

Use of infliximab in a patient with rheumatoid arthritis and chronic hepatitis B

Eloisa Doubrawa¹, Renê Augusto de Mattos Ricca¹, Tiago Osternack Malucelli¹,
Vanessa Irusta Dal Pizzol¹, Danilo Hamilko de Barros², Eduardo Santos Paiva³

ABSTRACT

Anti-TNF- α agents have emerged as a potent treatment for patients with rheumatoid arthritis unresponsive to conventional disease-modifying antirheumatic drugs. Increased susceptibility to infections induced by these drugs is the main complication of their use. Reactivation of hepatitis B virus (HBV) is one of the most worrisome side effects in patients with HBV infection receiving anti-TNF- α . We report the case of a 56-year-old male patient with stable hepatitis B and good response to the antiviral combination of lamivudine and tenofovir when infliximab was started. The patient went into remission. During the 30-month treatment with the biologic, his liver function remained stable, with no HBV reactivation.

Keywords: rheumatoid arthritis, hepatitis B, therapeutics.

© 2012 Elsevier Editora Ltda. All rights reserved.

INTRODUCTION

Tumor necrosis factor alpha (TNF- α) is a mediator involved in inflammation and cell immune response which plays an important role in the defense against infection.¹ In hepatitis B virus (HBV) infection, that cytokine promotes an increase in viral clearance by inhibiting HBV replication in hepatocytes. In chronic hepatitis C its role in controlling viral replication does not seem fundamental, although it comprises different actions such as induction of apoptosis of hepatocytes, maintenance of inflammatory response, and contribution to the genesis of hepatic fibrosis.²

The major complication of using anti-TNF- α agents for treating rheumatoid arthritis (RA) and other autoimmune disorders is the increased susceptibility to several infections. The risk increases in individuals chronically infected and the drug-induced immunosuppression might reactivate the infectious process.

Infliximab (IFX) is one of the most used biological agents for treating patients with RA. According to the literature, its safety and efficacy have not been well established when used in patients with RA in the presence of HBV infection.

We report the case of a male patient with RA and chronic hepatitis B, on lamivudine and tenofovir, who used IFX for 30 months and had no HBV reactivation during the whole treatment period.

CASE REPORT

The patient is a 56-year-old male, with RA and positive for rheumatoid factor for 11 years. When he started rheumatologic follow-up five years before, he was diagnosed with chronic hepatitis B.

On the occasion of his first visit to our service, he had active disease with 30-minute morning stiffness. His physical examination then showed synovitis in his wrist, metacarpophalangeal, and proximal interphalangeal joints. In addition, the following findings were observed: erythrocyte sedimentation rate (ESR), 12 mm/h; C-reactive protein (CRP), 0.5 mg/dL (< 0.33); and Disease Activity Score 28 (DAS28), 5.63. The patient had radiographic erosions in the left fifth metatarsophalangeal joint, right second metacarpophalangeal joint, and right second proximal interphalangeal joint, and was not on any medication for RA, but had already used chloroquine diphosphate (250 mg) for six months. Regarding hepatitis B,

Received on 02/21/2011. Approved on 05/08/2012. The authors declare no conflict of interest.

Rheumatology Service of the Hospital de Clínicas, Universidade Federal do Paraná – HC/UFPR.

1. Resident physician in Rheumatology, Hospital de Clínicas, Universidade Federal do Paraná – HC/UFPR

2. Resident physician in Internal Medicine, HC/UFPR

3. Assistant Professor of Rheumatology, HC/UFPR

Correspondence to: Eloisa Doubrawa. Rua Nilo Cairo, 36/105 – Centro. Curitiba, PR, Brazil. CEP: 80060-050. E-mail: eloisadoubrawa@yahoo.com.br

the patient was on lamivudine (150 mg/day) and, on that occasion, he was HBeAg negative, his viral load was below 20,000 copies, and his liver biopsy showed grade II fibrosis. Hydroxychloroquine (400 mg/day) was introduced to control the joint manifestations.

On his first return after two months, synovitis was identified in his hands, right wrist, and right foot. Intra-articular corticosteroid infiltration was performed in his right fifth metatarsophalangeal joint and right wrist, and sulfasalazine (1 g/day) was added to treatment.

Six months after introducing the second disease-modifying antirheumatic drug (DMARD), his symptoms improved and the morning stiffness disappeared. On physical examination only the third metacarpophalangeal joint was affected. The dose of sulfasalazine was increased to 2 g/day and hydroxychloroquine was maintained.

At the beginning of the treatment the patient had controlled hepatitis B (normal transaminase levels and decreasing viral load) and responded well to lamivudine (150 mg/day) and tenofovir (300 mg/day). In the following months his disease activity became worse and the dose of sulfasalazine was increased to 3 g/day. As he did not respond to the change in treatment, biologic therapy was introduced.

Infliximab was started at the dose of 200 mg every eight weeks. On that occasion the patient had high levels of disease activity markers as follows: ESR, 40 mm/h; CRP, 2.40 mg/dL (<0.33); DAS28, 5.68; and Health Assessment Questionnaire (HAQ), 0.75. After three months his response to treatment was moderate as follows: 0.79-drop in DAS28 (from 5.68 to 4.89); HAQ, 0.315; and ESR, 31. After 14 months he had synovitis only in his left shoulder, DAS28 of 2.36, and ESR of 4 mm/h.

During the whole anti-TNF- α treatment period, the patient's liver function remained stable, with no oscillations in transaminases, and he turned HBV-DNA negative. Currently, 30 months after introducing IFX, he maintains a good response to treatment, with involvement of only his left shoulder.

DISCUSSION

The anti-TNF- α agents emerged as a potent treatment for patients with RA who do not respond to conventional DMARDs. Although the efficacy of biologic therapy for a number of autoimmune diseases has been confirmed, the risk of infection associated with those agents has been well documented.^{3,4} Reactivation of HBV is one of the well-known side effects in patients with HBV infection, who receive cytotoxic drugs or immunosuppressive treatment.⁵

Data from animal models have shown that cytokines TNF- α and IFN- γ could act synergically in inhibiting the expression and replication of HBV genes, leading to the reduction of virus intracellular transcription. In addition, TNF- α induced by HBV antigens seems beneficial to viral clearance.⁶ Thus, the anti-TNF- α action could induce the loss of the antiviral mechanism, reactivating the disease or determining the appearance of HBV resistance.

The safety and efficacy of using anti-TNF- α agents in patients with HBV infection have not been well established. Due to the low frequency of positivity for infectious serologies in patients on anti-TNF therapy,⁷ randomized controlled studies lack and there is little evidence restricted to case series showing the relative safety of biologic therapy in those patients. One of the most severe complications reported was IFX-induced fulminant hepatitis in a patient with Still's disease and chronic hepatitis B with no previous antiviral treatment, for which reactivation of a pre-core HBV mutant promoted by the anti-TNF- α agent was suggested.⁸

Evidence of HBV or HCV infection should be investigated in all candidates to anti-TNF therapy, by using serological tests (HBsAg, anti-HBsAg, anti-HBC, and anti-HCV). In cases of active HBV infection, the viral load should be measured.²

Infliximab-induced autoimmune hepatitis has been reported and should be considered as the differential diagnosis for hepatitis B reactivation. In such cases, the liver injury is predominantly hepatocellular, and the diagnosis is made through clinical suspicion, with a temporal relationship to drug exposure, negative viral serology, and presence of autoantibodies.⁹

Some studies have recommended the use of prophylactic antiviral therapy with lamivudine or tenofovir in patients with hepatitis B and concomitant treatment with anti-TNF- α agents.¹ That practice, however, has been questioned by several authors who claim that the risk-benefit ratio of prophylactic antiviral therapy in patients receiving a long course of immunosuppression is undetermined, and that prolonged treatment with lamivudine can be related to the development of resistant HBV strains.¹⁰ Thus, the prophylactic use of antivirals for candidates to biologic therapy should be careful, and not routinely recommended.¹¹

Many questions regarding anti-TNF- α agents and hepatitis B remain unanswered because of the lack of controlled studies. So far, the most efficient agent in such cases remains unknown, as remains the risk after interrupting the immunosuppressive treatment in the presence of immune reconstitution response. Finally, the risks and benefits of anti-TNF- α agents in those patients should be assessed, making the decision for the most adequate treatment easier in that group of high-risk patients.

REFERENCES

1. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. *Rheumatology (Oxford)* 2006; 45(10):1294-7.
2. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. *J Gastroenterol Hepatol* 2006; 21(9):1366-71.
3. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343(22):1594-602.
4. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor alpha neutralizing agent. *N Engl J Med* 2001; 345(15):1098-104.
5. Yeo W, Chan PKS, Zhong S, Ho WM, Steinberg JL, Tam JS *et al.* Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; 62(3):299-307.
6. Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 2003; 62(7):686-7.
7. Silva BSP, Endo AC, Medeiros AC, Gonçalves C, Moraes JCB, Bonfã E *et al.* Frequência de anticorpos aos agentes etiológicos da síndrome da imunodeficiência adquirida, sífilis, hepatites virais B e C e doença de Chagas em pacientes reumatológicos em tratamento com antifator de necrose tumoral (TNF). *Rev Bras Reumatol* 2009; 49(5):590-8.
8. Kuwabara H, Fukuda A, Tsuda Y, Shibayama Y. Precore mutant hepatitis B virus-associated fulminant hepatitis during infliximab therapy for rheumatoid arthritis. *Clin Rheumatol* 2010. Available from: <http://www.springerlink.com/content/k443180g1n860u03/fulltext.pdf>. [Accessed on 9th April, 2010].
9. Aithal GP. Hepatotoxicity related to antirheumatic drugs. *Nat Rev Rheumatol* 2011; 7(3):139-50.
10. Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis* 2006; 65(8):983-9.
11. Di Marco V, Marzano A, Lampertico P, Andreone P, Santantonio T, Almasio PL *et al.* Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology* 2004; 40(4):883-91.