Possible Reactivation of Potential Hepatitis B Virus Occult Infection by Tumor Necrosis Factor-α Blocker in the Treatment of Rheumatic Diseases

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ABSTRACT. ***Objective.*** To assess the safety of anti-tumor necrosis factor (TNF-α) therapy in patients with rheumatic diseases in terms of the reactivation of potential hepatitis B virus (HBV) occult infection.

Methods. Patients who had taken anti-TNF-α for the treatment of rheumatic diseases from January 2002 to May 2008 were included in the study. In this patient group, we retrospectively investigated a series of serum aminotransferase levels, HBV serologic status, the type of anti-TNF-α therapy, duration of the anti-TNF-α treatment, and concurrent use of hepatotoxic drugs.

Results. A total of 266 cases were documented using 3 serologic markers for HBV infection: HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), and HBV core IgG Ab (HBcAb). Of these, 8 cases had chronic hepatitis B (HBsAg+), 170 cases were HBcAb-negative, and 88 cases were identified as having potential HBV occult infections represented by HBsAg-negative and HBcAb-positive, irrespective of the status of the HBsAb.

The frequency of clinically significant (> 2 times normal value) and persistent increase (> 2 consecutive tests) of aminotransferase levels was significantly higher in the group with a potential HBV occult infection compared to the HBcAb-negative group. In the multiple logistic regression analysis controlling for various potential confounding factors such as prophylactic anti-tuberculosis medication, methotrexate, nonsteroidal antiinflammatory drugs, and the type of anti-TNF-α therapy, only potential HBV occult infection was a significant risk factor for abnormal liver function test (LFT).

Conclusion. All rheumatic patients who plan to take anti-TNF-α treatment should undergo a test for HBV serology, including HBcAb, and have a close followup with an LFT test during therapy. Further prospective studies for hepatitis B viral load using HBV-polymerase chain reaction in patients who are HbcAb positive are needed to identify whether the abnormal LFT comes from the reactivation of occult HBV infection. (J Rheumatol First Release Dec 15 2009; doi: 10.3899/jrheum.090436)

Key Indexing Terms:
TUMOR NECROSIS FACTOR-α BLOCKER
HEPATITIS B VIRUS
OCCULT INFECTION
RHEUMATIC DISEASES

Tumor necrosis factor-α (TNF-α), one of the most important proinflammatory cytokines, plays a key role in the immune or inflammatory responses to infectious diseases as well as several rheumatic diseases.

TNF-α blocker has been proposed as an effective therapeutic option for refractory or severe rheumatoid arthritis (RA) and spondyloarthropathy. In addition, several clinical trials have reported that there is a significant beneficial effect from TNF-α blocker on early RA[1-3], a finding that supports the earlier administration of TNF-α blocker. Therefore, it is expected that the administration of TNF-α blocker will be expanded.

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Supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea (A084794).

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Accepted for publication September 23, 2009.

However, in considering the important role of TNF-α in the integrated host defense system against infection, it has been suspected that TNF-α blockers are associated with an increased susceptibility to various pathogens. TNF-α inhibits hepatitis B virus (HBV) replication and plays an important role in clearing HBV from infected hepatocytes by stimulating HBV-specific T cell responses[4]. Therefore, inhibition of TNF-α enables the virus to evade the host antiviral defense mechanism, resulting in an increase in viral replication. There have been dozens of case reports concerning the use of TNF-α blockers in chronic HBV carrier patients[5-10]. Guidelines have been suggested for the assessment and management of chronic HBV infection in patients who are receiving or will receive TNF-α blocker[11,12].

However, there have been few studies addressing whether the use of TNF-α blocker in potential HBV occult infection is safe. Occult HBV infection is defined as the detection of HBV DNA despite HBV surface antigen (HBsAg) negativity, with or without the presence of HBV surface antibody (HBsAb). Occult HBV infection can be derived from viral mutants that are not recognized by commercially available assays for HBsAg or by very low levels of viral replication. However, because the technology for detection of HBV DNA is not available in many centers, and HBV DNA in blood, hepatocytes, or monocytes cannot be detected easily, potential HBV occult infection [negative HBsAg and positive IgG HBV core antibody (HBcAb) with or without anti-HBs instead of a test for HBV DNA] has been proposed. Several reports suggest that potential HBV occult infection has a low but substantial risk of viral reactivation in the condition of immunosuppression[13]. So it is important for clinicians to note that viral reactivation can also occur in HBsAg-negative patients.

We aim to assess the safety of anti-TNF-α therapy in patients with rheumatic diseases and potential HBV occult infection in terms of the reactivation of HBV infection, using significantly elevated aminotransferase level as a surrogate marker of possible reactivation of occult infection.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of subjects who had taken anti-TNF-α (infliximab, etanercept, or adalimumab) drugs for the treatment of rheumatic diseases from January 2002 to May 2008 at the Hospital for Rheumatic Diseases, Hanyang University. Of these patients, we included those with well-documented serologic status for HBsAg, HBsAb, and HBcAb and investigated the duration of disease, the type and duration of anti-TNF-α therapy, and a series of serum aminotransferase levels. Concurrent use of known potential hepatotoxic drugs, prophylactic tuberculosis (TB) medication, nonsteroidal antiinflammatory drugs (NSAID), and methotrexate (MTX) was also investigated. Patients were divided into 2 groups according to their HBcAb status, a marker that suggests previous exposure to HBV. We then compared the frequency of abnormal liver function tests (LFT) between the HBcAb-positive and -negative groups. A clinically significant LFT abnormality was defined by a 2-fold or greater increase of serum aminotransferase level than standard on a normal range at more than 2 consecutive tests on serial monitoring after the start of anti-TNF-α therapy.

All statistical analyses were conducted using the SPSS package for Windows (version 12.0). The effects of HBcAb status on the LFT abnormality were evaluated using chi-square tests and multivariate logistic regression.

RESULTS

Of 266 cases with a well-documented serologic status for HBsAg, HBsAb, and HBcAb, 8 cases with positive HBsAg were excluded. The clinical characteristics of this study group are summarized in Table 1. The average age of the individuals in the HBcAb-positive group was 51.17 ± 13.45 years, significantly older than for the individuals in the HBcAb-negative group (36.09 ± 13.01). The female-to-male ratio and the duration of the administration of TNF-α blocker did not differ significantly between the 2 groups.

The frequency of clinically significant and persistent increases in aminotransferase levels was significantly higher in the HBcAb-positive group compared with the HBcAb-negative group [15.9% vs 5.9%, respectively; OR = 1.84, 95% confidence interval (CI) = 1.25-2.71, p = 0.009; Table 2].

In the HBcAb-positive group, the mean time until LFT abnormality was 6.93 ± 9.47 months after starting TNF-α blocker and the mean duration of the abnormality was 3.79 ± 2.18 months.

In multiple logistic regression analysis controlling for HBcAb, isoniazid (INH), NSAID, MTX, and type of anti-TNF-α therapy, only potential HBV occult infection represented by positive HBcAb was a significant risk factor for abnormal LFT (OR = 3.29, 95% CI = 1.36-7.97, p = 0.008), suggesting possible reactivation of an indolent HBV infection as a result of the anti-TNF-α therapy (Table 3).

DISCUSSION

The availability of TNF-α blockers for the treatment of patients with rheumatic diseases has dramatically changed the clinical course and prognosis of these diseases. At the same time, the adverse effects of TNF-α blockers, such as increasing susceptibility to infection, demyelinating disease, systemic lupus erythematosus, and malignancy have also been on the rise[14]. Therefore, clinicians need to have concrete guidelines for predicting and preventing the side effects of TNF-α blockers. For example, screening for TB infection is mandatory before the initiation of TNF-α blocker, and recommendations for prevention and management of TB in patients using TNF-α blockers have been established[15].

HBV infection is one of the most common and important causes of chronic liver disease, and it is estimated that there are about 350 million people worldwide with chronic HBV infection[16]. South Korea is one of the countries with prevalent HBV infection (about 3-5%), making HBV a serious health problem[17].

In HBV infection, clearance of the intracellular virus is dependent upon the innate and adaptive immune system, including antiviral cytokines such as interferon-γ and

Table 1. Patient characteristics.

Characteristic	HBcAb-Positive Group	HBcAb-Negative Group	p
Number	88	170	—
Age, yrs, mean ± SD	51.17 ± 13.45	36.09 ± 13.01	< 0.01
Sex, female/male (female %)	45/43 (51.1)	79/91 (46.5)	0.477
Disease entity (n)			
RA	45	57	
AS	41	95	—
JRA	—	15	
PsA	2	3	
Type of TNF-α blocker (n)			
Etanercept	60	133	
Infliximab	12	25	—
Adalimumab	16	12	
Treatment duration of TNF-α blocker, months, mean ± SD	24.72 ± 16.44	26.66 ± 14.45	0.33

SD: standard deviation; RA: rheumatoid arthritis; AS: ankylosing spondylitis; JRA: juvenile rheumatoid arthritis; PsA: psoriatic arthritis; TNF-α: tumor necrosis factor-α.

Table 2. Comparison of LFT abnormality between HBcAb-positive group and HBcAb-negative group.

	HBcAb-Positive Group, n = 88	HBcAb-Negative Group, n = 170	p	OR (95% CI)
Patients with abnormal LFT, no. (%)	14 (15.9)	10 (5.9)	0.009	1.84 (1.25–2.71)
Patients with normal LFT, no. (%)	74 (84.1)	160 (94.1)		

LFT: liver function test; CI: confidence interval.

Table 3. Multiple logistic regression analysis of LFT abnormality controlling for HBcAb, INH, NSAID, MTX, and the type of TNF-α blocker.

	p	OR (95% CI)
HBcAb	0.008	3.29 (1.36–7.97)
INH	0.52	0.74 (0.30–1.81)
NSAID	0.60	1.31 (0.46–3.68)
MTX	0.84	0.91 (0.37–2.24)
Type of TNF-α blocker	0.39	1.36 (0.67–2.73)

LFT: liver function test; INH: isoniazid; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; TNF: tumor necrosis factor.

TNF-α, which can downregulate viral replication[4,18]. So the suppression of the immune system that follows chemotherapy, immunosuppressive therapy, or several other biologic agents may stimulate viral replication in the absence of host antiviral defense mechanisms. In the field of hematooncology, the association between HBV reactivation and chemotherapy is well known[19,20], and preemptive antiviral therapy has been suggested for HBsAg-positive patients who are receiving or will receive chemotherapy[21].

With the use of TNF-α blocker for the treatment of Crohn's disease and several rheumatic diseases, case reports of HBV reactivation in patients with HBsAg after receiving TNF-α blocker have also been published[5-10]. Among the 8 HBsAg-positive patients excluded from our study, 1 patient was treated with lamivudine before and during anti-TNF-α therapy, and remained stable, with no viral reactivation. However, TNF-α blocker was given to the other 7 patients without antiviral therapy, and in 2 of them, viral reactivation was documented and antiviral treatment with lamivudine was initiated.

Therefore, guidelines have been drawn up for the assessment and management of HBV reactivation with TNF-α blocker therapy[11,12]. The authors of these guidelines strongly recommend screening for HBV infection, HBV vaccination in patients with planned TNF-α blocker therapy, and prophylactic antiviral therapy and regular HBV DNA monitoring before and after anti-TNF-α therapy in patients with HBsAg.

However, current recommendations mainly focus on HBsAg-positive subjects, although HBV reactivation is also possible in patients with occult HBV infection who are persistently HBsAg-negative.

In general, recovery from acute HBV infection is characterized by the absence of detectable HBV DNA and HBsAg in peripheral blood and liver using the currently available assay, and by the production of HBsAb, the neutralizing antibody against HBsAg[22]. However, the existence of residual HBV DNA in the serum, liver or peripheral monocytes after recovery from HBV infection, even decades later, has

been reported[23,24]. So the possibility of occult HBV infection, defined as detection of HBV DNA and independent of HBV antibody status should be considered before the use of specific therapies that target immunity despite negative HBsAg.

Indeed, there have been several published case reports of occult HBV infection being reactivated by biologic agents, including rituximab and infliximab[25-27]. These case reports, including a case of death due to fulminant hepatitis[25], emphasize the need to be aware of HBV occult infection and to define the guidelines for HBV occult infection before or during therapy with biologic agents.

In our study, we could not define occult HBV infection because HBV DNA results were not available for most subjects. Instead, HBcAb positivity could be representative of potential HBV occult infection. When the frequency of LFT abnormality was compared between the 2 groups divided by HBcAb status, the frequency of clinically significant and persistent increase in aminotransferase level was significantly higher in the HBcAb-positive group than in the HBcAb-negative group. Since we did not have HBV-DNA data, we could not confirm the association of abnormal LFT with reactivation of HBV occult infection. However, multiple logistic regression analysis showing only HBcAb positivity as a risk factor for increased aminotransferase level suggested the possible link between abnormal LFT with reactivation of HBV occult infection after TNF-α blocker therapy.

Although the frequency of abnormal LFT was significantly higher in the HBcAb-positive group, there were no deaths, and elevated LFT was normalized within 3 months for almost all cases. This finding may reflect a clinically less important transient viral reactivation, or may result from a population sample size too small to detect rare fulminate cases. Therefore, further studies including a large number of subjects are needed to confirm that LFT abnormality is higher in patients who are HBcAb-positive and to clarify the incidence of fulminate cases.

In the baseline characteristics, there was a significant difference in the age distribution between the 2 groups. One possible reason for reduced prevalence of HBcAb-positive in the younger population is the introduction of a national HBV vaccination program after 1983 in South Korea. The population below age 30 to 40 years seems to have less chance to be infected with HBV than the older age group.

To our knowledge, our study includes the largest number of patients with potential occult HBV infection in the world, despite the limitations including the retrospective nature of this study and the lack of HBV DNA results.

We have observed that patients who are HBcAb-positive have an increased risk of abnormal serum aminotransferase levels after receiving TNF-α blocker, suggesting the possible reactivation of potential HBV occult infection. Thus, all rheumatic patients who plan to take anti-TNF-α treatment should undergo a test for HBV serology, including HBcAb, and have a close followup with the LFT test during therapy. Further large prospective studies for hepatitis B viral load using HBV-DNA polymerase chain reaction in patients with HBcAb are needed to determine whether abnormal LFT after TNF-α blocker therapy results from the reactivation of HBV.

REFERENCES

1. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
2. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
3. St. Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-43.
4. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med 2004;350:1118-29.
5. 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.
6. 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;12:974-6.
7. 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.
8. 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 2006;45:1294-7.
9. Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol 2008;35:421-4.
10. Carroll MB, Bond MI. Use of tumor necrosis factor-alpha inhibitors in patients with chronic hepatitis B infection. Semin Arthritis Rheum 2008;38:208-17.
11. 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;65:983-9.
12. 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.
13. Zingarelli S, Frassi M, Bazzani C, Scarsi M, Puoti M, Airo P. Use of tumor necrosis factor-alpha-blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. J Rheumatol 2009;36:1188-94.
14. Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. Semin Arthritis Rheum 2005;34:819-36.
15. Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor

alpha. Arthritis Rheum 2005;52:2968-74.
16. Yun H, Kim D, Kim S, Kang S, Jeong S, Cheon Y, et al. High prevalence of HBV and HCV infection among intravenous drug users in Korea. J Med Virol 2008;80:1570-5.
17. Lee DH, Kim JH, Nam JJ, Kim HR, Shin HR. Epidemiological findings of hepatitis B infection based on 1998 National Health and Nutrition Survey in Korea. J Korean Med Sci 2002;17:457-62.
18. Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. Annu Rev Immunol 2001;19:65-91.
19. Yeo W, Chan PK, 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;62:299-307.
20. Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology 2006;43:209-20.
21. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507-39.
22. Bertoletti A, Ferrari C. Kinetics of the immune response during HBV and HCV infection. Hepatology 2003;38:4-13.
23. Marusawa H, Uemoto S, Hijikata M, Ueda Y, Tanaka K, Shimotohno K, et al. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 2000;31:488-95.
24. Yuki N, Nagaoka T, Yamashiro M, Mochizuki K, Kaneko A, Yamamoto K, et al. Long-term histologic and virologic outcomes of acute self-limited hepatitis B. Hepatology 2003;37:1172-9.
25. Sarrecchia C, Cappelli A, Aiello P. HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. J Infect Chemother 2005;11:189-91.
26. Madonia S, Orlando A, Scimeca D, Olivo M, Rossi F, Cottone M. Occult hepatitis B and infliximab-induced HBV reactivation. Inflamm Bowel Dis 2007;13:508-9.
27. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 2001;344:68-9.