



Research Article

Budesonide Combination A Better Clinical Approach in Comparison to Cyclosporine in Treatment of Autoimmune Hepatitis

Authors

Rasmirekha Behera¹, Sushant Sethi²

¹Dept of Pharmacology I.M.S & SUM Hospital Bhubaneswar, India

²Dept of Gastroenterology Apollo Hospital Bhubaneswar, India

Abstract

Autoimmune hepatitis (AIH) is an uncommon though serious and potentially life-threatening disease which requires prompt recognition and treatment. In cases unresponsive to conventional treatment, achieving disease remission can be difficult. Keeping this in background in this study a comparison has been made between Budesonide combination with that of immunosuppressant i.e cyclosporine in treatment of Autoimmune Hepatitis.

Methods: 30 AIH patients were included in this study. All patients were divided into two groups i.e group A and B. 15 patients Group A were treated with Budesonide 9mg/kg/day with Azathioprine 2mg/kg/day and 15 patients Group B were treated with Cyclosporine 3mg/kg/day. All the drugs were administered for 6 months.

Result: All the patients with Budesonide and Azathioprine therapy were found to Antinuclear antibody negative after 6 months and more than 10 patients of Group A were found to have decrease in level of AST and ALT after 6 months. In patients with Cyclosporine therapy only 9 patients were found to be ANA negative after 6 months. Less than 10 patients were found to have decrease in levels of AST and ALT after 6 months in group B.

Conclusion: Group A patients demonstrated a good biochemical response after 6 months of therapy in comparison to Group B patients. From this it is concluded that patients with Budesonide and Azathioprine therapy shows a significant improvement in AIH after 6 months in comparison to Cyclosporine therapy.

Keywords: Autoimmune Hepatitis, Budesonide, Azathioprine, Cyclosporine, Alanine aminotransferase, Aspartate aminotransferase, Antinuclear Antibody, Immunosuppressant.

Introduction

Autoimmune hepatitis (AIH) is a complex immune mediated liver disease that is diagnosed histologically by interface hepatitis and high serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and immunoglobulin G (IgG) and presence of autoantibodies.⁽¹⁾ AIH can be asymptomatic or

present in various forms from subclinical disease to acute liver failure and end-stage liver disease.⁽²⁾ AIH is divided in Type 1 and Type 2, the latter being rare in adults and representing 30% of juvenile AIH. The distinction is made serologically: type 1 AIH is positive for anti-nuclear antibodies (ANA), and/or anti-smooth muscle antibodies (SMA), while type 2 AIH is

positive for anti-liver kidney microsomal antibodies type 1 (anti-LKM 1) and/or anti-liver cytosol type 1 (anti-LC1)⁽³⁾ The exact mechanisms for the immune tolerance break-down in AIH have not been described yet, but there is growing evidence that a genetic predisposition, molecular mimicry, and an imbalance between effector and regulatory immunity are key pathologic components for disease development. Several lines of evidence support the central role of impaired T cell number and function.⁽¹⁾ Further putative triggers (e.g viruses) for AIH have also been linked to the hypothesis of molecular mimicry and cross-reactivity between foreign epitopes and hepatic antigens⁽⁴⁾. This includes hepatitis A virus (HAV)⁽⁵⁾ hepatitis C virus (HCV)⁽⁶⁾, hepatitis E virus (HEV)⁽⁷⁾ measles⁽⁸⁾ Epstein-Barr virus (EBV)⁽⁹⁾ and herpes simplex virus.⁽¹⁰⁾ Several drugs (e.g minocycline, nitrofurantoin, melatonin, diclofenac, statins and orinidazole which may be involved in precipitating AIH. It is important to clarify that drug-induced AIH is completely different entity from drug-induced liver injury (DILI); however, overlap syndromes have been described in up to 9% of cases in which AIH and DILI are indistinguishable from each other.⁽¹¹⁾ The diagnosis of AIH is based on the presence of specific autoantibodies, immunoglobulin levels and histology as well as the absence of acute viral serology.^(12,13) Anti-SLA (anti-soluble liver antigen) is highly specific for the diagnosis of AIH.^(14,15) The classical histological hallmark of AIH is interface hepatitis characterized by inflammation and erosion at the junction of the hepatic parenchyma with the portal tracts. Centrilobular lesions and necrosis are present when the disease is severe and progressive. Acute cases may appear histologically indistinct to drug induced liver injury.⁽¹⁶⁾ Fibrosis and cirrhosis may already be evident in subacute disease.⁽¹²⁾ Absolute indications for treatment are a serum AST greater than 10 times the upper limit of normal or an AST greater than 5 times the upper limit of normal in conjunction with a serum

globulin level greater than 2 times the upper limit of normal. Bridging or multilobular necrosis at presentation is an absolute indication for treatment given the risk of progression to cirrhosis.⁽¹⁷⁾ Furthermore incapacitating systemic symptoms such as fatigue and arthralgia are also considered absolute indications for treatment.⁽¹⁷⁾ Diseases that can resemble autoimmune hepatitis must also be excluded by appropriate tests and these include virus-related, drug-induced, alcoholic, hereditary (Wilson disease, hereditary hemochromatosis), meta-bolic (nonalcoholic fatty liver disease (NAFLD), and immune-mediated cholestatic diseases (PBC and PSC).⁽¹⁸⁾ The aim of treatment is disease remission, which is reached if the following criteria are met: (1) absence of clinical symptoms; (2) normal transaminase levels; and (3) normal IgG levels. In children /adolescents, negative or very low-titre autoantibodies (< 1:20 for ANA/SMA; < 1:10 for anti-LKM1) are an additional criterion of remission.⁽¹⁹⁾ Formalized diagnostic criteria ensure the application of a standardized diagnostic algorithm,⁽²⁰⁾ and diagnostic scoring system provide an evaluation template that can support the diagnosis in difficult cases.^(20,21,22) Successful treatment aims at reducing inflammation and preventing progressive fibrosis while minimizing side effects associated with therapy.⁽²³⁾ Standard treatment approaches have remained static for decades, since Prednisolone with or without azathioprine (AZA) was first introduced in the 1950s – 1960s.⁽²⁴⁾ Although definitions of therapeutic endpoints were heterogenous across the reviewed studies, most defined treatment response as resolution of clinical symptoms and normalization of transaminase and immunoglobulin G (IgG) levels within 6 months after initiation of therapy.^(25,26,27,28) Currently, initial standard therapy consists of corticosteroids (prednisone or prednisolone) with or without AZA.^(23,29) Most patients respond very well to standard therapy. If appropriately managed, and alternative treatment modalities are needed only for the minority whom cannot tolerate or do not respond

to usual approaches. Overall, 10-15% of patients on standard therapy discontinue due to intolerable side effects.⁽³⁰⁾ and up to 18% of those who present with jaundice fail initial treatment.⁽³¹⁾ Budesonide is a synthetic glucocorticoid with a more than 90% hepatic first pass effect. It is associated with low corticosteroidal bioavailability and low steroid specific side effects.⁽³²⁾ Bone marrow suppression is the major side effect of azathioprine, whereas steroid specific side effects, such as moon face, acne, buffalo hump, hirsutism, striae, diabetes, and glaucoma, often occur in patients treated with prednisolone.⁽³³⁾ The frequency of side effects was low Budesonide is an appropriate induction option in treatment-naïve patients without advanced fibrosis, in those with steroid-related side effects, and in those at risk of adverse effects for steroids including those with metabolic bone disease and brittle diabetes. The presence of obesity, hypertension, or osteopenia that might be worsened by prednisone treatment also support consideration of the budesonide regimen.⁽³⁴⁾ A simplified diagnostic scoring system has been developed to ease clinical application.⁽²¹⁾ It evaluates four clinical categories and renders nine possible grades.⁽²¹⁾ The original revised scoring system has greater sensitivity for autoimmune hepatitis (100% vs 95%).⁽²²⁾ whereas the simplified scoring system has superior specificity (90% vs 73%) and accuracy (92% vs 82%), using clinical judgment as the gold standard.⁽²²⁾ Oral budesonide is an alternative to prednisolone and lessens systemic steroid side effects. It can be given at doses of 3 mg twice or thrice daily in combination with azathioprine.⁽³⁵⁾ Budesonide in combination with azathioprine has emerged as an alternative frontline treatment for autoimmune hepatitis.⁽³⁴⁾ Cyclosporine has been administered in doses of 2 to 5mg body weight with dose adjustments to achieve trough levels of 100 to 300 ng/ml.^(34,36,37) Cyclosporine A belong to the group of calcineurin inhibitors (CNI) which find widespread application as immunosuppressive drugs by inhibiting T cell activation and IL-2

production.⁽³⁸⁾ In this study the treatment outcome is compared between Budesonide with azathioprine and Cyclosporine in patients of autoimmune hepatitis.

Material and Methods

The study was conducted in the department of Gastroenterology Apollo Hospital Bhubaneswar for 6 months from October 2019 to March 2020.

Inclusion Criteria

1. Patients are selected between 18 to 60 yrs diagnosed with Autoimmune Hepatitis with Obesity, Hypertension and Diabetes.
2. Disease refractory to steroids and azathioprine.
3. Patients with bone marrow suppression & opportunistic infection due to Azathioprine
4. Patients with prednisolone dependence and steroid side effects.

Exclusion Criteria

1. Patients above 60yrs and below 18yrs of age.
2. Patients with cirrhosis.

Patients were divided into two groups i.e Group: A and Group: B. In each group 15 patients were included. Group A patients were given Budesonide 9mg/day with Azathioprine with a dose of 2mg/kg/day. Group B patients were given Cyclosporine 3mg/kg/day. The drugs were given for 6 months to both the groups. Patients diagnosed with AIH with Obesity, Hypertension, Diabetes and with steroid dependence are considered for Group A and given Budesonide and Azathioprine combination. Patients diagnosed with AIH but refractory to steroids and Azathioprine therapy and showing bone marrow suppression, opportunistic infection are categorized as Group B and considered for cyclosporine therapy.

The diagnostic criteria of the IAIHG require the presence of compatible laboratory serum aspartate (AST) and alanine aminotransferase (ALT) abnormalities, hypergammaglobulinemia and increased serum IgG level, serological (ANA, SMA or anti-LKM1 positivity and histological

findings (interface hepatitis with or without plasma cell infiltration.⁽²⁰⁾)

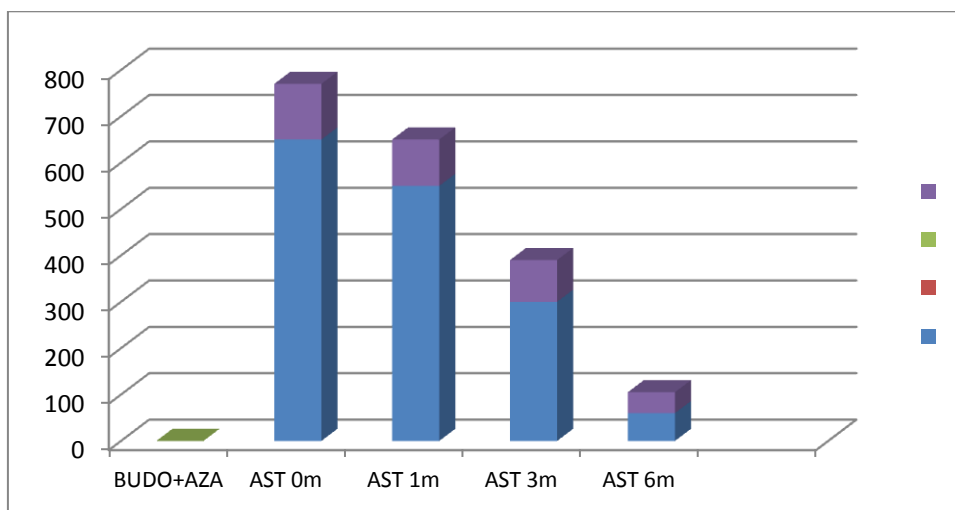
Statistical Analysis: Statistical Analysis was done by applying paired t-test. As there are 30 samples degree of freedom is 29. P value found to be less than 0.05 and the difference observed is significant.

Result

Result were compared with values of AST, ALT and ANA. Evaluation of all the parameters were done at 0 month, 1 month, 3 month and 6 month intervals. Values of ALT & AST represented in U/L

Table:1 Budesonide with Azathioprine Therapy (Group: A 15 patients)

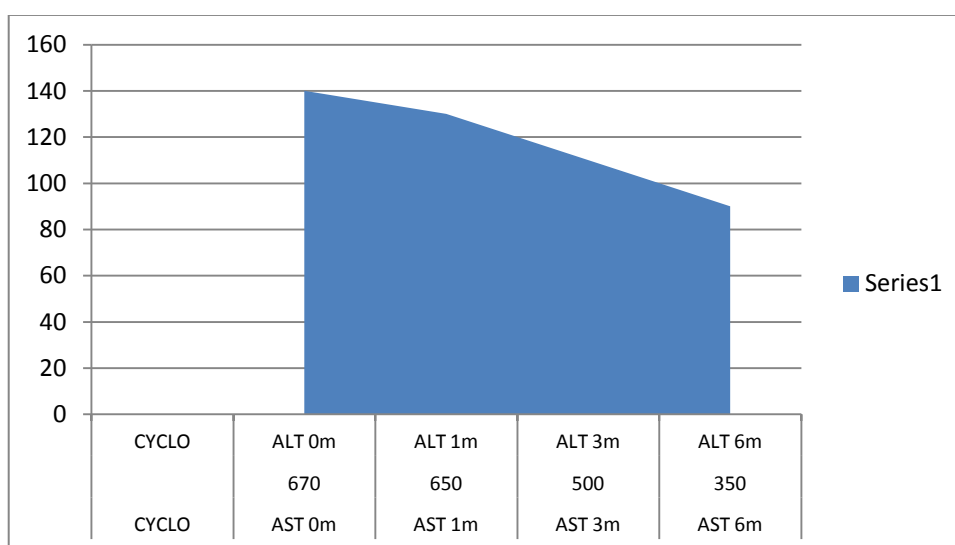
Parameters	0 month	1 month	3 month	6 month
AST	650	550	300	60
ALT	120	100	90	45
ANA	+++	++	-	-



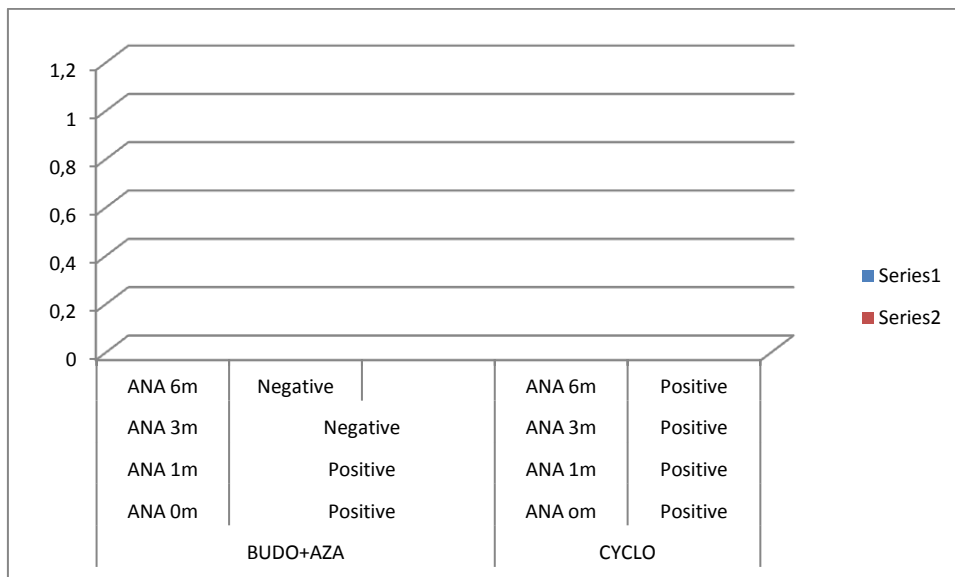
Graph-1 shows enzyme level after 1,3 & 6 months of Budesonide and Azathioprine therapy

Table: 2 Cyclosporin Therapy (Group:B 15 patients)

Parameters	0 month	1 month	3 month	6 month
AST	670	650	500	350
ALT	140	130	110	90
ANA	+++	++	++	+



Graph: 2- shows enzyme levels after 1,3 and 6 months of Cyclosporine therapy



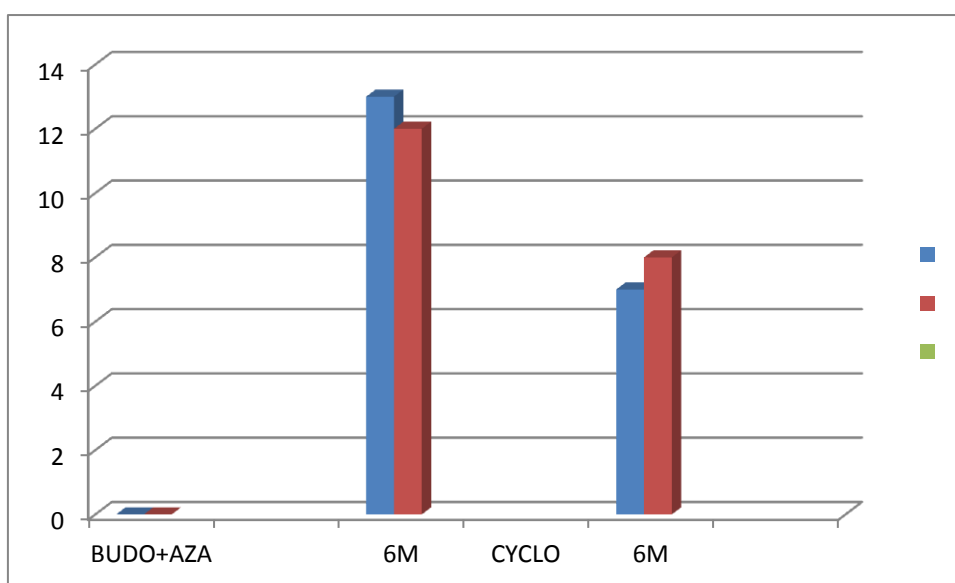
Graph: 3 shows the comparison of ANA responses after Budosonide with Azathioprine therapy and Cyclosporine therapy

Table 3 Group: A Budesonide with Azathioprine (15 patients) Response after 1,3,6 months represented in numbers

Budesonide and Azathioprine Therapy			
Parameters	1 month	3 month	6 month
↓ in AST	6	8	13
↓ in ALT	7	9	12
ANA-	5	13	15

Table 4 Group: B Cyclosporin Therapy (15 patients) Response after 1,3,6 months represented in numbers

Cyclosporine Therapy			
	1 month	3 month	6 month
↓ in AST	5	6	7
↓ in ALT	6	7	8
ANA-	4	6	9



Graph: 4 shows the Comparison of responses between Budesonide with Azathioprine therapy and Cyclosporine Therapy (Represented in no)

It is observed from the above table 3 and table 4 that all the patients with Budesonide and Azathioprine therapy were found to Antinuclear antibody negative after 6 months of drug administration. More than 10 patients were found to have decrease in level of AST and ALT after 6 months of drug administration. In patients with Cyclosporine therapy only 9 patients were found to be ANA negative after 6 months of drug administration & less than 10 patients were found to have decrease in levels of AST and ALT. Graph 1 & 2 shows that there is decrease in enzyme levels after administration of drugs in both Group A and Group B. But the decrease in enzyme level is more in Group A in comparison to Group B. It signifies better response of disease activity in Budesonide with Azathioprine administration in comparison to Cyclosporine therapy. Again from the graph 4 it is observed that no of patients showing improvement in all parameters after 6 months of drug administration is more in Group A. Graph 3 shows all the patients in Group A are ANA negative after 6 months of drug administration.

Discussion

Budesonide is a synthetic corticosteroid with topical anti-inflammatory properties and less steroid-specific side effects due to high first pass hepatic metabolism. Budesonide is a less desirable option in patients with cirrhosis due to impaired hepatic metabolism and increased systemic bioavailability, as well as the potential for increased risk of portal vein thrombosis.^(39,40) Most patients respond very well to standard therapy if appropriately managed and alternative treatment modalities are needed only for the minority whom cannot tolerate or do not respond to usual approaches. Overall, 10%-15% of patients on standard therapy discontinue due to intolerable side effects and up to 18% of those who present with jaundice fail initial treatment.^(41,42) Cyclosporine is calcineurin inhibitor highly effective for prevention of graft rejection reaction. Cyclosporine reported to be effective in variable

doses and duration of treatment in patients of AIH not responding to Azathioprine and Prednisolone.⁽⁴³⁾

Conclusion

The present study shows improvement with Budesonide and Azathioprine therapy in all parameters after 6 months of drug administration. Group A patients demonstrated a good biochemical response after 6 months of therapy in comparison to Group B patients. Also the Antinuclear antibody were found to be negative in all patients with Budesonide and Azathioprine therapy after 6 months. From this it is concluded that patients with Budesonide and Azathioprine therapy shows a significant improvement in AIH after 6 months in comparison to Cyclosporin therapy.

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