Autoimmunity Reviews 11 (2012) 330–334

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome

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ARTICLE INFO

Article history:
Received 4 September 2011
Accepted 26 September 2011
Available online 6 October 2011

Keywords:
Autoimmune hepatitis
Primary biliary cirrhosis
Overlap syndrome
Liver fibrosis
Steroid side effects
Budesonide
Prednisone

ABSTRACT

Background and aim: The aim of the present study was to assess the efficacy and tolerability of budesonide as an alternative first line treatment option for autoimmune hepatitis (AIH) and the overlap syndrome.
Methods: A total of 18 AIH or overlap syndrome patients were evaluated. Outcomes of treatment by the end of the study were defined as treatment failure, partial response, complete response and remission.
Results: Complete response and remission were achieved in 61.1% (11/18) of patients, while 38.9% (7/18) of patients were considered treatment failures. Liver fibrosis was observed in 55.5% of patients' biopsies. More patients with liver fibrosis failed to respond to treatment compared to patients without fibrosis, a difference bordering on statistical significance (60% vs. 12.5%; $p=0.066$). Although statistically insignificant, the presence of at least one side effect was observed more frequently in patients with fibrosis compared to those without fibrosis (80% vs. 37.5%; $p=0.145$). Overall, side effects occurred significantly more commonly in non-responders than responders (100% vs. 36%; $p=0.013$).
Conclusions: 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. The presence of liver fibrosis may increase the likelihood of treatment failure as well as the risk of developing side effects. Our study findings suggest that budesonide may be effective in a select group of AIH patients. Further studies are needed to determine its exact place for the treatment of AIH and overlap syndrome.

Contents

1. Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology characterized by circulating autoantibodies,

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doi:10.1016/j.autrev.2011.09.006

hypergammaglobulinaemia and interface hepatitis [1]. The working model for its pathogenesis showed that a combination of environmental factors, a failure of anti-inflammatory and pro-inflammatoryresponses, genetic susceptibility and presence same target auto-antigens are playing an important role in the development of AIH [2–7]. Conventional therapy for AIH consists of prednisone alone or in combination with azathioprine, which are effective in more than 80% of patients [8,9]. Other agents such as mycophenolate mofetil, cyclosporine-A and tacrolimus have been used in AIH patients but, they are usually preferred in patients resistant to conventional therapy [10,11]. The high remission rate observed with conventional therapy has made the study of novel drugs difficult. On the other hand, prednisolone side effects are still frequent, sometimes severe enough to require drug discontinuation. Alternative steroids which are equivalent to prednisolone in controlling the disease and have less steroid related side effects are needed.

Budesonide has been evaluated for the management of AIH in a few small case-based studies with conflicting results [12–16]. Recently, a large population-based study showed budesonide to be just as effective as prednisone for the treatment AIH, albeit with better tolerability [17]. In this study, we aimed to evaluate the efficacy and tolerability of budesonide as an alternative first line treatment option for AIH and the overlap syndrome.

2. Patients and methods

2.1. Patient selection

Patients diagnosed with either AIH or AIH-primary biliary cirrhosis (PBC) overlap syndrome between May 2009 and June 2011 in two centers from Turkey and one from France were retrospectively evaluated. Patients were initially treated by budesonide were included in study. A diagnosis of either definite or probable AIH was made based on simplified criteria put forth by the International Autoimmune Hepatitis Group (IAIHG), whereas the AIH/PBC overlap syndrome was diagnosed according to criteria suggested by Chazouilleres et al. [18,19]. All patients had serum alanine aminotransferase (ALT) levels or serum aspartate aminotransferase (AST) levels >3 times higher than the upper limit of normal (ULN) and markers of viral hepatitis were also negative. All patients had no findings of cirrhosis on liver biopsy.

2.2. Laboratory assays

Viral markers as well as serum immunoglobulin G (IgG) levels were measured using commercially available ELISA kits. Titres of antimitochondrial antibody (AMA) and its anti-M2 fraction were measured by immunoblotting, while the indirect immunofluorescence technique was used to measure titres of antinuclear antibody (ANA), smooth muscle antibody (SMA), soluble liver antigen (SLA) and liver–kidney microsomal antibodies (LKM). A titre of 1/40 or above for ANA, SMA, SLA, LKM and AMA-M2 was considered positive. Only in one patient, these autoantibodies were considered to be positive at a titre of 1/50 or above.

2.3. Histopathological examination

In all patients, a diagnosis of AIH was confirmed by liver biopsy, which was not repeated in any patient during follow-up. Liver biopsies were evaluated with particular reference to histological activity, fibrosis and biliary changes.

2.4. Statistical analyses

Descriptive statistics were used to summarize the data; the categorical variables were expressed as percentages and continuous variables were expressed as means and ranges. The X2 or Fisher exact test was used to test associations between two categorical variables. Mann Whitney-U test was used for comparison of variables between two groups. Statistical analyses were performed by SPSS (Statistical Package for the Social Sciences) 15.0 and p values <0.05 were considered as significant.

2.5. Treatment protocol

Treatment with budesonide was initiated at a daily dose of 9 mg in combination with 50 mg azathioprine. In the event of a complete response, doses were reduced to 6 mg daily after three months, and subsequently to 3 mg daily after 6 months. Patients who failed to respond or who could not tolerate treatment were switched to a regime of prednisone at a dose of 40 mg daily (Fig. 1). Patients with AIH–PBC overlap syndrome also received ursodeoxycholic acid as an adjuvant to immunosuppressive therapy. Intolerance was defined as the development of one or more budesonide-related side effect(s) that required discontinuation of the drug. Patients in whom AST and/or ALT levels either increased or remained stable for 3 months despite initiation of treatment with budesonide, as well as patients who showed intolerance to the drug were considered treatment failures. A complete response was defined as the presence of a drop in AST and/or ALT to levels less than twice the UNL of the reference range after 3 months or a 50% fall in AST and/or ALT after 1 month of treatment. Patients in whom ALT or AST levels did not fall to less than two times the UNL after 3 months of treatment or without at least an 80% decrease in ALT/AST levels from baseline during therapy were considered partial response. Remission was defined as the normalization of AST and/or ALT while under budesonide treatment. Patients were considered to have relapsed in the event of a rise in AST and/or ALT levels more than three-fold the UNL following initial response to treatment after remission had been achieved. Steroid related side effects such as weight gain>3 kg, moon face, acne, hirsutism, skin striae, buffalo hump and diabetes mellitus were noted in each patient during budesonide therapy.

3. Results

A total of 18 (15 female, 3 male) patients with mean age of 38.6 (range 21–71 years) were included in the study. Fourteen patients had AIH alone, 4 patients had AIH/PBC overlap. The mean duration of treatment with budesonide was 9.2 months (range 1.5–24 months). ANA was positive in 13 patients, SMA in nine, SLA and LKM in one and AMA in three patients. Only one patient fulfilled the criteria for AIH despite being negative for autoantibodies. Demographics and clinical characteristics of the 18 patients treated with budesonide are summarized in Tables 1 and 2.

By the end of the study period, a complete response was observed in 11 of the 18 (61.1%) patients treated with budesonide whereas 7 (38.9%) patients failed to respond. With regard to findings on liver biopsy, 10/18 (55.5%) patients had fibrosis to varying degrees while 8/18 (44.5%) had without fibrosis. Treatment failure was more commonly observed in patients with liver fibrosis than patients without fibrosis, a difference bordering on statistical significance (60% vs. 12.5%, $p=0.066$). Although not statistically significant, steroid related side effects were higher in patients with liver fibrosis compared to patients without fibrosis (80% vs 37.5%, $p=0.145$).

During the first three months of treatment, a response to budesonide was observed in 12 patients (10 complete response, 2 partial response). The initial dose of budesonide was maintained for a total 6 months in both of the partial responders whose initial ALT levels were highly elevated ($28\times$UNL and $22\times$UNL respectively), while doses of budesonide were reduced in the complete responders. By the end of the six-month treatment period, ALT decreased to levels lower than $2\times$UNL in one of the patients who had shown an initial partial response. ALT levels in the other patient, who was subsequently