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The Effectiveness and Tolerability of Budesonide in Treatment of Autoimmune Hepatitis: A Systematic Review

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ABSTRACT
Background: Budesonide was effective in treating and keeping short-term remission with a fewer steroid-specific side effects in contrast to prednisone. Contradicting outcomes were detailed on the efficiency of budesonide in the management of Autoimmune Hepatitis. This review aiming at evaluating the use of budesonide for the treatment of autoimmune hepatitis.
Methods: An electronic search was conducted in MEDLINE and EMBASE using these keywords steroids, autoimmune, liver, effectiveness, and side effects. The search was limited to clinical setting which resulted in 24 clinical studies.
Results: The total number of AIH patients included in this review were 386 of which 304 females (78.7%), the sample size ranged from 9 patients to 207 and the mean age ranged from 13 years in to 54. Concerning the efficacy of Budesonide, it ranged from 15% to 78% as the end points were different among the included studies. Regarding the tolerability and side effects like Moon faces or cushingoid features, acne, heartburn, hirsutism, alopecia, osteoporosis, diabetes mellitus and easy bruising. Side effects reported in X studies and the incidence ranged from 28% to 56%.
Conclusion: Budesonide could be a promising treatment option especially in patients prone to corticosteroid side effects like elderly individuals and postmenopausal women with high risk for osteoporosis or children with risk for impaired growth.
Keywords: Hepatitis, Autoimmune, Liver, Treatment, Tolerability, Effectiveness

INTRODUCTION

Autoimmune hepatitis (AIH) is an inflammatory disorder characterized by high serum levels of aminotransferases and immunoglobulin G occurs mainly in females, the presence of autoantibodies serologically, and by interface hepatitis histologically, of an unknown etiology [(1)]. This inflammatory condition can cause cirrhosis and also increments the chance of hepatocellular carcinoma [(2)]. Diagnosis of AIH is depend on histologic, biochemical, and serologic findings, in addition to signs and symptoms [(3)]. AIH has good response to immunosuppressant's and the response is outcome dependent [(4)].

The conventional corticosteroids (prednisolone or prednisone) alone or as combination with azathioprine comprises the current standard treatment and has a high remission rate in almost 80% of patients 3 years later [(5)]. Sixty-five percent to 80% of patients have an effective reaction to the therapy, and while few patients are able to stay in remission after drug discontinuation, the majority of patients, particularly those already have cirrhosis, need long-term maintenance therapy [(2)]. Prednisolone is the first line corticosteroid as it is very effective in reversing intrahepatic inflammation [(6)]. In any case, up to 44% of patients experience the adverse effects of symptoms prompted by prednisolone when it utilized alone as, and furthermore when combined with azathioprine still in no less than 10% of patients causes prednisolone-particular reactions [(5)]. Ten to 15% of patients estimated are resistant to standard treatment and stay as refractory patients with a requirement for other treatrment agents [(7)]. There are restricted information concerning the significance of cyclosporine [(8)], mycophenolate mofetil [(9)], ursodiol [(10)], tacrolimus [(11)], Cyclophosphamide [(12)], methotrexate [(13)], and mercaptopurine in AIH [(14)].

Budesonide is a nonhalogenated glucocorticoid effective as topical therapy of rhinitis, asthma, and inflammatory bowel disease [(15)]. Since that it is 15 to 20 times higher glucocorticoid receptor binding affinity, the efficacy of budesonide on liver inflammatory activity is much more than that of prednisolone [(16)]. Budesonide is derived from 16α-hydroxyprednisolone as a synthetic corticosteroid [(17)] and effective in the liver as anti-inflammatory agent with lower systemic adverse effects [(18)], as it has a hepatic first-pass clearance of > 90% following oral use [(3)]. In three previous pilot studies, contradicting outcomes were detailed on

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the efficiency of budesonide in the management of AIH [18-20].

The first multicenter randomized trial on the treatment of AIH with budesonide was published in 2010 [3]. Reduced regimen of 40 mg of prednisone in 105 patients was compared to 9 mg of budesonide per day in 102 patients; and the two groups were received azathioprine (1-2 mg/kg/day) [3]. Budesonide was effective in treating and keeping short-term remission with a fewer steroid-specific side effects in contrast to prednisone. Sixty percent of patients in the budesonide group accomplished normal levels of aminotransferase compared to 39% in the prednisone group [3]. Budesonide is contraindicated in patients with liver cirrhosis as it was increased systemic side effects [16]. The reactions of corticosteroids are notable and incorporate skin break out, hirsutism, the redistribution of muscle to fat ratio, weight pick up, osteoporosis, hyperglycemia, cataracts, and mental abnormalities [21]. This review aiming at evaluating the use of budesonide for the treatment of AIH.

METHODS

An electronic search was conducted in MEDLINE and EMBASE using these keywords steroids, autoimmune, liver, effectiveness, and side effects. The search was limited to clinical setting which resulted in 24 clinical studies. The eligible studies then screened by title and abstract to exclude irrelevant, duplicated and review studies. Finally, nine studies met the inclusion criteria which include the studies evaluated the use of budesonide for the treatment of autoimmune hepatitis. The data were extracted from the included studies to the data extraction forms contained study design, sample size, age of patients, type of liver hepatitis, comparison drugs, regimen of the drug, side effects and effectiveness of the drug.

RESULTS

The search of the literature, after exclusion of irrelevant, duplicated and review studies, revealed nine studies met the inclusion criteria. Included studies aimed to evaluate the use of budesonide for the treatment of autoimmune hepatitis (AIH).

The study design of the included studies were prospective randomized controlled trials in **Manns *et al.*** and **Woynarowski *et al.*** [3, 22], five open-label studies with small sample sizes [18-20, 23, 24], one retrospective chart review of **Zandieh *et al.*** [25] and one retrospective analysis conducted by **Peiseler *et al.*** [26].

The total number of AIH patients included in this review were 386 of which 304 females (78.7%), the sample size ranged from 9 patients in **Schuler *et al.*** **and Zandieh *et al.*** [24, 25] and 207 in **Manns *et al.*** [3], the mean age ranged from 13 years in **Woynarowski *et al.*** [22] to 54 in **Czaja *et al.*** [20] and not reported in **Peiseler *et al.*** [26].

Regarding the steroid type and dose used, Budesonide 3 mg/ day in **Wiegand *et al.*** [19], **Woynarowski *et al.*** [22] and Zandieh ***et al.*** [25], 6-8 mg /day in **Danielsson *et al.*** [18], 6-15 mg/day in **Schuler *et al.*** [24] and 9 mg/day in other studies ([3, 20, 23, 26]. All included studies were used Azathioprine as adjunct immunosuppressant except for **Wiegand *et al.*** [19] and **Schuler *et al.*** [24] used no Prednisolone as comparator corticosteroid with a dose range of 5-40 mg/day. Concerning the efficacy of Budesonide, it ranged from 15% in [22] to 78% in [25] as the end points were different among the included studies.

Regarding the tolerability and side effects like Moon faces or cushingoid features, acne, heartburn, hirsutism, alopecia, osteoporosis, diabetes mellitus and easy bruising. Side effects reported in 6 studies and the incidence ranged from 28% in **Manns *et al.*** [3], to 56% in **Schuler *et al.*** [24].

Table (1): The included studies outcomes regarding effectiveness and safety of steroids in treatment of AIH

Study	Study design	Sample size	Age of patients	Type of liver hepatitis	Types of steroids	Regimen of the drug	Side effects of drugs rate	Effectiveness of the drug
Manns *et al.*	A double-blind randomized controlled multicenter study	207 patients 160 women	Mean age = 40, range= 10–70	Acute auto-immune hepatitis	Budesonide Prednisolone Azathioprine	-Budesonide 9 mg /day reduced to 6 mg /day on remission. Prednisolone 40-30 mg / day then tapered	No adverse effects noted with Budesonide 72/100 (72%) In prednisolone 48/103 (46.6%) had at least one steroid specific side effect moon facies	budesonide was effective in (47.0%) while prednisone was effective in (18.4%) ($p < 0.001$)
Danielsson *et al.*	Open pilot 36 weeks duration	13 patients with Cirrhosis	Mean age 47 y 19-70	Auto-immune chronic active hepatitis	Prednisolone Budesonide Azathioprine	Initial: 6-8 mg/day 3 times daily (mean 6.3) for 6-10 weeks Maintenance: 2-6 mg/day	No cushingoid effects noted cortisol levels were lower in patients. with cirrhosis	Most patients. Had decrease in ALT within 12 weeks; 3 patients. had relapse after reduction to maintenance dose
Czaja *et al.*	Open pilot 24 weeks	N = 10; 8 women Cirrhosis : 2 (20%) patients	Mean age 54 y (range 31-73)	Auto-immune hepatitis	Budesonide Azathioprine Prednisone	Budesonide = 9 mg/day for 24weeks Azathioprine= 50-100 mg/day in 5/10 Prednisone= 5-15 mg/day in	At least 2 of the following occurred in the 3 patients who developed drug toxicity: cushingoid features, weight gain, hirsutism, alopecia, and easy bruising Drug toxicity: 3/10 (30%)	Remission: 3/10 (30%) Treatment failure: 4/10 40% Drug toxicity: 3/10 (30%)
Csepregi *et al.*	Open pilot 24 weeks	N = 18; 12 women with cirrhosis	Mean age 45.4 y (range 21-68)	Autoimmune hepatitis	Budesonide Azathioprine Prednisone	Budesonide = 9 mg/day for 24week. Azathioprine= 50-100 mg/day in5/8(63%) refractory. Prednisone= 10-40 mg/day in5/8 (63%) refractory patients	6/18 (33%) patients. Noted adverse effects: abdominal pain (n = 1); weight gain>3 kg (n = 3); acne (n = 2); alopecia (n = 1) All adverse effects were in patients. with cirrhosis	Remission: 7/10 (70%) newly treated patients.; 8/8(100%) refractory patients. Treatment failure: 2 of the 3 non-responders had cirrhosis Drug toxicity: 1/18 (withdrawal for gastrointestinal symptoms)

Zandieh *et al*.	A retrospective chart review	N = 9 women with cirrhosis	Mean age 39 (range 12-66)	Refractory or side effects of standard therapy	Budesonide Azathioprine Prednisone	Ranged from 3 mg every other day to 9 mg daily, Prednisone 10-15mg/day in 6/9 patients.	Not-reported	Complete response in 78% of patients.
Schuler *et al*.	Open pilot,52 weeks	N = 9	38.4 ± 17	Not-reported	Budesonide Azathioprine	Budesonide = 6-15 mg/day Azathioprine= 100 mg/day in 33% of patients	56% exhibited acne, weight gain or cushingoid features; diminished effects noted after dose reduction	Complete remission: 4/9 (44%) of patients.; partial remission: 2/9 (22%) of patients
Wiegand *et al*.	Open pilot 12 weeks	N = 14;	Mean (SD) age 38.2 (17.3)	Auto-immune hepatitis	Budesonide	Day 1: 3 mg twice daily; day 2: 3 mg 3 times daily; remission: 3 mg twice daily for 9 weeks	Leukocytosis (36%); hypercholesterolemia (29%); cushingoid features (21%); acne (14%); heartburn (14%); weight gain (14%)	Complete remission 7/14 (50%) patients.; partial remission 3/14 (21.4%) patients.; failure 2/14 (14.3%) patients.; exclusion 2/14 (14.3%)
Woynarowski *et al*.	A double-blind randomized active-controlled multicenter trial	46 11 males and 35 females	Mean age = 13 Range = 9-17	Auto-immune hepatitis	Budesonide Azathioprine Prednisone	Budesonide = 3 mg twice or 3 times daily. Prednisone 40 mg/day tapered to 10 mg/day), both with azathioprine 1-2 mg/kg/day, followed by a 6 months of open-label budesonide therapy	Weight gain	Budesonide was effective in 16% and prednisone was effective in 15%. After 6 months, nor in the percentage of patients who experienced biochemical remission
Peiseler *et al.*	A retrospective analysis	60 patients (51 female)	Not-reported	Auto-immune hepatitis	Prednisone Budesonide	9 mg per day maintenance dose was 6-12mg	Weight gain (9 patients), osteoporosis (7 patients) and diabetes mellitus (4 patients)	The remission occurred in 67% after 24 months

DISCUSSION

The AIH treatment has been used as prednisone alone or in combination with azathioprine dependent in adults [27] and children [28]. The AIH remission definition differs between studies, and the clinical, biochemical, immunologic, and histological status assessment may be involved. AIH remission was defined as normal serum ALT by **Alvarez *et al***. [29] and defined as normal ALT in the absence of clinical symptoms by **Cuarterolo *et al.*** [30]. Normalized serum AST activity was the outcome measure used by **Aw *et al.*** [31]. The standardization of aminotransferase action as entire or almost total endpoint was characterized by a few creators [32]. The abatement rate with standard corticosteroids and azathioprine treatment comes to around 80% when a solitary variable, for example, aminotransferase standardization, is the result measure. Budesonide when joined with azathioprine can incite and keep up abatement in AIH, and they demonstrated an essentially bring down frequency of steroid-particular reactions contrasted and standard prednisone treatment, when controlled with azathioprine [3].

The critical appraisal of the included studies revealed that all included trials have very small sample size except the randomized clinical trial which recruited 207 AIH patients [3] which showed no difference in the efficacy and safety from the other studies but the results may be more accurate as the RCT has a definitive end point. The efficacy of Budesonide was ranged from 15% in [22] to 78% in [25], this wide range of difference in the efficacy may be due to the difference of the definition of the end point and the time needed to the remission to take place. Side effects ranged from 28% in **Manns *et al.*** [3], to 56% in **Schuler *et al.*** [24].

Budesonide seems to have less adverse effects on bone metabolism concerning increased bone density compared to conventional steroid treatment [20, 26] this might be speculated that the observed differences are influenced by different extent of liver disease regarding chronic hepatic inflammation and fibrosis as well as previous corticosteroid therapy over years, which may alter saturation and affinity of corticosteroid receptors, metabolic pathways and hepatic clearance of systemically active metabolites (table 1).

The major advantage of budesonide could be equal efficacy in the long-term treatment, but a lower rate of side effects compared with prednisone. Limitations of this review were because of the retrospective design of some studies included, budesonide-induced adverse reactions formal evaluation could not be done so that any conclusions regarding to safety of budesonide should be drawn cautiously and small sample sizes of the majority of the included studies as they were open pilot studies.

CONCLUSION

Future randomized control trials were needed to support these findings regarding budesonide and its safety. Budesonide could be a promising treatment option especially in patients prone to corticosteroid side effects like elderly individuals and postmenopausal women with high risk for osteoporosis or children with risk for impaired growth. Further studies should investigate whether liver function improvement related biochemically with decreased systemic bioavailability of budesonide and clinically with lower systemic side effects.

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