroid-specific side effects.

Statistical Analyses

Complete response rates of 35% and 17.5% were expected for patients with budesonide and prednisone, respectively. With 102 patients assessable per treatment group, a one-sided χ^2 test at the α-level of 2.5% had a power of approximately 80% to detect a difference as assumed. The study was conducted with the use of a 3-stage group sequential adaptive design with possible sample size adjustments at each of the 2 planned interim analyses.[18] A classical group sequential test design of O'Brien/Fleming type[18] was appropriate. For (one-sided) $\alpha = .025$, the critical values were given by 3.471, 2.454, and 2.004 for the first, second, and third analysis, respectively. The planned information rates were 0.333, 0.667, and 1, respectively.

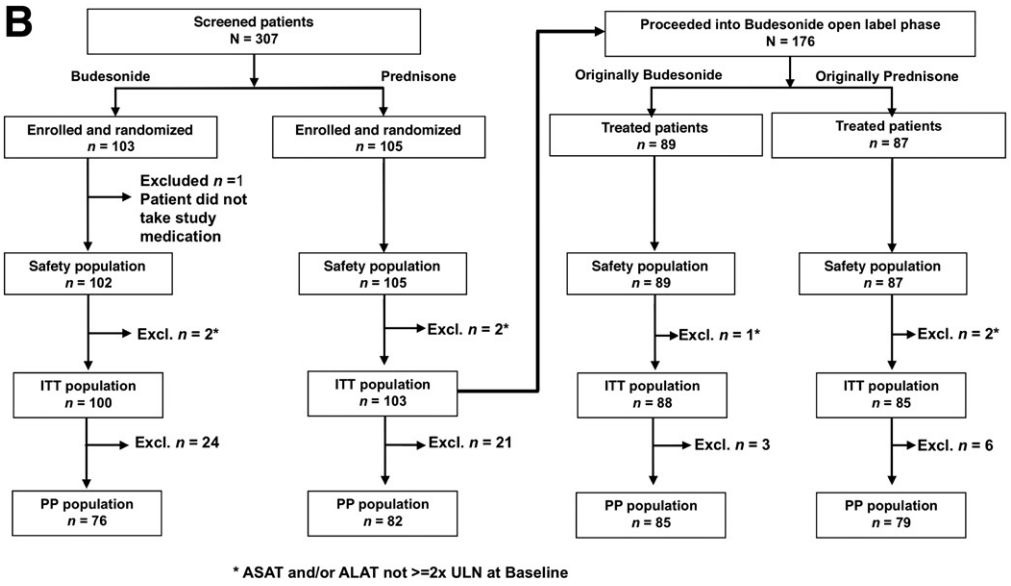
The primary analysis was the comparison of the 2 treatment groups on the basis of the complete response rate in the intention-to-treat (ITT) population of segment A. For confirmatory hypothesis testing in the interim analyses as well as in the final analysis, the inverse normal method of combining *P* values of the one-sided shifted asymptotic χ^2 test for comparing 2 rates according to Lehmacher and Wassmer[19] was applied. At each of the planned analyses the differences between complete response rates and the corresponding 97.5% lower limit

A



*Patients showing biochemical remission after 3 months of treatment could continue with Segment B after visit 4.
** Months 7 to 12: All patients received budesonide (3 mg TID/BID).

B



* ASAT and/or ALAT not >=2x ULN at Baseline

Figure 1. (*A*) Schematic representation of double-blind, randomized, active-controlled, multicenter phase IIb study that evaluated prednisone and azathioprine against budesonide and azathioprine in autoimmune hepatitis. In weeks 1 and 2 of segment A, all patients received 3 mg of budesonide 3 times daily (TID) or 40 mg/d prednisone, respectively. After 2 weeks the dose of budesonide was tapered to 3 mg twice daily (BID), and a low-dose regimen for prednisone could be implemented in patients with serum AST and ALT within the normal range (ie, complete biochemical remission). Patients without complete biochemical remission continued to receive 3 mg of budesonide TID and the high-dose prednisone regimen. The dose of budesonide could be increased to 3 mg TID or decreased to 3 mg BID, depending on serum AST and ALT levels at subsequent visits. Prednisone dose was tapered down according to the fixed-dose regimen selected at the 2-week visit (high-dose regimen or low-dose regimen). Segments A and B were scheduled to last 6 months each. Patients who showed biochemical remission after 3 months in segment A were eligible to enter segment B. Patients without biochemical remission at month 6 could proceed to segment B at the investigator's discretion. In segment B, patients who had received prednisone were switched to budesonide in an open-label fashion. (*B*) Screening, treatment, and open-label treatment of the study patients (CONSORT flow diagram). Of 307 patients screened, 99 patients were ineligible for the study protocol. Those patients who showed biochemical remission at month 3 and at month 6 were eligible to enter segment B, and those patients without biochemical remission at month 6 were able to proceed to segment B at the investigator's discretion. Major protocol violations that resulted in an exclusion from the per-protocol analysis set included the violation of an inclusion or exclusion criterion, the intake of prohibited concomitant medication, and the administration of study medication for $<$28 days.

of the one-sided confidence interval (CI) is provided to estimate the treatment effect.

Planned subpopulation analyses for rates of complete response and rates of complete biochemical remission include HAI Knodell fibrosis score at baseline (0–1 vs 3–4), gender (male/female), type of AIH (type 1 only, type 2, and/or type 3 only or in combination with type 1, type 3 only or in combination with type 1 or type 2), country and AST/ALT activity at baseline (≥4× ULN, <4× ULN). Subpopulation analysis by body weight (>60 kg or ≤60 kg at baseline in patients >18 years of age) was performed post hoc.

The safety population comprised all randomly assigned patients who had taken ≥1 dose of study medication. The ITT population consisted of all patients in the safety population who had AST and/or ALT >ULN at baseline. The per protocol (PP) population comprised all ITT patients who completed or prematurely terminated the study without a major protocol deviation and in whom the reason for premature termination was an adverse event or lack of efficacy.

Descriptive statistical methods were used to analyze all variables other than the primary efficacy end point. All *P* values are the result of 1-sided shifted asymptomatic χ^2 tests for comparing 2 rates except for the analysis of the incidence of commonly associated steroid-specific side effects at month 6 and month 12 (McNemar's test for paired observations).

Study Conduct

Institutional review boards at all participating centers approved the protocol. All patients 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. Data analysis was performed by the authors, Andrea Kreter/ClinResearch, and the sponsor, based on a statistical analysis plan finalized before unblinding of the study.

Results

Study Population

A total of 307 patients were screened. Of these, 99 did not meet the inclusion criteria, such that 208 patients were enrolled and randomly assigned to the budesonide (n = 103) and the prednisone (n = 105) treatment arms between March 2001 and November 2006. One patient randomly assigned to budesonide took no study drug so the safety population comprised 207 patients (Figure 1*B*). A definite diagnosis of AIH with an aggregate AIH score >15 according to the IAIHG scoring system[16] was confirmed in 77.5% (79/102) of the patients in the budesonide group and 80.0% (83/105) of the patients in the prednisone group. A probable diagnosis of AIH (aggregate score of 10–15 points) was found in 20.6% (21/102) of the budesonide group and 18.1% (19/105) of the prednisone group. Four patients were excluded from the ITT population (n = 203) because AST and/or ALT did not exceed ULN at baseline. The PP population consisted of 158 patients (24 patients in the budesonide group and 21 patients in the prednisone group were excluded for major protocol violations) (Figure 1*B*). Of the 207 treated patients, 92/102 (90.2%) budesonide patients and 88/105 (83.8%) prednisone patients completed segment A. Reasons for premature withdrawal were lack of efficacy (3 budesonide, 12 prednisone), adverse events (3 budesonide, 3 prednisone), and lack of compliance with the study protocol (4 budesonide, 2 prednisone). Of 180 patients who completed segment A, 176 entered segment B. The last patient completed the study on November 30, 2007.

The 2 treatment groups were similar in terms of demographics and baseline characteristics other than a lower proportion of females in the budesonide group (69.6% vs 84.8%; $P = .009$) (Table 1). Regarding the activity and features of AIH, there was a lower proportion of human leukocyte antigen (HLA) DR3 carriers and a higher proportion of HLA DR4 carriers in the budesonide group, fewer patients with a normal response to ACTH injection, and more patients with rosetting on histology (all differences were nonsignificant) (Table 2). Patients with an increased risk for progression and mortality as indicated by the presence of interface hepatitis at baseline[20] were equally distributed between the treatment groups (interface hepatitis n = 50 and n = 57 in the budesonide and prednisone groups, respectively; Table 1). Five patients had received prior systemic glucocorticoid treatment before inclusion. Of these, 2 patients were randomly assigned to the budesonide group and 3 patients to the prednisone group. Patients with the less frequently occurring liver-kidney microsomal type 1 (LKM-1) autoantibodies (AIH type 2, n = 8) and anti–soluble liver antigen/liver pancreas (SLA/LP) autoantibodies (AIH type 3, n = 32) were present only at low numbers.

Treatment compliance did not differ between the groups and was more than 95% in both treatment groups.

Efficacy

The primary efficacy end point, complete response to therapy at the last visit of segment A, was reached in 47/100 (47.0%) budesonide-treated patients compared with 19/103 (18.4%) prednisone-treated patients ($P < .001$; CI: 16.2). A similar difference was observed in the PP population (budesonide 35/76 [46.1%], prednisone 14/82 [17.1%]; $P < .001$; CI: 15.1). No significant difference was observed in the rate of complete response between patients initially randomly assigned to budesonide or prednisone at the completion of segment B, during which all patients received

Table 1. Demographic and Baseline Characteristics (Safety Population)

	Budesonide (n = 102)	Prednisone (n = 105)
Gender		
Male, n (%)	31 (30.4)	16 (15.2)[a]
Female, n (%)	71 (69.6)	89 (84.8)
Ethnic origin		
White, n (%)	99 (97.1)	104 (99.0)
Other, n (%)	3 (2.9)	1 (1.0)
Age (*y*), mean ± SD	36.0 ± 17.0	38.0 ± 19.0
BMI (kg/m^2), mean ± SD	24.3 ± 5.20	23.9 ± 5.3
Autoimmune hepatitis score, mean ± SD	17.2 ± 3.0	17.6 ± 3.0
Diseases associated with AIH, n (%)	27 (26.5)	28 (26.7)
HLA status		
HLA DR3 (yes), n (%)	42 (41.2)	54 (51.4)
HLA DR4 (yes), n (%)	38 (37.3)	31 (29.5)
Serology		
Anti-HAV (positive), n (%)	24 (23.5)	23 (21.9)
Anti-HBc (positive), n (%)	6 (5.9)	8 (7.6)
HBsAg (positive), n (%)	0	1 (1.0)
Anti-HCV (positive), n (%)	0	1 (1.0)
TPMT test (positive), n (%)	96 (94.1)	99 (94.3)
Other biopsy assessments		
Interface hepatitis, n (%)	50 (49.0)	57 (54.3)
Predominantly lymphocytoplasmatic infiltrate, n (%)	56 (54.9)	58 (55.2)
Rosetting of liver cells, n (%)	11 (10.8)	4 (3.8)
Biliary changes, n (%)	8 (7.8)	5 (4.8)
Liver function parameters		
Albumin concentration (*g/dL*), mean ± SD	4.38 ± 0.52	4.41 ± 0.48
Alkaline phosphatase activity (*U/L*), mean ± SD	194 ± 127	197 ± 145
γ-GT activity (*U/L*), mean ± SD	162 ± 148	181 ± 200
Total bilirubin concentration (*mg/dL*), mean ± SD	2.5 ± 4.4	2.6 ± 4.4
AST activity (*U/L*), mean ± SD	316 ± 373	341 ± 428
ALT activity (*U/L*), mean ± SD	399 ± 435	451 ± 530
Immunoglobulins		
IgG concentration (*mg/dL*), mean ± SD	2428 ± 918	2396 ± 886
γ-Globulin concentration (*g/dL*), mean ± SD	2.35 ± 0.93	2.29 ± 0.83
ACTH test		
Normal response at 30 or 60 minutes, n (%)	64 (62.7)	74 (70.5)
Predefined steroid-specific symptoms, n (%)	13 (12.7)	13 (12.4)

ACTH, adrenocorticotrophic hormone; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; γ-GT, γ-glutamyltransferase; HAV, hepatitis A virus; HBc, antibody to hepatitis B core antigen; HBsAG, hepatitis B surface antigen; HCV, hepatitis C virus; HLA, human leukocyte antigen; IgG, immunoglobulin G; TPMT, thiopurine *S*-methyltransferase.
[a]$P = .009$ vs budesonide group.

budesonide (Figure 2*A*). The proportion of patients with a complete response at the end of segment B was 95/173 (54.8%), which was mainly because of a reduction of steroid side effects.

Levels of IgG and total γ globulins were comparable in both treatment groups at 12 months, but IgG normalization was achieved later in the budesonide arm (data not shown).

A significantly higher rate of complete response at month 6 was observed with budesonide compared with prednisone in both female and male patients (Figure 2*B*). Males showed a numerically higher complete response rate than females in the budesonide group (Figure 2*B*). In addition, in a post hoc analysis significantly higher rates of complete response at month 6 were observed with budesonide versus prednisone regardless of the variables body weight, HLA type DR3, or HLA type DR4 status (≤60 kg: 12/20 vs 2/19; $P < .001$; CI: 24.0; >60 kg: 31/60 vs 13/55; $P = .001$; CI: 11.1; HLA_{DR3}: 13/28 vs 8/44; $P = .005$; CI: 6.5; HLA_{DR4}: 12/24 vs 3/22; $P = .004$; CI: 11.8).

The potential influence of inflammatory activity was investigated by comparing patients showing high (≥4× ULN) and lower (<4× ULN) aminotransferase levels. Significantly higher rates of complete biochemical response were observed in the budesonide treatment arm than in the prednisone treatment arm in both subpopulations (Figure 2*C*). In contrast to prednisone, patients within the budesonide cohort who had lower aminotransferase activity at baseline showed a higher complete response rate than those with higher activity (Figure 2*C*). The complete biochemical remission rate (ie, serum AST and ALT within normal range at the end of segment A) was 60/100 (60.0%) in the budesonide group versus 40/103 (38.8%) in the prednisone group ($P = .001$; CI: 7.7) for the ITT population and 46/76 (60.5%)

Table 2. Diagnosis and Features of Autoimmune Hepatitis at Baseline (Safety Population)

	Budesonide (n = 102)	Prednisone (n = 105)
Alkaline phosphatase-to-aminotransferase ratio		
>3.0	6 (5.9)[a]	5 (4.8)
1.5–3.0	10 (9.8)	15 (14.3)
<1.5	84 (82.4)	85 (81.0)
Serum globulins or IgG level		
Below normal	0	3 (2.9)
1.0–1.5× normal	54 (52.9)	52 (49.5)
>1.5–2.0× normal	26 (25.5)	25 (23.8)
>2× normal	22 (21.6)	25 (23.8)
Titer of antibodies to nucleus, smooth muscle, or liver/kidney microsome type 1[b]		
Adults <1:40	0	1 (1.0)
Adults 1:40	3 (2.9)	3 (2.9)
Adults 1:80, children >1:10	13 (12.7)	12 (11.4)
Adults >1:80, children >1:20	86 (84.3)	89 (84.8)
Mitochondrial antibodies		
Yes	2 (2.0)	3 (2.9)
No	100 (98.0)	102 (97.1)
Hepatitis viral markers		
Positive	4 (3.9)	4 (3.8)
Negative	98 (96.1)	100 (95.2)
Other autoimmune disease		
No	79 (77.5)	79 (75.2)
Yes	22 (21.6)	25 (23.8)
Exposure to toxic drugs		
Yes	0	0
No	102 (100.0)	105 (100.0)
Alcohol consumption		
>60 g/d	0	0
25–60 g/d	0	1 (1.0)
<25 g/d	102 (100.0)	104 (99.0)
Immunologic features		
No	28 (27.5)	19 (18.1)
HLA DR3 or DR4	60 (58.8)	70 (66.7)
Other autoantibodies	4 (3.9)	5 (4.8)
HLA DR3 or DR4 and other autoantibodies	4 (3.9)	4 (3.8)
Histologic score[c]		
−5	1 (1.0)	2 (1.9)
0	1 (1.0)	1 (1.0)
+1	24 (23.5)	22 (21.0)
+2	3 (2.9)	1 (1.0)
+3	26 (25.5)	26 (24.8)
+4	36 (35.3)	47 (44.8)
+5	10 (9.8)	6 (5.7)

AIH, autoimmune hepatitis; HLA, human leukocyte antigen; IgG, immunoglobulin G; SLA/LP, soluble liver antigen/liver pancreas.
[a]All values are n (%).
[b]These antibodies are presented according to the AIH score of Alvarez et al[16], which omits SLA/LP, although these autoantibodies were determined in all patients.
[c]Presented is the sum of score points for liver histology according to the AIH score of Alvarez et al.[16]

versus 29/82 (35.4%) for the PP population ($P < .001$; CI: 10.1). However, when the biochemical response was defined as a reduction of ALT activity to <2× ULN, a biochemical response was observed in 89/100 (89.0%) of the budesonide-treated patients and in 83/103 (80.6%) of the prednisone-treated patients (NS; Figure 2*D*). When patients with AIH >18 years of age are analyzed separately, complete biochemical remission rates were also similar (54/81 (66.7%) in the budesonide treatment group and 31/76 (40.8%) in the prednisone treatment group ($P < .001$; CI: 10.8), indicating that the inclusion of children does not affect the overall results of this study.

Other subgroup analyses were performed to examine a possible influence of gender (planned), body weight (in patients >18 years of age, planned), and HLA type (DR3 vs DR4,[21] post hoc). In terms of complete biochemical remission rates at the end of segment A, the between-group difference was significant for males but not females (Figure 3*A*). Patients weighing >60 kg showed a significantly higher complete biochemical remission rate in the budesonide group than in the prednisone group, which was not observed among patients ≤60 kg (Figure 3*B*). Type of HLA allele did not influence the biochemical response (Figure 3*C*). Other subpopulation analyses as described in "Materi-

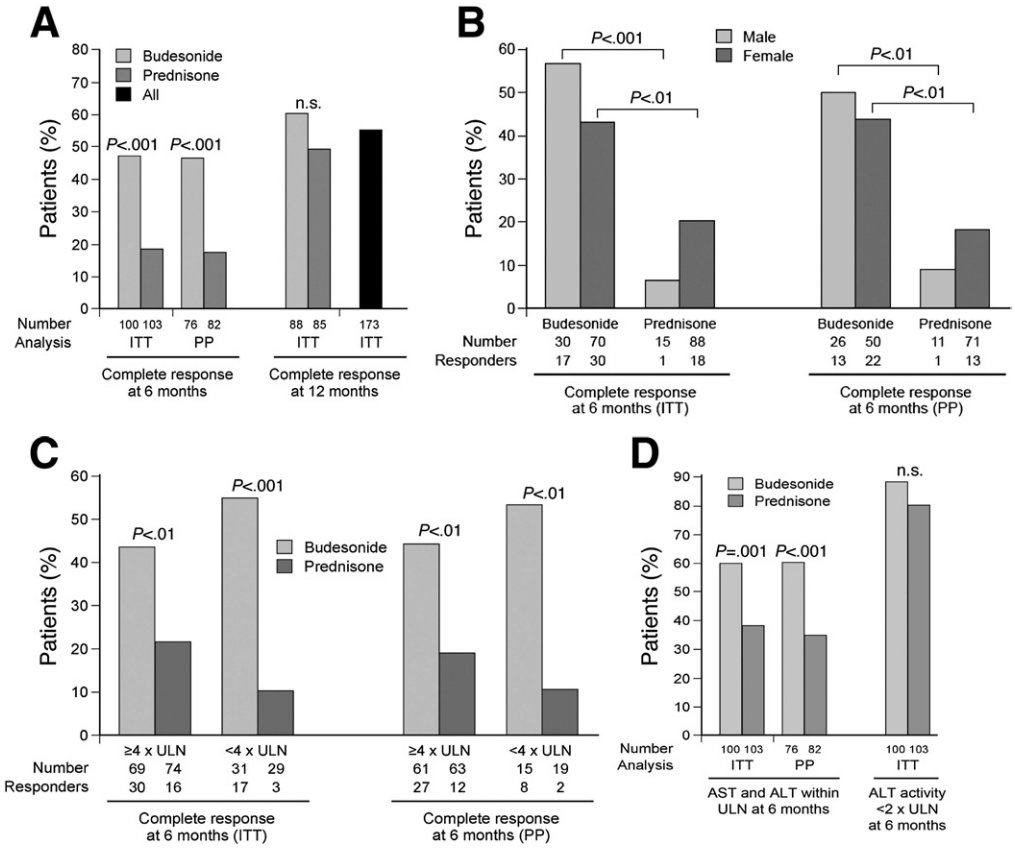


Figure 2. (*A*) Complete response (defined as serum AST and ALT within normal range and absence of steroid-specific side effects) for the intention-to-treat (ITT) and per protocol (PP) populations. (*B*) Complete response rate at month 6 (end of segment A) according to gender. (*C*) Complete response rate at month 6 according to baseline aminotransferase level. (*D*) Complete biochemical remission rate at month 6 compared with the biochemical remission defined as ALT activity <2× ULN at month 6.

als and Methods" showed no effect of these variables on complete biochemical remission rates.

Safety and Tolerability

Both study medications were well tolerated. Treatment-emergent adverse drug reactions reported in the budesonide (n = 102) and prednisone (n = 105) cohorts included weight increase (5.9%/19.0%), headache (11.8%/7.6%), mood alterations (9.8%/7.6%), muscular weakness (4.9%/7.6%), hypertension (2.9%/6.7%), and insomnia (1.0%/4.8%). At month 6, the incidence of predefined steroid-specific side effects was significantly lower in the budesonide group than in the prednisone arm in both the ITT and PP populations (Table 3). When side effects were assessed after the completion of segment B, there was a reduction of approximately 40% in the incidence of commonly associated steroid-specific side effects among patients converted from prednisone to budesonide (39/87 [44.8%] at entry to segment B; 23/87 [26.4%] at month 12; $P < .002$).

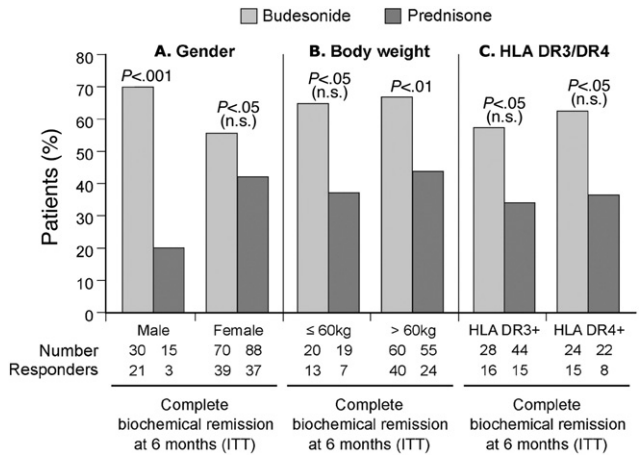


Figure 3. Complete biochemical remission (serum AST and ALT within normal range) at month 6 according to gender (*A*), body weight (*B*), and type of HLA allele (*C*). *P* values were calculated by 1-sided asymptotic χ^2 test; significance is defined as $P = .025$; n.s., not significant.

Discussion

The results of this study show that budesonide in combination with azathioprine is capable of inducing and maintaining remission in AIH, and they showed a significantly lower incidence of steroid-specific side effects compared with standard prednisone therapy, when administered with azathioprine.

This is the first study to directly compare budesonide to prednisone with the use of prednisone doses that represent and even slightly exceed the 30-mg dose that is generally used for patients receiving concomitant azathioprine.[6,22] Unlike other trials, we used a stringent definition for response, namely complete normalization of biochemistry in the absence of predefined steroid-specific side effects. This

Table 3. Predefined Steroid-Specific Side Effects Observed and Reported Throughout Segment A

	ITT		PP	
	Budesonide (n = 100)	Prednisone (n = 103)	Budesonide (n = 76)	Prednisone (n = 82)
No SSSEs throughout segment A, n (%)[a]	72 (72.0)	48 (46.6)	55 (72.4%)	37 (45.1)
At least 1 SSSE throughout segment A, n (%)[b]	26 (26.0)	53 (51.5)	21 (27.6)	45 (54.9)
Moon face	10 (10.0)	43 (41.7)	8 (10.5)	36 (43.9)
Acne	8 (8.0)	15 (14.6)	7 (9.2)	13 (15.9)
Hirsutism	9 (9.0)	3 (2.9)	8 (10.5)	3 (3.7)
Skin striae	2 (2.0)	4 (3.9)	1 (1.3)	4 (4.9)
Buffalo hump	1 (1.0)	4 (3.9)	1 (1.3)	4 (4.9)
Diabetes[c]	4 (4.0)	0	4 (5.3)	0
Increased intraocular pressure	0	0	0	0
Glaucoma	0	0	0	0

ITT, intention to treat; PP, per protocol; SSSE, steroid-specific side effect.
[a]Difference (lowest level of 97.5% confidence interval) for ITT: 25.4% (12.3%); $P < .001$; PP: 27.2% (12.5%); $P < .001$.
[b]Predefined SSSEs.
[c]Two of the 4 reported diabetes events were determined to be preexisting and 1 was described as a transient elevation of glycosylated hemoglobin.

stringent definition was chosen because, first, well-tolerated induction of complete biochemical remission (ie, serum AST and ALT within normal range) is likely to reduce long-term hepatic damage, and, second, residual aminotransferase activity almost universally leads to relapse after drug withdrawal. The sensitivity of this definition is shown by the fact that a more relaxed definition of remission (aminotransferase activity within twice the ULN) showed little difference between groups (budesonide, 89.0%; prednisone, 80.6%; NS).

We considered whether baseline differences between study groups could have influenced the observed results. Gender, body weight (and hence the dose of drug per kilogram), and the presence of immunogenetic markers such as HLA DR3/DR4 are variables with a potential to influence outcome,[21] and both gender and the presence of HLA DR3 were unequally distributed between groups. Although male patients showed a higher biochemical remission rate than females, the total number of males in both treatment arms was too small to have a significant effect on the overall findings of the study. In addition, the distribution of HLA DR3/DR4 was not found to have a significant effect on the biochemical remission rate. In the prednisone group, patients with lower body weight received a higher milligram per kilogram dose, but the frequency of biochemical responders in this group was lower compared with heavier patients. Thus, variations in baseline characteristics between the study groups are not believed to have confounded the observed difference in response rates.

Budesonide therapy was associated with a lower incidence of steroid-specific side effects than prednisone. Moreover, switching from a previous regimen of prednisone and azathioprine to budesonide and azathioprine led to an approximately 40% reduction of the incidence of steroid-specific side effects.

A debate has been long standing about whether AIH is a single disease or a more heterogeneous entity.[23] Autoantibodies may be used to subclassify AIH, with antinuclear antibodies characterizing type 1 disease, LKM-1 antibodies identifying type 2, and SLA/LP antibodies characterizing type 3.[24,25] Compared with type 1, patients with type 2 AIH are generally younger at the time of onset, relapse more frequently, require liver transplantation more often, and exhibit a higher incidence of acute disease onset. Here, the treatment response according to autoantibody profile was analyzed, and no significant differences between serologic subtypes were found. The improved complete response rate seen with budesonide versus prednisone was maintained for all 3 serologic subtypes of AIH (data not shown).

In conclusion, this study shows that budesonide in combination with azathioprine is able to induce and maintain remission in patients with AIH without evidence of cirrhosis. In addition, budesonide therapy offers the advantage of fewer steroid-specific side effects than with prednisone therapy. Budesonide may be associated with improved efficacy compared with prednisone when each drug is administered in combination with azathioprine, but further studies are needed to evaluate the effect of budesonide on other long-term steroid-specific side effects such as bone metabolism. The combination of budesonide with azathioprine may therefore become a new standard of care for noncirrhotic patients with AIH.

Appendix

In addition to the authors of this manuscript, other members of the European AIH-BUC study group include the following:

Estonia: R. Salupere; Finland: H. Nuutinen; Germany: Ch. Arnold, U. Beuers, Ch. Schramm, A. Csepregi, P.R. Galle, U. Fölsch, W. Hempfling, E. Hennes, K. Herzer, S. Kanzler, S. Koletzko, P. Malfertheiner, M. Melter, L. Mendoza, C. Niederau, B. Rodeck, J. Wiegand, B. Wigginghaus; Hungary: M. Albonyi, L. Dalmi; Israel: Y. Baruch, R. Oren, R. Tur-

Kaspa; Poland: A. Boron-Kaczmarska, Z. Gonciarz; Russia: O. Alexeeva, V. Isakov, S. Krishtopenko, V. Radchenko; Sweden: K. Hagen, A. Nemeth; The Netherlands: P.L.M. Jansen, A. van den Berg; Slovakia: F. Gazdik.

References

1. Desmet VJ, Gerber M, Hoofnagle JH, et al. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513–1520.
2. Soloway RD, Summerskill WH, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology 1972;63:820–833.
3. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1973; 1:735–737.
4. Kirk AP, Jain S, Pocock S, et al. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut 1980;21:78–93.
5. Czaja AJ, Manns MP. Advances in the diagnosis, pathogenesis and management of autoimmune hepatitis. Gastroenterology 2010;139:58–72.e4.
6. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193–2213.
7. Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges. Gastroenterology 2001;120:1502–1517.
8. Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. J Hepatol 2000;33:371–375.
9. Hennes EM, Oo YH, Schramm C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? Am J Gastroenterol 2008;103:3063–3070.
10. Fernandez NF, Redeker AG, Vierling JM, et al. Cyclosporine therapy in patients with steroid resistant autoimmune hepatitis. Am J Gastroenterol 1999;94:241–248.
11. Van Thiel DH, Wright H, Carroll P, et al. Tacrolimus: a potential new treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. Am J Gastroenterol 1995;90:771–776.
12. Thalen A, Brattsand R. Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. Arzneimittelforschung 1979;29:1687–1690.
13. Danielson A, Prytz H. Oral budesonide for treatment of autoimmune chronic hepatitis. Aliment Pharmacol Ther 1994;8:585–590.
14. Czaja AJ, Lindor KD. Failure of budesonide in a pilot study of treatment-dependent autoimmune hepatitis. Gastroenterology 2000;119:1312–1316.
15. Wiegand J, Schuler A, Kanzler S, et al. Budesonide in previously untreated autoimmune hepatitis. Liver Int 2005;25:927–934.
16. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929–938.
17. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431–435.
18. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549–556.
19. Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics 1999;55:1286–1290.
20. Czaja AJ. Special clinical challenges in autoimmune hepatitis: the elderly, males, pregnancy, mild disease, fulminant onset, and nonwhite patients. Semin Liver Dis 2009;29:315–330.
21. Czaja AJ, Carpenter HA, Santrach PJ, et al. Significance of HLA DR4 in type 1 autoimmune hepatitis. Gastroenterology 1993; 105:1502–1507.
22. Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006;354: 54–66.
23. Czaja AJ, Manns MP. The validity and importance of subtypes in autoimmune hepatitis: a point of view. Am J Gastroenterol 1995; 90:1206–1211.
24. Manns M, Gerken G, Kyriatsoulis A, et al. Characterisation of a new subgroup of autoimmune chronic active hepatitis by autoantibodies against a soluble liver antigen. Lancet 1987;1:292–294.
25. Kanzler S, Weidemann C, Gerken G, et al. Clinical significance of autoantibodies to soluble liver antigen in autoimmune hepatitis. J Hepatol 1999;31:635–640.

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The statistical analysis of the entire data sets pertaining to efficacy (specifically primary and major secondary efficacy end points) and safety (specifically, serious adverse events as defined in federal guidelines) have been independently confirmed by a biostatistician who is not employed by the corporate entity; the corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and analysis.

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Additional members of the European AIH-BUC-Study Group are listed in the Appendix.

Conflicts of interest

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