Research Article

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Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis

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Background & Aims: Autoimmune hepatitis is a chronic inflammatory liver disease that leads to liver cirrhosis and corresponding complications, if left untreated. Current standard treatment with azathioprine and prednisolone induces remission in the vast majority of patients. However, for those patients not responding to standard treatment or not tolerating these drugs, few alternatives can be used and their effectiveness might be limited.

We sought to analyze the safety and efficacy of off-label treatment with infliximab in a cohort of eleven patients with difficult-to-treat autoimmune hepatitis.

Methods: Patients with difficult-to-treat autoimmune hepatitis who could not be brought into remission with standard treatment, either due to drug intolerance or to insufficient drug impact, were treated off-label with infliximab for a minimum of six months. Patient files were reviewed retrospectively.

Results: Treatment with infliximab led to reduction of inflammation, evidenced by a decrease in transaminases (mean AST prior treatment 475 U/L ± 466, mean AST during treatment 43 U/L ± 32) as well as in immunoglobulins (pretreatment mean IgG 24.8 mg/dl ± 10.1, mean IgG during treatment 17.38 mg/dl ± 6). Infectious complications occurred in seven out of eleven patients and close monitoring was necessary.

Conclusions: Infliximab may be considered as rescue therapy in patients with difficult-to-treat autoimmune hepatitis, albeit treatment may be associated with infectious complications.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown cause. It is characterized by elevated transaminases, hypergammaglobulinemia, autoantibodies, and a liver biopsy compatible with autoimmune hepatitis [1]. Standard treatment comprises azathioprine and prednisolone and, in the absence of cirrhosis, leads to complete biochemical response rates in up to 77% of patients after six months of treatment [2].

However, around 5% of patients experience intolerance or toxicity while about 10% do not respond sufficiently to those standard treatment options [3]. Alternative treatments include budesonide [4], mycophenolate mofetil (MMF) [5], 6-thioguanine [6], cyclophosphamide [7], cyclosporine A (CsA) [8] or tacrolimus (FK) [9], however, these treatments have mostly been tested in small case series rather than controlled trials, and have demonstrated only variable effectiveness. Therefore, identification of efficient rescue treatment options is urgently needed for these difficult-to-treat patients. Research has shown that sufficient treatment leads to normalization of transaminases and gammaglobulins, including IgG, and also results in long-term survival comparable to the normal patient population [10]. At the same time, failure to achieve a complete biochemical remission has been shown to result in worse long-term outcomes [11]. Optimization of treatment plays, therefore, a major role in long-term prognosis and quality of life for patients with difficult-to-treat autoimmune hepatitis [3].

Infliximab is a recombinant humanized chimeric antibody currently used for the treatment of rheumatoid arthritis, psoriasis arthritis and plaque psoriasis, ankylosing spondylitis, ulcerative colitis, and colitis Crohn [12]. Autoimmune reactions during therapy, including the development of a *lupus*-like syndrome [13] or even cases of autoimmune-like hepatitis [14], have been described. The mechanism of action, besides the direct neutralization of soluble TNF-alpha, includes a proapoptotic effect on lymphocytes and decreased GM-CSF production by T cells [15]. GM-CSF is a proinflammatory cytokine that has been described to play a role in different autoimmune diseases. Reduction of GM-CSF production has been shown to influence T-cell pathogenicity [16]. Another possible effect may lay in the decrease of a subset of CD8+ effector memory T cells [17]. The latter may contribute to increased susceptibility to intracellular pathogens, but may also contribute to reduced disease activity in autoimmune diseases.

In 2001, our team treated the first patient off-label with infliximab. The patient responded well while developing numerous infectious side effects [18]. This article reviews the treatment history of 11 patients with difficult-to-treat AIH, who subsequently received repeated infliximab infusions. Overall, patients responded well to treatment with long lasting remissions

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achieved in more than 60% of the patients. Conversely, infectious side effects, some of them requiring hospitalization, were frequently seen in this group of patients. Therefore, infliximab warrants further evaluation as rescue treatment for patients with severe and difficult-to-treat AIH.

Patients and methods

Eleven patients (seven female and four male) with difficult-to-treat autoimmune hepatitis fulfilled the criteria for AIH according to the criteria of the International Autoimmune Hepatitis Study Group (REF 19) or the simplified criteria (REF 20). Other liver diseases, including metabolic and viral hepatitis, were excluded. Median age of the patient population was 42 years (range 28–75 years). All patients had initially received standard treatment upon diagnosis of AIH, consisting of azathioprine 1–1.5 mg/kg and prednisolone 1 mg/kg body weight, which was rapidly tapered to a maintenance dose of 5–20 mg/d (see Table 2 for details) and did not yield desired remission rates. Five patients developed azathioprine intolerance, and one patient developed azathioprine-associated pancreatitis. In the 5 remaining patients, the combination of azathioprine and prednisolone was not sufficient for disease control with elevated transaminases (more than two times the upper limit of normal) and immunoglobulins. Seven patients (64%) had histologically confirmed cirrhosis at the time of rescue treatment initiation. Patient 10 had a histological diagnosis of giant-cell hepatitis in addition to AIH. All patients except for patient 10 (diagnosed 10 months prior to initiation of rescue treatment) were diagnosed more than five years ago, prior to treatment initiation with infliximab. Various other drugs had been used in these patients, including cyclophosphamide, cyclosporine, tacrolimus and adalimumab (see Table 1 for details). The latter had been given to two patients, the rationale for switching to infliximab was the higher peak serum level reached with the intravenous application as well as reports that efficacy of the different substances may differ in different individuals. As no further approved treatment options were available for these patients, infliximab was chosen as an alternative course of medication (details in Table 2) due to the severity of their disease and the existing co-morbidities. Patient details are given in Table 1 and the treatment regimen is depicted in Fig. 2. Prednisolone and, if tolerable, other immunosuppressant drugs, as indicated, were continued in all but one patient throughout infliximab treatment (Tables 1 and 2).

This study represents a retrospective analysis of patients receiving infliximab on an individual basis as rescue treatment. Patients gave consent after thorough information about the off-label-use and lack of experience with infliximab treatment in autoimmune hepatitis. All patients received chest X-ray and quantiferon® testing, to exclude active or latent tuberculosis and received a complete laboratory analysis, including autoantibodies, prior to treatment initiation. Furthermore, all patients received abdominal ultrasound prior to infliximab infusion.

Infusions were given at time points 0, after two weeks, and after six weeks of initial infusion, and thereafter every four to eight weeks depending on laboratory and clinical course (Fig. 2). All patients received 5 mg/kg bodyweight infliximab according to the manufacturer's instructions under close medical surveillance.

Results

Patient characteristics

Eleven patients with AIH were treated, with initial findings about patient 1 already published previously [18]. Prior to infliximab treatment, all patients had been treated with other immunosuppressive regimens with insufficient response or intolerance (Table 2). Patients received a liver biopsy prior to initiation of infliximab treatment (median mHAI was 9.2 ± 2.3 under ongoing immunosuppressive treatment). Seven patients were found to have cirrhosis at the initiation of infliximab treatment. All patients showed elevated transaminases (mean AST 475 U/L, mean ALT 609 U/L) and IgG (mean 24.8 mg/dl), reflecting disease activity. All patients fulfilled criteria for the diagnosis of autoimmune hepatitis [19,20].

All patients had anti-nuclear antibodies prior to treatment, all but patient 7 had anti-smooth muscle antibodies. Patient 5 and patient 10 had SLA/LP antibodies, in addition.

Seven patients had experienced serious side effects from steroid medication prior to the introduction of infliximab: four patients had developed severe osteoporosis despite prophylactic treatment with vitamin D, calcium and bisphosphonates; pre-existent depression exacerbated in two patients upon steroid treatment; diabetes levels were altered in two patients upon steroid treatment; and three patients experienced substantial weight gain (summarized in Table 2). All but one patient were maintained on lower dose steroid treatment (5–20 mg/d) throughout infliximab treatment. MMF was introduced in seven patients prior to infliximab treatment, of which five patients had developed azathioprine intolerance and two showed insufficient response. Biochemical remission was not reached in any patient using MMF. In addition, two patients developed gastrointestinal side effects. Two patients continued MMF throughout infliximab treatment.

Cyclophosphamide was used in two patients, of which one developed toxic hepatitis. While the other patient responded well, treatment was stopped after the maximum cumulative dose was reached. Two patients had received adalimumab with some effect but they failed to achieve full remission.

Efficacy

All patients showed a marked decrease in transaminases after three infusions: mean AST serum levels prior to first infliximab infusion were 475 U/L ± 466 and dropped to 43 U/L ± 32 during treatment. Mean ALT levels prior to infliximab therapy stood at 609 U/L ± 831 and declined to 53 U/L ± 50 after the third infusion. For IgG, only nine patients could be included in the analysis (no data for patient 1 and 7). Pre-treatment mean levels for serum IgG were 24.8 mg/dl ± 10.1, and dropped to 17.38 mg/dl ± 6 after three infliximab infusions (Fig. 1).

Eight of the eleven patients experienced a normalization of transaminases after introduction of infliximab. Six of nine patients with available IgG levels before and after infliximab showed an additional normalization of IgG levels, corresponding to a complete biochemical remission. Five patients received a follow-up liver biopsy, which showed a reduction of inflammation, expressed as modified histological activity index (mHAI).

We discontinued treatment in three patients due to full remission: infliximab medication was terminated in patients 6 and 7, after eight months of treatment. Twelve months after withdrawal, patient 6 remains stable on MMF monotherapy, and patient 7 remains stable on azathioprine/prednisolone combination therapy.

Treatment of patient 5 was discontinued after seven months of full laboratory remission and was restarted with good response after experiencing another flare, several months later.

Patient 2 developed a flare under ongoing therapy (see below), which was therefore discontinued due to insufficient efficacy.

Since first treatment with infliximab in 2001 [18], patient 1 has been intermittently on treatment and has shown a good response every time. At present, the patient is in good health. Similarly, patient 3 has been receiving infliximab therapy for more than three years now, and is well.