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Budesonide as a first line therapy in autoimmune hepatitis: A systematic review

Ibrahim Mahmoud Ajwah[1], Mohammed Abdullah Albalawi[1], Bashayer Jazza Alenazi[1], Saif Mohammed Alamri[1], Faris Essa Qubays[1], Abdullah Mahmoud Ajwah[1], Abdullah Saeed Alghamdi[1], Nader Awad Alanazi[1], Abdul wahab Ali Asseri[1], Kholoud Abdullah Algamdi[1], Solaiman Hosaian Alenezi[1], Ahmad Jamil Makai[1], Mohamed Omar Amer[2]

1. Internal Medicine Resident, King Salman Armed Forced Hospital, Tabuk, Saudi Arabia
2. Head of Gastroenterology Department, Gastroenterology and Hepatology Consultant, King Salman Armed Forced Hospital, Tabuk, Saudi Arabia

RESEARCH

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Corresponding Author:
Ibrahim Mahmoud Ajwah
King Salman Armed Forced Hospital PO Box 3458 Tabuk 51937, Saudi Arabia.
Email: aj.wa@hotmail.com

ABSTRACT

Background
Autoimmune hepatitis (AIH) Is a chronic liver disease with female predominance. Treatment of this condition required usually a long-term corticosteroid therapy.

Aims
Current review aimed to summarize the efficacy of budesonide as a first line treatment in AIH.

Methods
Pub Med , Google Scholar , and EBSCO databases were systematically search for relevant articles . The terms autoimmune hepatitis , budesonide, prednisolone and azathioprine were used. Out of hundred and six, only five fulfilled the inclusion criteria.

Results
Out of 106 articles, only 5 included in this review. All patients included in current review were steroid naive. Budesonide in dose of 3mg trice a day was the used in 2 out of 5 studies both document complete platelet response in 50–80 per cent. Azathioprine was added to budesonide in 3 out of 5 studies, 60 per cent of the budesonide treated patient had a complete platelet response versus 30–40 per cent of prednisolone treated group.

Conclusion
In non-cirrhotic AIH patients, budesonide was as effective as prednisolone with fewer steroid related side effects.

Key Words
Autoimmune hepatitis, budesonide, azathioprine

What this study adds:

1. What is known about this subject?
Prednisolone monotherapy or combined with azathioprine is a standard treatment regimen for AIH.

2. What new information is offered in this study?
Budesonide is a promising synthetic corticosteroid for treatment of AIH with low steroid related side effects.

3. What are the implications for research, policy, or practice?
Budesonide as well as other agent such as cyclophosphamide, are investigatory medication. Patients with AIH should be treated with the standard medications.

Background

Autoimmune hepatitis (AIH) is a chronic liver disease characterized biochemically by elevation in serum aminotransferases (AST- ALT) and immunoglobulin G (IgG), serologically by the presence of autoantibodies such as anti-nuclear antibody , anti-smooth antibody , and anti -liver kidney microsomal antibody or anti -soluble liver antigen antibody and histologically by interface hepatitis.[1] As a

result of this chronic inflammatory process, cirrhosis and subsequently occurrence of hepatocellular carcinoma.[2]

Corticosteroid in the form of high dose prednisolone or a lower dose of prednisolone in combination with azathioprine is the standard treatment of AIH with remission rate reaching up to 80 per cent. Since majority of the patients will require a long-term maintenance therapy, they are at increased risk of steroid related side effect (10–44 per cent).[2]

To avoid such a risk , budesonide, a synthetic steroid with high hepatic first pass effect and low steroid related side effects was used in clinical trials and compared with the standard treatment regarding it is efficacy and side effects profile.[3]

The current review aimed to summarize the available studies that investigated budesonide as a first line treatment for AIH.

Method

A systematic electronic search was conducted including the Pub Med , Google Scholar, and EBSCO using the following terms in different combinations : autoimmune hepatitis , budesonide, prednisolone and azathioprine. We included all full texts randomized controlled trials and observational , studies investigated budesonide as a first line treatment for AIH. Studies published in abstracts were not included . Hundred and six articles were identified , only five of them fulfilled the inclusion and exclusion criteria . The abstracts and full texts were screened independently by two authors (MB, AI). The authors extracted the data , and then the author's names , year and region of publication , the study type, period of study, and the result were reported. Table 1 The PRISMA Chart was used in the current survey (Figure 1).

Results

After exclusion of irrelevant and duplicated studies as well as review articles , five studies met the inclusion criteria.[4-8] Included studies aimed to evaluate the use of budesonide as a first line treatment for AIH . The total number of AIH patients included in this review were 290, the sample size ranged from 7 in Wiegand et al.[4] study to 207 in Manns et al.[6] The studies duration range between 3–9 months.

Budesonide in dose of 3mg thrice a day as a monotherapy was assessed in two studies . Wiegand et al.,[4] included 12 patients with autoimmune hepatitis , complete remission was achieved in 7 out of 12 (58%). Similarly, Csepregi and collage,[5] conducted a pilot study where 83% of the patients accomplished complete clinical and biochemical remission. Combining budesonide with azathioprine was also investigated in autoimmune hepatitis. Manns et al.,[6] conducted a randomized trial included 207 autoimmune hepatitis patients who were assigned to receive either budesonide at dose of 3mg two or three times daily or prednisone at 40mg daily . Both regiments were combined with azathioprine (1 to 2mg/kg daily). Complete biochemical remission was significantly higher among budesonide treated patients compared with those who received prednisolone (47 and 18 percent, respectively). In addition, fewer glucocorticoid -related side effects were observed in budesonide group . The efficacy of budesonide and azathioprine combination was also shown in the study by Efe et al.[7] In this study authors concluded that budesonide is an effective treatment option for the management of AIH , with a low incidence of side effects in patients without findings of advanced liver disease.

Concerning paediatric patients , oral budesonide with azathioprine can induce and maintain remission in paediatric patients with autoimmune hepatitis and may be considered an alternative therapy to prednisone, this result has been reported by Woynarowski 8 who compared oral budesonide with oral prednisone in combination with azathioprine In autoimmune hepatitis patients aged 9–17 years and observed a comparable percentage of remission among the two study arms.

Discussion

Once indicated, treatment of autoimmune hepatitis should be initiated. Two established treatment regimens for severe autoimmune hepatitis (AIH) are equally effective and include high dose of prednisone (60mg daily) or a lower dose (30mg daily) co-administered with azathioprine (50mg or 1–2mg/kg body weight). Both regiments are recommended in clinical guidelines. For instance, the American Association for the Study of Liver Diseases (AASLD) recommend both treatment options, with the latter being preferred.[9]

Although the combination regiment is the preferred one , treatment should be individualized . As an illustration, prednisone as a sole medication is a reasonable choice in individuals with cytopenia , pregnancy and active malignancies.[10-12]

Corticosteroid-related side effects are the most common causes for premature drug withdrawal in autoimmune hepatitis. It is ranging from cosmetic side effect such as

weight gain, acne and alopecia to as severe as osteopenia with vertebral compression, diabetes, psychosis and pancreatitis.[13,14]

To avoid such a serious side effects. Budesonide, a synthetic steroid with a high hepatic first pass metabolism and less steroid related side effects , were evaluated in five randomized control trials as an alternative to prednisone in the treatment of AIH.[4-8]

Finally, with the exception of Manns et al.[6] study, all included trials have very small sample size . The efficacy of budesonide was ranged from 16% in Woynarowski et al.[8] study to 83% in Csepregi et al.[5] study, this variation in the efficacy could be explained by different treatment duration as well as definition of remission.

Conclusion

In absence of advance liver disease , budesonide is a promising treatment option especially for patients prone to develop steroid specific side effects such as osteoporosis in postmenopausal females. Current studies support usage of budesonide. More randomized trials are needed to validate this finding and provide a solid information about both efficacy as indicated biochemically and histologically as well as information about long term safety.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Table 1: The included studies outcomes regarding effectiveness of budesonide

	Author–Year	Methods	Results
1	Wiegand et al[4] 2005	Study design: open, uncontrolled multicenter phase IIA trial. Study aim: To assessed the efficacy and safety of BUD in AIH. Inclusion criteria: Patients (age 10–70 years) with the first diagnosis of AIH according to the scoring system of the International Autoimmune Hepatitis Group.2 Treatment regimen: 3mg BUD thrice daily. Follow-up duration: 3 months Primary endpoint: induction of remission. Definition of remission: Drop of AST and ALT ≥ two times the upper limit of normal.	Study completer; 12 participants (4 male, 8 female) Result: complete remission: 7 out of 12 (58%) Partial remission: 3 out of 12 (25%) Therapy was tolerated well in (83.3%). Limitation: Long term efficacy and safety con not be concluded due to short follow up duration. Conclusion: BUD monotherapy was effective in the induction of remission and well tolerated in treatment naïve patients with AIH.
2	Csepregi et al[5] 2006	Study design: Opine pilot study. Study aim: To assessed the efficacy and safety of BUD in AIH. Inclusion criteria: AIH diagnosed based on the International Autoimmune Hepatitis Group. Treatment regimen: BUD 3mg thrice daily Follow-up duration: At least 24 weeks. Primary endpoint: induction of remission. Definition of remission: Absence of clinical symptoms, normal serum ALT, ALP, and IgG levels.	Study completer: 7 Participants Result: Fifteen (83%) patients had a complete clinical and biochemical remission. Ten patients, including five with acute hepatitis, were given BUD as first-line therapy, of which seven enter remission. Limitation: Small sample size, short follow-up duration. Conclusion: BUD is effective in remission induction in the majority of AIH patients. Side effects and treatment failure was mainly observed in patients with liver cirrhosis.
3	Manns et al[6] 2010	Study design: Prospective double-blind Randomized active controlled trial. Study aim: compared the effects of BUD and prednisone, both in combination with azathioprine. Inclusion criteria: Participants 10–70 years of age with diagnosis of AIH according to the criteria of the International Autoimmune Hepatitis Group. Treatment regimen: AZA (1–2mg/kg/d).) plus either BUD (3mg, three times daily or twice daily) or prednisone (40mg/d, tapered to 10mg/d). Follow-up duration: 6 months Primary endpoint: induction of remission Definition of remission: normal serum levels of aspartate aminotransferase and alanine aminotransferase, without predefined steroid-specific side effects, at 6 months.	Study completer: 207 completers. 102: BUD- AZA versus 105 Prednisone-AZA Result: complete biochemical in 60% of BUD group versus 38.8% of prednisone group (P = .001; CI: 7.7) Limitation: Conclusion: Oral BUD, in combination with azathioprine, induces and maintains remission in patients with noncirrhotic AIH, with a low rate of steroid-specific side effects.
		Study design: Multicenter, retrospective study. Study aim: To assess the efficacy and tolerability of BUD as	Study completer: 18 Participants (15 females, 3 male) Result: Complete response and remission were achieved in 61.1% (11/18) of patients, while 38.9% (7/18) of patients were considered treatment failures.

4	Efe et al[7] 2011	an alternative first line treatment option for AIH. Inclusion criteria: AIH patient who initially treated with BUD. Treatment regimen: Daily 9mg BUD plus 50mg AZA. Follow-up duration: mean of 9.2 months Primary endpoint: induction of remission. Definition of remission: normalization of AST and/or ALT while under budesonide treatment.	Limitation: Small sample size. Conclusion: BUD is an effective treatment option for the management of AIH, with a low incidence of side effects in patients without findings of advanced liver disease.
5	Woynarowskiet al[8] 2013	Study design: prospective, double-blind, randomized, active-controlled, multicenter phase IIb study. Study aim: To compare oral BUD with oral prednisone in combination with AZA In AIH patients. Inclusion criteria: Patients with AIH aged 9-17 years. Treatment regimen: BUD (3mg twice or 3 times daily) vs prednisone (40mg/day tapered to 10mg/day), both with AZA (1-2mg/kg/day) Follow-up duration: 6 months Primary endpoint: Complete response to therapy. Definition of remission: complete biochemical remission.	Study completer: 46 Participants (11 males and 35 females) Result: 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. Limitation: relatively short study period. Conclusion: Oral BUD with AZA can induce and maintain remission in pediatric patients with AIH and may be considered an alternative therapy to prednisone.

Abbreviations: AIH: Autoimmune hepatitis, BUD: Budesonide, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AZA: Azathioprine.

Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart)