Reactivation of Hepatitis B Viral Infection in Inactive HBsAg Carriers Following Anti-Tumor Necrosis Factor-α Therapy

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ABSTRACT. ***Objective.*** To investigate whether anti-tumor necrosis factor-α (TNF-α) therapy can influence the reactivation of hepatitis B virus (HBV) infection in inactive HBsAg carriers.

Methods. The medical records of 103 patients [59 with ankylosing spondylitis (AS), 41 with rheumatoid arthritis (RA), 2 with juvenile RA, and 1 with psoriatic arthritis] who had been treated with anti-TNF-α therapy were reviewed retrospectively. Data on seropositivity of HBV, HBV load, and serum aminotransferases prior to and after initiation of anti-TNF-α therapy were obtained.

Results. Eight patients were inactive HBsAg carriers, and all of them had normal liver function and undetectable HBV load prior to anti-TNF-α therapy. Reactivation of hepatitis B occurred in 1 patient during the course of anti-TNF-α therapy. After the third infusion of infliximab 5 mg/kg at Week 6, a blood test showed that the patient had normal liver function. When the patient returned for the fourth infusion of infliximab at Week 14, a blood test showed markedly elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels (457 and 1054 IU/l, respectively) and increased viral DNA by HBV polymerase chain reaction (PCR). The fourth infliximab infusion was canceled, and entecavir 0.5 mg/day was prescribed. Then AST/ALT levels began to decrease and returned to normal range after 3 months. Followup HBV PCR showed negative results.

Conclusion. We found 1 HBV reactivation case among 8 inactive HBsAg carriers following anti-TNF-α therapy. This finding supports the prophylactic use of antiviral agents in HBV carriers, even if they have normal liver function or an undetectable viral load. (J Rheumatol First Release Oct 1 2009; doi:10.3899/jrheum.081324)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANKYLOSING SPONDYLITIS HEPATITIS B VIRUS
ANTI-TUMOR NECROSIS FACTOR-α THERAPY INACTIVE HBsAg CARRIERS

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that plays a key role in the host response to several types of infection and other stimuli[1]. Various observations strongly implicate TNF-α in the pathogenesis of rheumatoid arthritis (RA) and ankylosing spondylitis (AS)[2], and increased TNF-α production propagates rheumatoid synovitis, promotes osteoclast formation, and results in characteristic bone and joint destruction[3]. Significantly higher TNF-α serum levels have been found in patients with AS, and increased expression of TNF-α was detected in sacroiliac joint specimens from patients with AS[4]. Thus, anti-TNF-α therapy has greatly affected the current treatment of RA and AS, but it has adverse reactions such as tuberculosis reactivation[5,6]. Presently, the literature regarding the safety of anti-TNF-α therapy in chronic viral infection settings is limited.

Hepatitis B virus (HBV) causes chronic disease in about 5% of infected individuals, or nearly 350 million people worldwide[7]. Previous studies support the role of TNF-α in the host antiviral response[8], and animal models have demonstrated an impaired antiviral response upon administration of TNF-α antibodies[9]. Further, neutralization of TNF-α impaired viral clearance and promoted chronic viral infection[10,11]. To date, several case reports have shown that inhibition of TNF-α facilitates HBV reactivation and replication and can cause fulminant hepatic failure or fatal outcomes[12-16]. Moreover, it has become clear in the literature that patients with chronic HBV infection are at increased risk for HBV reactivation and that prophylactic antiviral treatment is warranted[17]. Previous reports reviewing the literature suggested that treatment guidelines should recommend mandatory use of antiviral agents if alanine amino-

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transferase (ALT) rises above the upper limit of normal and HBV DNA titer is increased, which led to controversy over the use of prophylaxis in inactive HBsAg carriers with normal liver enzyme levels and an undetectable viral load[18,19]. However, more recent guidelines on the use of antiviral agents in patients receiving immunosuppressive agents published in 2007 recommended antiviral prophylaxis in inactive HBsAb carriers[20], mandating antiviral prophylaxis in patients with positive HBsAg prior to any immunosuppressive treatment.

The purpose of our study was to evaluate the outcome of HBV carriers who had been treated with anti-TNF therapy. Most cases evaluated in this study were inactive HBsAg carriers with normal liver function and an undetectable viral load, and anti-TNF therapy had been initiated before the revised American Association for the Study of Liver Diseases (AASLD) Practice Guidelines were published. Our results support the conclusion that antiviral prophylaxis is recommended in HBV carriers, even if they have normal liver function or an undetectable viral load.

MATERIALS AND METHODS

The medical records of 103 Korean patients who had been treated with anti-TNF-α therapy were reviewed retrospectively. Fifty-nine patients had AS, 41 had RA, 2 had juvenile RA, and 1 had psoriatic arthritis. All patients were seen at the Division of Rheumatology, Gangnam Severance Hospital, Seoul, Korea, between January 2006 and September 2008, and fulfilled the classification criteria of the American College of Rheumatology for each disease. Inactive HBsAg carriers with normal liver function and an undetectable viral load under no specific antiviral therapy were enrolled in this study, and those with any other liver disease or abnormal liver function test results prior to anti-TNF-α therapy were excluded. There were no patients with HBsAg and elevated liver enzymes, increased viral load, or positive HBeAg because we did not initiate anti-TNF-α therapy in those cases. We obtained data on HBV seropositivity (HBsAg, HBeAg, anti-HBs, anti-HBc, and anti-HBe), HBV load (HBV DNA), and serum aminotransferase levels [aspartate aminotransferase (AST) and ALT].

RESULTS

Among 103 patients given anti-TNF-α therapy, 8 (3 with RA and 5 with AS) were inactive HBsAg carriers with documented HBsAg seropositivity and HBeAg seronegativity. Subject demographics and clinical data are summarized in Table 1. All patients had normal ALT/AST levels and undetectable HBV DNA by polymerase chain reaction (PCR) upon initiating anti-TNF-α therapy. All patients were treated with nonsteroidal antiinflammatory drugs, and some received methotrexate (10.0–17.5 mg/week) with low-dose glucocorticoids. Two patients with RA had sulfasalazine in addition to methotrexate. Two patients with AS received sulfasalazine prior to anti-TNF-α therapy. No patient presented any abnormality on liver function tests upon glucocorticoid or methotrexate use. Tuberculin skin test results were positive in 2 patients; thus isoniazid prophylaxis had been performed prior to anti-TNF-α therapy and followup liver enzyme tests showed normal liver enzyme levels.

Among the 8 inactive HBsAg carriers, hepatitis B reactivation occurred in 1 with AS who had been treated with infliximab (Patient 1) (12.5%, 95% CI 0–0.354). He had normal liver enzyme levels and negative HBV PCR results prior to infliximab infusion. The blood test, which was performed at the time of the third infusion of infliximab (5 mg/kg) at Week 6, revealed normal AST and ALT levels. When the patient revisited the clinic for the fourth infliximab infusion at Week 14, he complained of general weakness and right upper quadrant (RUQ) abdominal pain lasting for 3 days. Blood chemistry revealed markedly elevated AST and ALT levels (457 and 1054 IU/l, respectively), and HBV PCR showed an increased HBV load (3,130,000 IU/ml, reference value < 60 IU/ml). After the diagnosis of HBV infection reactivation, the fourth infliximab infusion was cancelled, and entecavir (0.5 mg/day) was prescribed. Thereafter, AST and ALT levels began to decrease and returned to normal after 3 months. Followup HBV PCR results were negative. Baseline and followup blood chemistry, serological profile, and viral load data of the patient are summarized in Table 2 and Figure 1.

With the exception of Patient 1, no other HBV infections reactivated during or after anti-TNF-α therapy.

DISCUSSION

According to our observations, 8 of 103 patients treated with anti-TNF blocker were inactive HBsAg carriers with normal liver function and an undetectable HBV load prior to initiation of anti-TNF therapy. Among them, 12.5% of patients (n = 1, 95% CI 0–0.354) experienced reactivation of hepatitis B during anti-TNF therapy, and we presumed that this exacerbation resulted from HBV reactivation by anti-TNF-α therapy. Due to the retrospective design of the study, mild reactivations could be overwhelmed.

The activity of chronic hepatitis B infection depends on the host's immune response to the virus; immunosuppressive therapy is known to alter this response. There are several theories as to how TNF-α inhibitors might reactivate hepatitis B. TNF-α has a biological activity and amino acid sequence similar to lymphotoxin, which inhibits viral replication. It has also been reported that infected cells are selectively killed by TNF-α[21]. The finding that recombinant human TNF-α has antiviral activity *in vitro* supports this hypothesis[22]. Serum and intrahepatic TNF-α expression is increased in patients with chronic HBV infection[23,24], indicating that TNF-α plays a role in suppressing viral replication by reducing intracellular HBV transcription. Moreover, virus-specific cytotoxic T cells inhibit HBV gene expression by secreting antiviral cytokines such as interferon-γ (IFN-γ) and TNF-α and induce apoptosis in HBV-infected hepatocytes[25].

Previous reports reviewing the literature suggested that treatment guidelines should recommend mandatory use of antiviral agents if ALT rises above the upper limit of normal and HBV DNA titer is increased[17,18]. There are several case

Table 1. Patient characteristics at the initiation of treatment and total duration of anti-TNF therapy.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age/sex	31/M	42/M	22/M	25/F	28/M	41/F	61/M	47/F
Diagnosis	AS	AS	AS	AS	AS	RA	RA	RA
Disease duration, mo	27	175	10	6	25	22	196	93
AST/ALT at baseline, IU/l	21/14	11/11	19/12	25/26	13/11	9/13	21/30	16/27
HBsAg	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
HBeAg	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Anti-HBe antibody	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Anti-TNF-α therapy	Infliximab	Etanercept	Etanercept	Infliximab	Adalimumab	Adalimumab	Etanercept	Etanercept
DMARD	—	SSZ	SSZ	—	—	MTX+SSZ	MTX	MTX+SSZ
TB prophylaxis	Done	Not needed	Not needed	Not Needed	Not needed	Not needed	Done	Not needed
Duration of anti-TNF therapy, wks	6	52	32	18	18	24	16	44

AST: aspartate aminotransferase; ALT: alanine aminotransferase; Ag: antigen; Ab: antibody; TB: tuberculosis; MTX: methotrexate; SSZ: sulfasalazine; TNF: tumor necrosis factor; AS: ankylosing spondylitis; RA: rheumatoid arthritis; DMARD: disease modifying antirheumatic drugs.

Table 2. Serologic profile and viral load of Patient 1.

	Prior to Anti-TNF Therapy	At Week 6	At Week 14	At Week 24
AST, IU/l	21	14	457	28
ALT, IU/l	14	10	1,054	23
Total bilirubin, mg/dl	0.7	0.6	1.5	0.8
Prothrombin time, INR	1.14	Not tested	1.27	1.14
Serologic profile				
HBsAg	Positive	Not tested	Positive	Positive
Anti-HBs antibody	Negative	Not tested	Negative	Negative
Anti-HBc antibody IgM	Negative	Not tested	Negative	Negative
HBeAg	Negative	Not tested	Negative	Negative
Anti-HBe antibody	Positive	Not tested	Positive	Positive
Viral load				
HBV PCR, IU/ml	Undetectable	Not performed	3,130,000	Undetectable

HBV: hepatitis B virus. For other abbreviations, see Table 1. PCR: polymerase chain reaction.

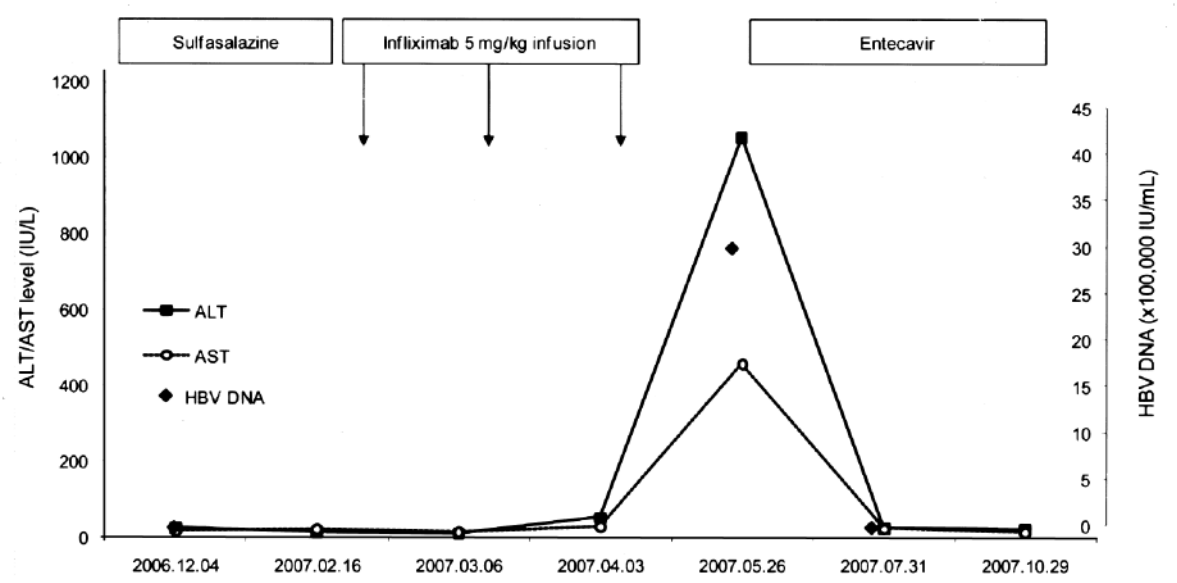

Figure 1. Course of serum HBV-DNA and AST/ALT levels of Patient 1.

reports of normalization of liver enzymes after lamivudine treatment during HBV reactivation following anti-TNF-α therapy[12,15], suggesting the effectiveness of lamivudine in the treatment or prevention of HBV reactivation in patients receiving immunosuppressive treatment. On the other hand, there are reports of severe HBV reactivation due to lamivudine resistance to immunosuppressive therapy[14,26]. According to the revised AASLD Practice Guidelines published in 2007[20], lamivudine alone would be sufficient for patients going through immunosuppressive therapy for less than 6 months, but longer durations of immunosuppressive therapy would require usage of entecavir or adefovir due to acquisition of viral resistance and breakthrough. Considering its fast action and efficacy, entecavir is the preferred treatment. The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines also stated that lamivudine may suffice for patients with low HBV DNA levels and a low risk of resistance. However, if HBV DNA level is high, entecavir or tenofovir was recommended to prevent reactivation[27]. The EASL International Consensus Conference on Hepatitis B advised 2 to 4 weeks of antiviral therapy before starting immunosuppressive therapy in patients with HBV[28]. Especially in patients receiving anti-TNF-α therapy, maintaining antiviral therapy at least 3 months after terminating anti-TNF-α therapy is recommended by investigators[18].

South Korea has been known as an endemic area for HBV infection. The prevalence of HBsAg was 4.1%–5.1% in South Korea, and most cases are due to vertical transmission[29]. At present, we usually prescribe antiviral agents to prevent HBV reactivation according to the current guidelines and if our patients show any abnormality in liver function or viral load, prophylaxis with antiviral agents would be initiated prior to anti-TNF-α therapy. However, the cases in our study received anti-TNF therapy before the current guidelines were available. According to the American College of Rheumatology 2008 recommendations, biologic agents are contraindicated only in chronic hepatitis B for those with significant liver injury, defined as chronic Child-Pugh classes B or C[30]. However, as shown in our study, reactivation of HBV infection can occur in healthy and inactive HBsAg carriers with an undetectable viral load, and this finding supports the conclusion that antiviral prophylaxis should be initiated if patients were receiving anti-TNF-α therapy, regardless of HBV DNA level and liver function.

In conclusion, our study showed that HBsAg-positive and HBeAg-negative inactive HBsAg carriers can have HBV reactivation and resultant liver disorders following anti-TNF-α therapy, even if they show no sign of HBV replication or liver function deterioration prior to anti-TNF-α therapy. This result suggests that screening for HBV infection and antiviral prophylaxis should be performed in all patients who are to receive anti-TNF-α therapy for rheumatic diseases.

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Correction

Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Reactivation of hepatitis B viral infection in inactive HBsAG carriers following anti-tumor necrosis factor-α therapy. J Rheumatol 2009;36: 2416-20. Results presented in Table 2 should appear as follows. We regret the error.

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Anti-HBs antibody	Negative	Not tested	Negative	Not tested
Anti-HBc antibody IgM	Negative	Not tested	Negative	Not tested
HBeAg	Negative	Not tested	Negative	Not tested
Anti-HBe antibody	Positive	Not tested	Positive	Not tested
Viral load				
HBV PCR, IU/ml	Undetectable	Not performed	3,130,000	Undetectable

HBV: hepatitis B virus. For other abbreviations, see Table 1. PCR: polymerase chain reaction.

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