Infliximab Therapy for Rheumatic Diseases in Patients with Chronic Hepatitis B or C

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ABSTRACT. ***Objective.*** To describe the safety of tumor necrosis factor-α blockade in 2 patients with inflammatory rheumatic disease with chronic hepatitis B and C.

Methods. We used infliximab therapy in 2 patients with chronic inflammatory joint disease and chronic hepatitis B or C. We describe the clinical and laboratory test data obtained in these patients during the first year of treatment. Disease activity, liver function tests, and HCV and HBV status were evaluated before infliximab therapy was started and were reevaluated before each infusion. Liver biopsy was performed in both patients before infliximab therapy.

Result. After more than one year of treatment, no worsening in liver function or virological status was observed, while a dramatic clinical improvement of joint disease was observed in both patients.

Conclusion. These cases suggest that infliximab therapy may be safe in some quiescent or controlled chronic HBV or HCV infection. (J Rheumatol 2004;31:107–9)

Key Indexing Terms:
INFLIXIMAB THERAPY HEPATITIS B HEPATITIS C

Infliximab, a monoclonal chimeric anti-tumor necrosis factor-α (TNF-α) antibody, has proved very effective in therapy of rheumatoid arthritis (RA), Crohn's disease, and spondyloarthropathies[1-6]. Because infliximab can decrease the macrophage TNF-α-dependent response, it should not be used in patients with overt infectious diseases. In the same way, chronic viral infections such as hepatitis B and C are still considered relative contraindications given the extreme paucity of data on the effect of infliximab on these conditions. We used infliximab therapy in 2 patients with chronic inflammatory joint disease and chronic hepatitis B or C. We describe the clinical and laboratory test data obtained in these patients during the first year of treatment.

MATERIALS AND METHODS

Patients. Case 1. This 32-year-old HLA-B27-positive man had had severe ankylosing spondylitis (AS) since 15 years of age. Chronic hepatitis B virus (HBV) infection was diagnosed in 1996 when he was 26 years old. He was a chronic HBs antigen carrier (Vitros, Ortho-Clinical Diagnostics), and HBV DNA was present with a level of 8.9×10^8 HBV DNA international units/ml in an in-house real-time polymerase chain reaction (PCR) assay based on Light-Cycler technology (Roche Applied Sciences, Indianapolis, IN, USA) with a lower detection cutoff of 50 IU/ml. Treatment with lamivudine (100 mg/day) was introduced at that time. The clinical manifestations of AS failed to respond to numerous nonsteroidal antiinflammatory drugs and add-on sulfasalazine followed by add-on methotrexate (MTX). In April 2001, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) rating was 9 and erythrocyte sedimentation rate (ESR) was 136 mm/h, with C-reactive protein (CRP) level of 215 mg/l (normal < 5). He had been taking lamivudine for one year. This therapy was effective, with an HBV DNA level maintained around 10^3–10^4 IU/ml and normalization of aminotransferase activities. This favorable response prompted us to consider intensification of the immunosuppressive regimen, including infliximab therapy, in order to control the AS. A liver biopsy showed mild inflammatory activity with portal and per portal fibrosis.

Case 2. A 66-year-old woman with a 2-year history of severe RA was referred to our department for infliximab treatment. The high level of RA activity manifested as persistent painful synovitis (Disease Activity Score-28, DAS28, was 5.7) and joint destruction despite MTX 10 mg weekly. Because of poor tolerance to MTX, the physician considered add-on infliximab therapy. Pretreatment tests showed chronic hepatitis C with positive serum HCV antibodies (Vitros, Ortho-Clinical Diagnostics, Raritan, NJ, USA), and positive HCV RNA detection by PCR (Cobas Amplicor v2.0, Roche Diagnostics, Pleasanton, CA, USA), and a viral load of 551,410 UI/ml (Versant™ HCV RNA 3.0 assay, Bayer Corporation, Berkeley, CA, USA). The HCV genotype was 1b (Inno-LipA HCV II, Innogenetics, Gand, Belgium). Aminotransferase activities were within the normal range. A liver biopsy showed mild inflammatory activity with portal fibrosis. These biological and histological results were not an indication for interferon therapy, which, in addition, might have worsened the RA[7].

Viral and hepatic status assessment. Liver function tests and HCV and HBV status were evaluated before infliximab therapy was started in both patients, and were reevaluated upon therapy before each infusion. Serum HBV DNA was quantified using our in-house real-time PCR assay, and serum HCV RNA level was measured by means of the Versant™ HCV RNA 3.0 assay. A liver biopsy was performed in both patients.

Treatment. After multidisciplinary discussion, informed consent was obtained from both patients, and infliximab therapy was started. Intravenous infusions were given at 0, 2, and 6 weeks, then at 8-weekly intervals, in a dosage of 5 mg/kg body weight in Case 1 and 3 mg/kg in Case 2. In Case 1, lamivudine was continuously given in parallel to infliximab.

Effectiveness assessment. Before each infusion the following variables

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were evaluated: aminotransferase activities, ESR, and CRP in both patients; and the BASDAI[8] in Case 1, the patient with ankylosing spondylitis (AS), and the DAS28 and American College of Rheumatology (ACR) response criteria[9,10] in Case 2, the patient with RA.

RESULTS

In both patients, infliximab induced a dramatic articular response, without activation of the chronic viral liver disease during the study period. In Case 1, at one year, the patient was virtually free of inflammatory symptoms, BASDAI was 0.5, ESR was 25 mm/h, and CRP 8 mg/l. The hepatic enzyme levels remained normal and serum HBV DNA levels slightly increased over time, but viral replication remained under control. The liver function tests showed no significant change (Figure 1). In Case 2, the manifestations of RA improved rapidly, with an ACR 70% response after the fourth infusion and a DAS28 score of 2.4; HCV RNA levels remained steady.

DISCUSSION

Our Case 1 is the first documented report of infliximab treatment in a patient with concomitant joint disease and hepatitis B infection. In this patient with extremely severe and active joint disease, our decision to use infliximab was based on recent studies[5,6] reporting benefits in refractory AS. In addition, the only alternatives to infliximab, i.e., high dose glucocorticoids and immunosuppressants, might have favored liver toxicity. As expected, marked improvements in all inflammatory symptoms occurred promptly and persisted throughout followup, substantially ameliorating the patient's quality of life.

In theory, the inhibition of TNF-α might result in potent immunosuppression, thereby worsening the chronic hepatitis B infection[11]. It should also be noted that potential infliximab-induced acute hepatic injury has been rarely reported[12]. In our patient under lamivudine therapy (Case 1), we found no evidence that infliximab therapy dramatically increased viral replication and/or exacerbated the chronic hepatitis. The consequences of the treatment with infliximab in hepatitis B with lamivudine are unknown and unpredictable. A longer followup is needed, however, to establish that longterm infliximab treatment does not promote progression of the liver infection.

Infliximab therapy without worsening of the hepatic status has been reported in one patient with hepatitis C[13]. Our Case 2 reinforces the possibility that infliximab therapy may be safe in chronic HCV infection without severe histological damage or major liver test abnormalities.

The 2 cases suggest that anti-TNF-α therapy may be effective and safe in some patients with severe inflammatory joint disease and chronic viral hepatitis. Prospective studies with liver biopsies before, during, and after treatment cessation are now needed to validate this hypothesis. We hope that the favorable results in our patients will encourage such studies.

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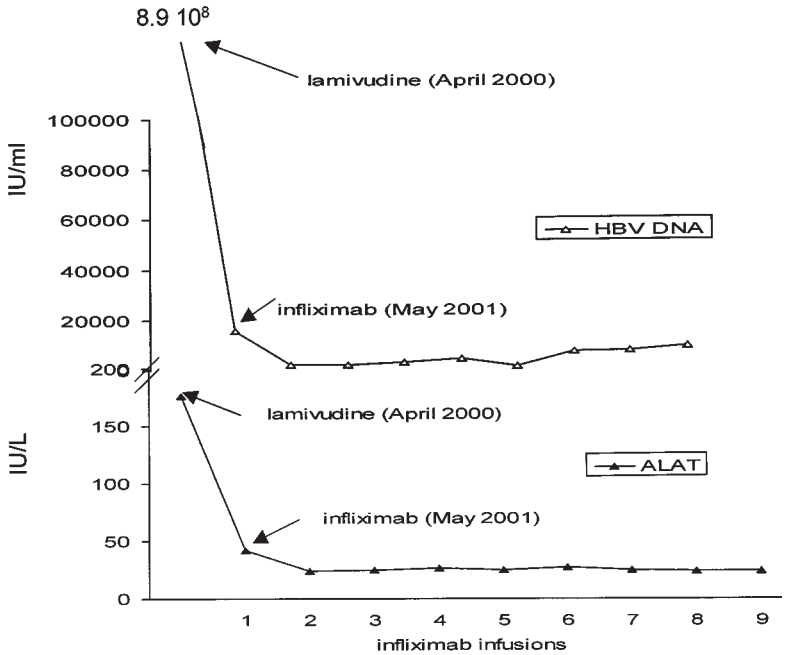

Figure 1. Case 1. Time-course of aminotransferase levels and HBV DNA in a patient with chronic hepatitis B treated with lamivudine during infliximab therapy for AS.

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