Successful Treatment of Refractory Autoimmune Hepatitis With Rituximab

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**KEY WORDS**
autoimmune hepatitis, children, treatment, rituximab

**ABBREVIATIONS**
AIH—autoimmune hepatitis
ALT—alanine aminotransferase
AST—aspartate aminotransferase
IgG—immunoglobulin G
MMF—mycophenolate mofetyl

Dr D’Agostino participated actively in the design and critical revision of the manuscript, and analysis of data; Dr Álvarez contributed to the design and conception, analyzed the data, and critically revised the manuscript; Dr Costaguta contributed to the design and conception, analyzed the data, and drafted and reviewed the manuscript; and all authors approved the final version of the manuscript.

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**abstract**

Autoimmune hepatitis is a severe liver disease in which ~10% of patients do not respond to standard treatment. We describe a new rescue therapy using anti-CD20 monoclonal antibodies (rituximab). Complete remission was obtained and maintained by using low doses of immunosuppressive drugs with repeated anti-CD20 infusions. *Pediatrics* 2013;132:e1–e5
Autoimmune hepatitis (AIH) is a disease of unknown etiology, characterized by a loss of tolerance against liver antigens, resulting in a progressive destruction of the hepatic parenchyma. Absence of response to standard immunosuppression or repeated relapses can lead to cirrhosis and liver failure. End-stage liver disease may occur in 10% to 20% of cases and liver transplantation may be necessary.

AIH is considered a T-cell–mediated autoimmune disease. Because B cells have been shown to play a significant role in several T-cell–mediated autoimmune diseases, some of these disorders could respond to anti-CD20 monoclonal antibodies (rituximab). Such a treatment would be of interest for a particular subset of patients with AIH refractory to other treatments, and contribute to diminish the number of patients eventually needing liver transplantation.

**PATIENTS**

**Case 1**

A 12-year-old girl was referred to our hospital with a 2-year history of jaundice associated with biological and histologic hallmarks of Type1 AIH. Despite treatment with prednisone over 12 months, her liver tests remained very abnormal with serum alanine aminotransferase (ALT) value of 531 IU/mL (normal <33 IU/mL), aspartate
aminotransferase (AST) 1366 (normal <35 IU/mL), total bilirubin 6.1 mg/dL (normal <1 mg/dL), gammaglutamyltransferase 135 IU/mL (normal <30 IU/mL), international normalized ratio = 1.8, and serum albumin 2.8 mg/dL (normal >3.2 mg/dL). Antinuclear antibodies and smooth muscle antibodies were positive at titers of 1/1280 and 1/160, respectively, and circulating immunoglobulin G (IgG) levels were very high, at 5500 mg/dL.

Triple therapy with mycophenolate mofetyl (MMF), cyclosporine, and prednisone was begun, but MMF had to be discontinued because of gastrointestinal complaints. Eighteen months after the beginning of treatment, the patient developed a Coombs-positive autoimmune hemolytic anemia, and sirolimus was added (serum levels of 5–10 ng/mL). In spite of achieving good control of the anemia, persistence of the liver disease (inflammatory activity grade 4, fibrosis stage 3) and the presence of severe side effects from calcineurin inhibitors led us to replace this regimen by rituximab at the dosage of 375 mg/m² weekly for 4 doses. Aminotransferases and IgG levels rapidly dropped, and normalized 8 months later (Fig 1). Complete normalization of ALT and AST was maintained with small doses of prednisone (6 mg per day) and azathioprine (1 mg/kg per day). Further infusions (1 dose of 375 mg/m²) every 4 months were arbitrarily administered to maintain remission. After a period of 26 months since the first dose of rituximab, no adverse event was observed (Fig 2). She moved to a foreign country, and was lost to further follow-up.

Case 2
A 13-year-old girl was referred to us with a 15-day history of jaundice, dark urine, asthenia, and pruritus. Serum ALT and AST were very high (ALT 1872 IU/mL; AST 1913 IU/mL). Total bilirubin was 4.3 mg%. Albumin and international normalized ratio were normal. Serological tests for hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein-Barr virus were negative. She tested positive for antinuclear antibodies (Titer 1/2560) and smooth muscle antibodies (1/160) and the IgG level was 2468 mg/dL. Liver histology supported the diagnosis of Type 1 AIH, with inflammation and fibrosis at Grade 2 and Stage 1, respectively (Fig 3). The patient was started on steroids (prednisone 40 mg per day) with normalization of ALT and AST at 4 weeks. Tapering was undertaken, but at the dosage of 20 mg per day she showed an asymptomatic rise of serum ALT and AST values. She was put back on 40 mg of prednisone, and azathioprine 50 mg per day was started. During the following months, serum aminotransferase level remained very high (Fig 1), without improvement after replacement of azathioprine by MMF at 1.5 g per day. Three months later, a second liver biopsy confirmed the worsening of inflammatory activity to Grade 4, and fibrosis to Stage 2. Treatment with cyclosporin was not offered in view of positivity for Epstein-Barr virus DNA found in liver tissue from the second biopsy, not seen in the first. Instead, we decided to use rituximab 375 mg/m² weekly for 4 doses. Three months later, the level of serum aminotransferases normalized (Fig 1), and serum IgG levels also returned to normal values (Fig 2). Prednisone 4 mg per day was maintained. Twenty-three months later, a flare of necroinflammatory activity, evidenced by high levels of serum aminotransferases (ALT 902 IU/mL, AST 353 IU/mL), was controlled with a new single dose of rituximab. Further infusions were then indicated every 6 months to maintain successful clinical and biochemical remission during the following 12 months, keeping prednisone at 4 mg per day and azathioprine at 1 mg/kg per day.

DISCUSSION
B cells are involved in the etiology of many autoimmune diseases in several
ways: first, through their secretion of autoantibodies; second, as antigen-presenting cells, inducing the activation of autoreactive T cells; third, by secretion of cytokines, such as interleukin-2, interferon-γ, tumor necrosis factor-α (Th1), or interleukin-6, and transforming growth factor-β (Th17). AIH is considered to be a T-cell-mediated disease; however, numerous observations would suggest that B cells are also involved in its pathogenesis: (1) immunoglobulin-secreting plasma cells are abundantly present in the liver lymphocyte infiltrates; (2) the level of specific autoantibodies and total IgG in sera have been found to correlate with disease activity; (3) in type 2 AIH, the CD4+ and CD8+ T-cell responses target the same antigen as B cells, and an overlap of B- and T-cell epitopes has been shown; and (4) plasma exchange has been shown to be effective for the management of refractory systemic autoimmune diseases. Finally, there are other published cases of patients who responded to rituximab treatment.

The 2 cases reported in this article show that anti-CD20 monoclonal antibody is an effective therapy. Remission of the disease probably needs a complete protocol of 4 weekly doses, and repeated doses at variable periods of time could be necessary in some patients despite persistent administration of usual maintenance doses of other drugs, such as prednisone or azathioprine.

After more than 10 years of use, rituximab has proven to be remarkably safe; however, side effects described in patients treated with anti-CD20 include a slight increase in the incidence of infectious diseases. Recently, a more severe complication consisting of a progressive, multifocal, eventually lethal encephalitis caused by the polyoma-virus John Cunningham virus, has been described months or years after the beginning of the treatment.

Altogether, according to previous clinical and experimental results and the cases presented here, rituximab may be considered as a rescue therapy in patients with AIH not responding to the usual immunosuppressive regimen.

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