



CASE REPORT

Subfulminant hepatitis B after infliximab in Crohn's disease: Need for HBV-screening?

Gunda Millonig, Michaela Kern, Othmar Ludwiczek, Karin Nachbaur, Wolfgang Vogel

Gunda Millonig, Michaela Kern, Othmar Ludwiczek, Karin Nachbaur, Wolfgang Vogel, Department of Gastroenterology and Hepatology, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria

Supported by the "Verein zur Förderung der Wissenschaft in Gastroenterologie und Hepatologie"

Correspondence to: Gunda Millonig, MD, Department of Gastroenterology and Hepatology, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria. gunda.millonig@uibk.ac.at

Telephone: +43-512-504-23401 Fax: +43-512-504-24052
Received: 2005-04-30 Accepted: 2005-06-09

Abstract

Infections are a major adverse effect during the treatment with anti-TNF- α . While exclusion of any bacterial infection and screening for tuberculosis are mandatory before initiating a therapy with anti-TNF- α -antibodies, there are no guidelines whether to screen for or how to deal with chronic viral infections such as hepatitis B. In this case report, we have described a patient with Crohn's disease who developed subfulminant hepatitis B after the fourth infusion of infliximab due to an unrecognized HBs-antigen carrier state. He recovered completely after lamivudine therapy was started, but this severe adverse event could have been prevented if screening for HBV and pre-emptive therapy with lamivudine would have been started prior to infliximab. We therefore strongly argue in favor of extended screening recommendations for infectious diseases including viral infections before considering a therapy with infliximab.

© 2006 The WJG Press. All rights reserved.

Key words: Hepatitis B; TNF alpha; Lamivudine

Millonig G, Kern M, Ludwiczek O, Nachbaur K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: Need for HBV-screening? *World J Gastroenterol* 2006; 12(6): 974-976

<http://www.wjgnet.com/1007-9327/12/974.asp>

INTRODUCTION

Infliximab has become the standard therapy for refractory,

steroid-dependent or fistulizing Crohn's disease^[4,14,19]. The association between the use of this monoclonal chimeric mouse antibody, and increased risk of severe bacterial infections^[16] and reactivation of tuberculosis^[6] has received much attention. The influence of infliximab on viral infections, however, has not been extensively investigated, and data that are available on reactivation of chronic viral infections such as hepatitis B and C and EBV are conflicting. Reijasse *et al*^[15] studied the viral kinetics of EBV in patients receiving immunosuppressive drugs including infliximab and found no increased viral load in them compared to the control group. Several case studies and investigations of small patient cohorts have reported that Crohn's disease in patients with documented pre-existing chronic hepatitis B or C was successfully treated with infliximab, without the drug causing any deterioration of the liver disease^[11,13,21]. In contrast to these publications, in their prospective study of Crohn's patients with coexisting chronic HBV-infection treated with infliximab, Esteve *et al*^[1] observed two severe hepatitis flare-ups during treatment with this drug. Ostuni *et al*^[12] reported on a patient with reactivated hepatitis B after therapy with infliximab and methotrexate. Michel *et al*^[8] observed fulminant hepatic failure in a patient with inactive chronic hepatitis B after being treated with infliximab but without signs of HBV-reactivation and therefore of unknown etiology.

Several authors have recommended pre-emptive treatment with lamivudine of HBV-carriers with Crohn's disease before starting infliximab-therapy^[1,8].

FDA-recommendations released in December 2004 also alert physicians to the danger of primary hepatotoxicity or reactivation of chronic viral hepatitis caused by the administration of infliximab.

CASE REPORT

We report here on a 50-year-old patient in whom Crohn's disease with terminal ileitis was diagnosed in January 2001. Initially he received a course of mesalamine. This, proving to be ineffective, was followed by a course of systemic steroids together with mesalamine. Steroid withdrawal was difficult, but in June 2003 steroids were discontinued and the patient was in complete remission until February 2004 when he had a relapse with abdominal pain and loose and bloody stools. Treatment was restarted with budesonide 3 mg t.i.d. and azathioprine 150 mg. Budesonide failed to improve the symptoms and steroid-therapy was switched

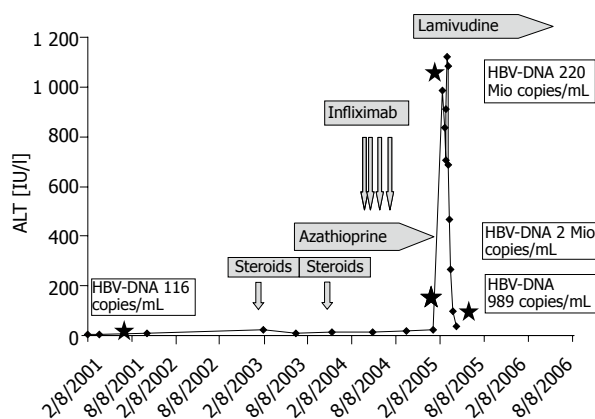


Figure 1 ALT remained within the normal range during therapy with prednisolone, azathioprine and during the infusions with infliximab. Only after the fourth infusion of infliximab, the patient developed a fulminant hepatitis with ALT up to 1 100 IU/L. HBV-DNA () quantification showed 220 mio copies/mL. Lamivudine (150 mg/d) was started and led to a rapid decrease in transaminases and HBV-DNA.

to systemic steroids (methylprednisolone 40 mg) again. Abdominal pain and bloody stools improved under this regimen but tapering of steroids was followed by an immediate relapse despite azathioprine 2 mg/kg for several months. Endoscopy showed ulcerating inflammation in the terminal ileum and capsule endoscopy revealed involvement of the distal jejunum. Bowel surgery was discussed with the patient, but he wished to try every possible medical treatment before going for surgery. We therefore re-assessed the situation and decided to add infliximab 5 mg/kg (total amount 400 mg) because of steroid-dependent disease. Tuberculosis was excluded by tuberculin-testing and chest X-ray. Blood tests showed mild leukocytosis (14 g/L), all other results including renal and liver function tests, c-reactive protein, iron metabolism, and vitamins were within normal ranges. There was no history of any other disease before the diagnosis of Crohn's disease, besides a mild reactive depression for which the patient has been on mirtazapine for more than a year. Transaminases were documented to be within normal ranges since 2001.

Infliximab was administered successfully at week 0, 2, and 6 followed by complete remission and rapid tapering of steroids. Basis therapy consisted at this time of azathioprine 150 mg, mirtazapine 30 mg, pantoprazole 40 mg and brotizolam 0.25 mg at night. The infusion at wk 6 was followed by 3 d of flu-like symptoms. One month after the third infliximab infusion, the patient came to the outpatient clinic because of abdominal discomfort and malaise. Blood tests showed signs of acute hepatitis (ALT 983 [normal <50 IU/L], AST 413 [normal <50 IU/L], γ GT 109 [normal <66 IU/L], LDH 237 [normal <232 IU/L], bilirubin 2.17 [normal <1.28 mg/dL] and a decreased prothrombin time of 63% [normal >70%]) (course of ALT Figure 1). Liver parenchyma was hyperechogenic in sonography but there were no signs of liver cirrhosis and as expected, there were no signs of mechanical cholestasis. The patient mentioned at this point that he had been immunized against hepatitis A and B six months before by his general practitioner because all other members of his family had undergone hepatitis B and he

intended to travel to Southern Europe during the summer holidays. No previous serological examination had been performed before immunization.

Complete work-up was done one week after his admission to the hospital. Hepatitis-serology revealed immunity against hepatitis A and negative serology and PCR for hepatitis C, but circulating HBs-antigen, no HBe-antigen but anti-HBe- and anti-HBc-antibodies, and negative anti-HBc-IgM were detected. Quantification of HBV-DNA showed >220 000 000 copies/mL (38 000 000 IU/mL). Other causes for hepatitis such as EBV, CMV, autoimmune hepatitis and acute Wilson's disease were ruled out. We suspected reactivation of hepatitis B from a previously unknown HBV-carrier state. This was corroborated by serology from a frozen serum sample from a previous visit in 2001 also showing the features of an HBs-antigen carrier but a low viral load with 116 copies/mL (20 IU/mL).

Antiviral therapy (lamivudine 150 mg daily) was started immediately after diagnosis. Despite the therapy, liver synthesis parameters transiently decreased and reached a nadir three weeks after the first manifestation with a prothrombin-time of 42% and bilirubin peak of 35 mg/dL. At the same time, the patient developed mild hepatic encephalopathy with increased sleepiness. One month after the diagnosis, the patient recovered, transaminases decreased and prothrombin-time normalized and HBV-DNA dropped to 2 000 000 copies/mL (340 000 IU/mL). The patient could be discharged and followed up in the outpatient clinic. The most recent visit two months after the acute hepatitis showed normal transaminases and HBV-DNA of 989 copies/mL (170 IU/mL).

DISCUSSION

While patients undergoing chemotherapy for malignancy have long been screened for chronic hepatitis B and treated prophylactically with lamivudine if positive, this has not been performed on a routine basis in patients with chronic inflammatory bowel disease requiring immunosuppressive regimens including infliximab. Our knowledge about the role of TNF- α in chronic viral hepatitis is sparse but there is evidence that TNF- α synergizes with interferons in suppressing viral replication^[2,7,22] and is essential in clearing HBV^[17]. A promoting effect for increased HBV-replication during treatment with anti-TNF-antibodies could be explained on this basis. But why HBs-antigen carriers, upon anti-TNF- α treatment, suddenly lose their tolerance against HBV and switch to a cytotoxic T-lymphocytic activation leading to hepatocyte injury and liver failure remains to be elucidated. At present we can only speculate that TNF- α might play an important role in maintaining tolerance in the HBs-antigen carrier state.

Till date there are only three case reports and one report of a small group of HBs-antigen carriers that suffered HBV-reactivation following administration of infliximab. Four patients developed fulminant hepatitis B^[1,8,12] while one patient had only moderately elevated transaminases^[20] that returned to normal without antiviral therapy. Esteve *et al* reported that two of their patients

showed severe reactivation and one died from hepatic failure, but another patient on lamivudine had no worsening of liver disease during infliximab-therapy^[1]. Stable HBV under lamivudine has also been reported by Oniankitan *et al*^[11] and Valle Garcia-Sanchez *et al*^[21]. Keeping these reports in mind and looking for other factors that might influence the course of HBV, we suggest that (1) the number of infliximab-infusions and (2) concomitant immunomodulatory therapy might influence the course of HBV-reactivation (azathioprine in our case and methotrexate therapy in the other cases with severe hepatitis).

In our patient HBV-reactivation was noted after the third infusion of infliximab. Previous treatment with steroids and azathioprine alone had not induced a flare-up in hepatitis B, although it is known that all types of immunosuppressive therapy can lead to a flare-up in hepatitis B. For steroids this has been documented most frequently in patients with hematological malignancies^[18]. Azathioprine and methotrexate have also been linked with HBV-recurrence. But while this occurred on treatment with azathioprine^[9], it took place only after the discontinuation of methotrexate^[3,5,10].

In conclusion, our report on a patient with Crohn's disease developing subfulminant hepatitis under infliximab treatment due to reactivation of a previously unknown HBs-antigen-carrier state draws attention to the need for screening patients with inflammatory bowel disease for hepatitis B and for antiviral prophylaxis in HBV-positive patients prior to therapy with anti-TNF- α antibodies.

ACKNOWLEDGMENTS

We thank Anna Schlögl, Gisela Egg, and Barbara Wimmer for technical and Rajam Csordas for editorial assistance.

REFERENCES

- Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365
- Feduchi E, Alonso MA, Carrasco L. Human gamma interferon and tumor necrosis factor exert a synergistic blockade on the replication of herpes simplex virus. *J Virol* 1989; **63**: 1354-1359
- Flowers MA, Heathcote J, Wanless IR, Sherman M, Reynolds WJ, Cameron RG, Levy GA, Inman RD. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. *Ann Intern Med* 1990; **112**: 381-382
- Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549
- Ito S, Nakazono K, Murasawa A, Mita Y, Hata K, Saito N, Kikuchi M, Yoshida K, Nakano M, Gejyo F. Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of low-dose methotrexate therapy in a rheumatoid arthritis patient. *Arthritis Rheum* 2001; **44**: 339-342
- Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098-1104
- Lucin P, Jonjic S, Messerle M, Polic B, Hengel H, Koszinowski UH. Late phase inhibition of murine cytomegalovirus replication by synergistic action of interferon-gamma and tumour necrosis factor. *J Gen Virol* 1994; **75** (Pt 1): 101-110
- 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**: 1624-1625
- Mok MY, Ng WL, Yuen MF, Wong RW, Lau CS. Safety of disease modifying anti-rheumatic agents in rheumatoid arthritis patients with chronic viral hepatitis. *Clin Exp Rheumatol* 2000; **18**: 363-368
- Narvaez J, Rodriguez-Moreno J, Martinez-Aguila MD, Clavaguera MT. Severe hepatitis linked to B virus infection after withdrawal of low dose methotrexate therapy. *J Rheumatol* 1998; **25**: 2037-2038
- Oniankitan O, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlowsky JM, Claudepierre P. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004; **31**: 107-109
- 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**: 686-687
- 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**: 1078-1082
- Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405
- Reijasse D, Le Pendeven C, Cosnes J, Dehee A, Gendre JP, Nicolas JC, Beaugerie L. Epstein-Barr virus viral load in Crohn's disease: effect of immunosuppressive therapy. *Inflamm Bowel Dis* 2004; **10**: 85-90
- Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol* 2001; **96**: 722-729
- Schlaak JF, Tully G, Lohr HF, Gerken G, Meyer zum Buschenfelde KH. HBV-specific immune defect in chronic hepatitis B (CHB) is correlated with a dysregulation of pro- and anti-inflammatory cytokines. *Clin Exp Immunol* 1999; **115**: 508-514
- Takai S, Tsurumi H, Ando K, Kasahara S, Sawada M, Yamada T, Hara T, Fukuno K, Takahashi T, Oyama M, Onishi H, Tomita E, Takami T, Imawari M, Moriwaki H. Prevalence of hepatitis B and C virus infection in haematological malignancies and liver injury following chemotherapy. *Eur J Haematol* 2005; **74**: 158-165
- Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029-1035
- Ueno Y, Tanaka S, Shimamoto M, Miyakawa Y, Hiyama T, Ito M, Kitadai Y, Yoshihara M, Sumii M, Chayama K. Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. *Dig Dis Sci* 2005; **50**: 163-166
- del Valle Garcia-Sanchez M, Gomez-Camacho F, Poyato-Gonzalez A, Iglesias-Flores EM, de Dios-Vega JF, Sancho-Zapatero R. Infliximab therapy in a patient with Crohn's disease and chronic hepatitis B virus infection. *Inflamm Bowel Dis* 2004; **10**: 701-702
- Wong GH, Goeddel DV. Tumour necrosis factors alpha and beta inhibit virus replication and synergize with interferons. *Nature* 1986; **323**: 819-822

S- Editor Guo SY L- Editor Elsevier HK E- Editor Kong LH