

Infliximab in Ankylosing Spondylitis Associated With Chronic Hepatitis B Infection. Role of Lamivudine Therapy

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Anti-tumor necrosis factor- α (TNF) therapy has been associated with reactivation of hepatitis B virus infection. Case reports have suggested the concomitant need of lamivudine treatment in patients with HBV infection treated with anti-TNF α agents. We describe a case of ankylosing spondylitis with positive HBV surface antigen (HBsAg) treated with infliximab and lamivudine. Clinical response was excellent but when lamivudine therapy was stopped, reactivation of replication viral occurred. After the reintroduction of lamivudine, viral replication was controlled and liver function tests were normalized. Preventive long-term lamivudine therapy is mandatory when anti-TNF α therapy is maintained in patients with chronic HBV infection.

Key words: Ankylosing spondylitis. Hepatitis B. Infliximab.

Infliximab en la espondilitis anquilosante asociada a infección crónica por el virus de la hepatitis B. Papel del tratamiento con lamivudina

El tratamiento con agentes contra el factor de necrosis tumoral (TNF) alfa se ha asociado a la reactivación de la infección crónica por el virus de la hepatitis B. Algunos casos publicados indican la necesidad de tratamiento crónico con lamivudina cuando se utilizan los agentes anti-TNF α . Describimos el caso de un paciente con espondilitis anquilosante y antígeno de superficie positivo tratado con infliximab y lamivudina. La respuesta clínica fue excelente, pero cuando el paciente interrumpió el tratamiento con lamivudina, se observó reactivación de la replicación viral. Una vez reinstaurado dicho tratamiento,

se controló nuevamente la replicación viral y se normalizaron las concentraciones de transaminasas. Esta observación indica que en pacientes con infección crónica por VHB que necesitan tratamiento anti-TNF α , se requiere un tratamiento preventivo a largo plazo con lamivudina.

Palabras clave: Espondilitis anquilosante. Hepatitis B. Infliximab.

Introduction

Infliximab, a chimeric monoclonal antibody directed against tumor necrosis factor (TNF) alpha, is a widely employed treatment in spondyloarthritis, rheumatoid arthritis, and Crohn's disease. Since its approval for use, questions have surfaced on its safety. Although the debate continues regarding the safety of TNF α antagonist treatment in patients with chronic hepatitis C virus infection, published data indicate that its use is relatively safe.^{1,2} On the other hand, chronic infection due to hepatitis B virus (HBV) seems to show an ever growing body of evidence, manifested through published cases, of a reactivation of the virus when treatment with anti-TNF α is started.³⁻¹⁰ HBV infection is one of the most common chronic viral infections worldwide and affects approximately 400 million persons.¹¹ We describe the case of a patient with ankylosing spondylitis (SA) and chronic HBV infection treated with lamivudine and infliximab.

Clinical Case

A 32-year-old white male was diagnosed with SA in 1996, being classified as such using the New York criteria. The serological profile for HBV showed he was HBsAg positive, had positive anti-HBe as well as HBc antibodies, and negative HBe antigen, and anti-HBs antibodies. ALT and AST determinations had always been normal.

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Manuscript received May 21, 2007; accepted for publication September 27, 2007.

Concentrations of Transaminases and Viral DNA During Treatment With Infliximab and Lamivudin

Date	ALT/AST, U/mL	Viral DNA, Copies/mL	Concomitant Treatment
April 2004	28/19	237	Lamivudin
November 2004	31/18	<200	Lamivudin
April 2005	20/18	397	Infliximab
June 2005	21/17	10 400	Infliximab
August 2005	27/21	284 000	Lamivudin
October 2005	162/65	38 900	Lamivudin
December 2005	61/33	18 300	Lamivudin + infliximab
March 2006	37/23	21 100	Lamivudin + infliximab
June 2006	41/21	5460	Lamivudin + infliximab
October 2006	24/15	13 100	Lamivudin + infliximab

Since 1996 he had received treatment with sulphasalazine and different non-steroidal anti-inflammatory (NSAID) drugs, in spite of which SA was persistently active, with a BASDAI of 6 (0-10), BASFI of 50 (0-100), nocturnal pain of 7 (0-10), and C-reactive protein (CRP) of 16.3 mg/dL, suggesting the use of infliximab.

In April 2004 the determination of the HBV viral DNA load was 237 copies/mL. Before receiving infliximab he began treatment with lamivudin, 100 mg day. In November 2004, the viral load was below 200 copies/mL (Table). The patient signed an informed consent and began treatment with infliximab, in April 2005 at a dose of 5 mg/kg on weeks 0, 2, 6, and afterward every 8 weeks. On week 12 he had improvement on the BASDAI of 70% and the CRP normalized. During follow-up, beginning in June 2005, after receiving 4 infusions of infliximab, there was an increase in viral replication, with a concomitant increase of transaminases. The patient accepted abandoning lamivudin treatment 4 weeks before. Treatment with lamivudin was reinstated, with a temporal suspension of infliximab and periodic controls of viral replication and transaminase concentrations. The patient continued treatment with infliximab and lamivudin, with a good control of SA symptoms (BASDAI <2), normal transaminases, and control of viral replication (Table).

Discussion

Published data indicated that the administration of infliximab in patients with chronic HBV infection leads to an increased risk of viral reactivation, but that this risk

is potentially controllable with lamivudin concomitant treatment.

Lamivudin is a retroviral inhibitor of reverse transcriptase which has shown its effectiveness for the control of viral reactivation in patients with chronic HBV infection who receive chemotherapy for oncohematological neoplasia and organ transplant.¹²⁻¹⁴ Although the pathogenic mechanisms are not entirely clear, experimental in vitro studies and animal models have shown that TNF inhibits HBV replication and stimulates T cell specific responses, which would imply the elimination of viruses from infected hepatocytes.¹⁵⁻¹⁷ These findings lead us to think that the administration of TNF α antagonists would increase the expression of viral antigens and the reactivation of viral replication.

Several cases of chronic infection with HPV and infliximab treatment for Crohn's disease, spondyloarthritis, and rheumatoid arthritis have been reported. Because the use of infliximab in Crohn's disease is limited, in many cases, to 3 doses, we will discuss mainly rheumatic diseases which require the continued administration of infliximab.

Oniankitan et al⁹ communicated a case of SA with chronic HBV infection treated with infliximab and methotrexate for 1 year without deterioration of liver function. In this case, 1 year before receiving infliximab, the patient had been treated with lamivudin and viral replication remained stable. Wendling et al⁸ published another case of SA with chronic HBV infection who received methotrexate and infliximab and showed a good therapeutic response. During follow-up, transaminases increased, as did the viral replication. Lamivudin was begun 4 months later and transaminases returned to normal levels and the viral load was undetectable. Ostuni et al³ communicated a case of rheumatoid arthritis and HBV infection which developed acute hepatitis and who, upon suspending treatment and starting lamivudin showed normalization of transaminase levels and control of viral replication. Our case confirms these findings. In addition, our case exemplifies that while treatment with lamivudin is maintained; replication is controlled, increasing rapidly upon suspension and reinstatement leads back to the initial effect. An additional problem is the possible appearance of resistance that occurs with prolonged use of lamivudin, something that has been seen in transplant patients.^{18,19} All of these questions require controlled studies and larger cohorts in order to be answered.

Until more data is available, it seems reasonable to recommend that: *a*) a serological HBV panel must be documented in all patients who are candidates to receive immunosuppressants in general and anti-TNF α in particular, and in those patients who have not been immunized, insure that this is done; *b*) if the patient is HBsAg positive, treatment with lamivudin must be started and control of viral replication achieved before using anti-TNF α therapy; *c*) if the patient is HBsAg negative and anti-HBc positive, monthly follow-up of HBsAg must

be carried out and if it becomes positive, install lamivudin treatment²⁰; *d*) once treatment has been installed, a strict control of ALT and HBV DNA must be followed (every 4-8 weeks) at least for 3 months after the last dose of treatment; and *e*) if a viral reactivation occurs, resistance and the possibility of sing another agent, such as adenofir, must be contemplated.

References

- Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Ann Rheum Dis.* 2003;62:1078-82.
- Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor therapy in patients with chronic viral infections: hepatitis B, hepatitis C and HIV infection. *Ann Rheum Dis.* 2004;63 Suppl II:ii18-24.
- 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;62:686-7.
- Michel M, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset Still's disease. *J Rheumatol.* 2003;30:1624-5.
- Esteve M, Saro C, González-Huix F, Suárez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut.* 2004;53:1363-5.
- García-Sánchez MV, Gómez F, Poyato A, Iglesias EM, De Dios JF. Infliximab therapy in a patient with Crohn's disease and chronic hepatitis B virus infection. *Inflamm Bowel Dis.* 2004;10:701-2.
- Ueno Y, Tanaka S, Shimamoto M, Miyanaka Y, Hiyama T, Ito M, et al. Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. *Dig Dis Sci.* 2005;50:163-6.
- Wendling D, Auge B, Betttinger D, Lohse A, Le Huede G, Bresson-Hadni S, et al. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthropathy. *Ann Rheum Dis.* 2005;64:788-9.
- Oniankitan O, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky JM, et al. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol.* 2004;31:107-9.
- Millonig G, Kern M, Ludwiczek O, Nachbaue K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: Need for HBV-screening? *World J Gastroenterol.* 2006;12:974-6.
- Lai CL, Ratziu V, Yuen MF, Poynard T. Viral hepatitis B. *Lancet.* 2003;362:2089-94.
- Yeo W, Chan PK, Zhang 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;62:299-307.
- Rossi G. Prophylaxis with lamivudine of hepatitis B reactivation in chronic HBsAg carriers with hemato-oncological neoplasias with chemotherapy. *Leuk Lymphoma.* 2003;44:759-66.
- Liu CJ, Lai MY, Lee PH, Chou NK, Chu SH, Chen PJ, et al. Lamivudine treatment for hepatitis B reactivation in HBsAg carriers after organ transplantation: a 4-year experience. *J Gastroenterol Hepatol.* 2001;16:1001-8.
- Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. *Science.* 1999;284:825-9.
- Kasahara S, Ando K, Saito K, Sekikawa K, Ito H, Ishikawa T, et al. Lack of tumour necrosis factor alpha induces impaired proliferation of hepatitis B virus-specific cytotoxic T lymphocytes. *J Virol.* 2003;77:2469-76.
- Wong GH, Goeddel DV. Tumour necrosis factors alpha and beta inhibit virus replication and synergize with interferons. *Nature.* 1986;323:819-22.
- Chan TM, Fang GX, Tang CS, Cheng IK, Lai KN, Ho SK. Preemptive lamivudine therapy based on HBV DNA level in HBsAg-positive kidney allograft recipients. *Hepatology.* 2002;36:1246-52.
- Fabrizi F, Dulai G, Dixit V, Bunnapradist S, Martin P. Lamivudine for the treatment of hepatitis B virus-related liver disease after renal transplantation: meta-analysis of clinical trials. *Transplantation.* 2004;77:859-64.
- 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;21:1366-71.