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Risk of hepatitis B reactivation in patients treated with tumor necrosis factor alpha inhibitors

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Summary

The use tumor necrosis factor (TNF-alpha) inhibitors has been increasing especially in patients with rheumatoid arthritis (RA). As TNF-alpha inhibitors are strongly immunosuppressive, the occurrence of hepatitis B virus (HBV) reactivation has recently been observed.

Reports suggest a higher risk of complicating HBV reactivation in carriers who are treated with TNF-alpha inhibitors. Therefore, HBV carriers are recommended to undergo prophylactic administration of nucleos(t)ide analogues (NAs).

Our literary analysis uncovered several characteristics of de novo hepatitis B due to TNF-alpha inhibitors. First, the time between the start of TNF-alpha inhibitors and the occurrence of de novo hepatitis was longer than one year. Second, patients were usually treated with additional non-biologic agents which also had immunosuppressive effects. Third, the disease could be fatal. Fourth, several types of TNF-alpha inhibitors exhibited a risk of developing de novo hepatitis. Although the incidence of de novo hepatitis B varied among reports (0 - 5%/year), it is suggested that patients with prior HBV infection are at risk of developing de novo hepatitis due to TNF-alpha inhibitors.

Many reports maintain that regular measurement of HBV DNA is effective in preventing de novo hepatitis. Prophylactic administration of NAs is also considered useful to avoid de novo hepatitis, although the issue of cost-effectiveness needs to be addressed. Lastly, whereas maintenance of circulating anti-HBs titer using HB vaccines may be effective in responders to prevent de novo hepatitis, further studies are required to clarify the utility of HB vaccination.

Introduction

Approximately 3 billion people have been exposed to the hepatitis B virus (HBV), and there are an estimated 350 million chronic carriers worldwide.[1-2] HBV infection is usually detected by the presence of hepatitis B surface antigen (HBsAg) in the serum, and clearance of HBsAg is generally considered as an indication of hepatitis B resolution. However, recent studies have shown that HBV replication persists at low levels in the liver and peripheral blood mononuclear cells for decades, even in HBsAg-negative patients with resolved HBV infection.[3-5] In such patients, HBV replication is suppressed by immune responses to HBV, for instance specific cytotoxic T lymphocyte-mediated responses.[3]

HBV reactivation in patients with resolved HBV infection has been reported in increasing numbers as the number of patients undergoing strong immunosuppressive therapy grows worldwide for malignant neoplasms, autoimmune disorders, and following transplantation for prevention of rejection. In patients like these with resolved HBV infection, reactivation of hepatitis B is recognized as de novo hepatitis B, which can lead to fulminant hepatic failure and often death.[6-7] Thus, de novo hepatitis B is becoming a well-recognized severe complication of immunosuppressive therapy that should be prevented.[6, 8]

The risk of developing de novo hepatitis B varies among immunosuppressive therapies; it is as high as 14 - 20% in patients who receive hematopoietic stem cell transplantation and as low as 1 - 3% in those who undergo conventional chemotherapies.[9-13] The introduction of rituximab, a genetically engineered chimeric anti-CD20 monoclonal antibody[14-15], in the treatment of CD20+ B-cell non-Hodgkin's lymphoma increased the risk of de novo hepatitis B. Hui et al.[16] analyzed the occurrence of de novo hepatitis B in patients who were treated for lymphoma and

reported that its risk was significantly higher in patients who received rituximab and steroids (12%) than in other patients (1%). Similarly, Yeo et al.[17] reported that the risk of de novo hepatitis B was significantly higher in patients who were treated with chemotherapy including rituximab (24%) than in those treated with chemotherapy only (0%). Because the introduction of rituximab increased the risk of de novo hepatitis B considerably in lymphoma patients, the need to examine the occurrence of HBV reactivation has emerged when a new agent that suppresses host immune responses is introduced.

TNF-alpha is a crucial pro-inflammatory and immunoregulatory cytokine in the pathogenesis of various inflammatory and autoimmune conditions. Inhibitors of TNF-alpha have recently been introduced in treatments for various kinds of autoimmune and inflammatory disorders, including rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. TNF-alpha inhibitors have revolutionized the therapeutic approaches and treatment paradigms for these patients. However, their optimal use requires consideration of possible adverse effects; increased risks of tuberculosis and other infections are a major concern in TNF-alpha treatment.[18] Complicating tuberculosis is considered to be caused by reactivation of latent tuberculosis.[19] A similar reactivation of HBV has also been reported, which leads to de novo hepatitis B and possibly fulminant hepatic failure and death. In the present review article, we summarize reports regarding reactivation of hepatitis B due to TNF-alpha inhibitors to clarify its characteristics and occurrence (Table 1).

Reactivation of hepatitis in HBV carriers

The majority of patients with a confirmed diagnosis of RA use

disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, but the rate of biologic agent use is rising rapidly.[20-21] Since both methotrexate[22-24] and biologic agents carry the danger of HBV reactivation, the advent of new biologic agents, such as TNF-alpha inhibitors, has increased this risk. Patients with RA who developed reactivation of hepatitis B due to TNF-alpha inhibitors were first reported in 2003.[25-29] Because these cases had been HBV carriers prior to starting TNF-alpha inhibitors, the authors recommended serological tests for HBV infection preliminary. Caroll et al. conducted a systemic literature review on HBV reactivation in carriers who were treated with TNF-alpha inhibitors for RA and reported that reactivation was seen in 6 (17%) of 35 patients.[26] They concluded that clinicians prescribing TNF-alpha inhibitors to HBsAg-positive patients should consider prophylactic antiviral therapy and close monitoring for any clinical or serological evidence of hepatitis. Reactivation of hepatitis B was also reported in patients with Crohn's disease who were treated with TNF-alpha inhibitors,[30-31] and thus reactivation became considered to be drug dependent and not disease dependent.

Prophylaxis using nucleos(t)ide analogues (NAs) has been reported to be effective in preventing the occurrence of hepatitis reactivation in HBV carriers.[32-36] Vassilopoulos et al.[35] administered lamivudine in 14 HBV carriers with RA who were treated with TNF-alpha inhibitors and showed that reactivation of hepatitis B did not occur in any patient except one. The appearance of lamivudine resistance was considered to be the cause of reactivation in this exceptional patient, and so the authors concluded that TNF-alpha inhibitors represented a safe option for patients with chronic HBV infection when combined with NAs. Zingarelli et al.[32] reported 20 patients with RA who were treated with DMARDs and/or TNF-alpha inhibitors. Prophylaxis and therapy with lamivudine were performed in patients with a high risk of

HBV reactivation, and no cases of viral reactivation were observed. Thus, it is likely that prophylaxis using NAs may prevent the occurrence of hepatitis reactivation in HBV carriers who are treated with TNF-alpha inhibitors. Indeed, Calabrese et al.[37] recommended that all HBsAg-positive patients be started on prophylactic anti-viral drugs before receiving immunosuppressive therapy. However, long-term follow-up studies in large groups of patients are required to ensure the safety of prophylaxis with NAs.

Descriptions of HBV reactivation due to TNF-alpha inhibitors in the guidelines of rheumatologist associations several years ago tended to be brief and passive. It was described that TNF-alpha inhibitor therapy should be avoided in patients with hepatitis B infection until more definitive data were available in the 2005 guidelines of The British Society for Rheumatology.[38] In the 2007 Japanese guidelines,[39] it was advised that TNF-alpha inhibitors should be avoided in patients with HBV infection. However, if the potential benefits of treatment with TNF-alpha inhibitors exceeded the risk of reactivation, such therapy could be pursued provided that patients were pre-treated with lamivudine.

Risk of de novo hepatitis B

Although it has become clear that HBsAg-positive patients are prone to developing HBV reactivation during TNF-alpha inhibitor therapy, little is known about the occurrence of de novo hepatitis B. Several cases of de novo hepatitis B due to TNF-alpha inhibitors have been reported recently.[40-43] Mondonia et al.[40] reported a 41-year-old woman with Crohn's disease who developed de novo hepatitis B after having been treated with prednisolone for 13 years and infliximab for 3 years. The hepatitis subsided with lamivudine administration. Montiel et al.[42] described a

73-year-old man with ankylosing spondylitis who developed de novo hepatitis 15 months after starting etanercept. The patient had also undergone treatment with prednisolone for 23 years. Although etanercept was discontinued when the hepatitis occurred, it could be re-started with concurrent lamivudine administration. Matsumoto et al.[41] reported a 71-year-old woman with RA who developed de novo hepatitis 22 months after starting treatment with infliximab, methotrexate, and prednisolone. Although entecavir was given when hepatitis occurred, the patient died of hepatic failure. Such case reports reveal several characteristics of de novo hepatitis B due to TNF-alpha inhibitors. First, the duration between the start of the drugs and the occurrence of de novo hepatitis was at least one year. Second, patients were treated not only with TNF-alpha inhibitors, but also with DMARDs and prednisolone, which themselves had immunosuppressive effects. Third, there was a risk of death from de novo hepatitis. Fourth, several kinds of TNF-alpha inhibitors appeared able to cause de novo hepatitis.

The incidence of HBV reactivation from occult HBV infection and ensuing de novo hepatitis B due to TNF-alpha inhibitor therapy in patients with RA has been reported by several groups. Charpin et al.[44] followed 21 patients with RA who were HBsAg-negative and hepatitis B core antibody (HBcAb)-positive before starting TNF-alpha inhibitors, and found that no patient developed HBV reactivation during a mean follow-up period of 27.2 months. They concluded that TNF-alpha inhibitor therapy was likely safe in patients with a past hepatitis B serological pattern. However, they also suggested that such patients required HBV virological follow-up, especially those with a low HBs antibody (HBsAb) titer at baseline because HBsAb decreased significantly during therapy. Caporali et al.[45] followed 67 patients with RA who also had HBV markers of past HBV infection, and found no elevations of HBV DNA in sera

or appearances of HBsAg during a mean follow-up period of 42.5 months. Of the 67 patients, 23 were treated with infliximab, 23 with etanercept, and 19 with adalimumab. Almost all patients underwent methotrexate (51 patients) and/or prednisolone (43 patients) administration in addition to TNF-alpha inhibitors. Tamori et al.[46] followed 50 patients with RA who were positive for HBcAb for a mean period of 23 months. All patients were treated with immunosuppressive agents such as methotrexate, prednisolone, and/or TNF-alpha inhibitors for more than 1 year. HBV reactivation was observed in 2 of 5 patients with HBsAg, compared with only in 1 of the remaining 45 patients without it. Therefore, HBV reactivation leading to de novo hepatitis B was observed in 2% (1%/year) of patients. It should be noted that the lone HBsAg-negative reactivation patient had been treated with methotrexate but not with TNF-alpha inhibitors. Mori[47] performed a cross-sectional analysis of 239 patients with RA who were treated with biological and/or non-biological agents, among whom 60 were found to have HBV markers indicating earlier HBV infection. Of these, 2 were signal-positive for serum HBV DNA but without ALT elevation or HBsAg positivity: one patient was treated with tacrolimus, prednisolone, and methotrexate, and the other was treated with adalimumab, prednisolone, and methotrexate. Whereas HBV DNA level in the former patient increased and HBsAg and HBeAg became weakly positive after 10 weeks, the latter patient became HBV DNA-negative without additional anti-viral therapy. The authors also concluded that biological and non-biological agents are relatively safe in RA patients with past HBV infection. Thus, these studies suggested that the occurrence of de novo hepatitis B was rare in RA patients who were treated with TNF-alpha inhibitors in addition to DMARDs over the medium term. A large-scale post-marketing surveillance study was carried out in Japan to determine the safety profile of infliximab in patients with RA.[18] All patients with RA who were

treated with infliximab were prospectively monitored for any adverse events for a period of 6 months after the initiation of infliximab. No cases of de novo hepatitis B were found. Although the follow-up period was short, the number of patients enrolled was over 5,000. This report indicated that de novo hepatitis B due to TNF-alpha inhibitors would be very rare over the short-term as well.

In contrast to the above mentioned reports, several studies have suggested a relatively high incidence of de novo hepatitis B due to TNF-alpha inhibitor therapy. Kim et al.[48] followed 266 patients with RA who were treated with TNF-alpha inhibitors and analyzed the occurrence of clinically significant (over 2 times higher than normal range) and persistent (2 or more incidences) alanine aminotransferase (ALT) elevation in relation to HBV markers. Elevation of ALT was significantly more frequent in patients with HBcAb (HBsAg negative) than in those without (16% vs. 6%, P = 0.009). In multiple logistic regression analysis controlling for various potential confounding factors, such as methotrexate, nonsteroidal anti-inflammatory drugs, and type of TNF-alpha inhibitor, only potential occult HBV infection was identified as a significant risk factor for ALT elevation, suggesting a close association between HBcAb-positivity and ALT elevation during TNF-alpha inhibitor therapy in RA patients. However, it cannot be confirmed whether ALT elevations in that study were indeed caused by reactivation of occult HBV because HBV DNA was not measured along with ALT. Urata et al.[49] prospectively followed 135 patients with RA who had HBV markers suggesting past HBV infection for 12 months. The cohort was treated with biological and/or non-biological anti-rheumatic agents and followed for a total mean period of approximately 20 months, including the period before follow-up. Serum HBV DNA was measured every 3 months during the study period, and revealed that HBV reactivation occurred in 7 patients (5%/year). HBV reactivation was significantly

associated with use of TNF-alpha inhibitors with a hazard ratio of 10.9 (P = 0.008). This study suggested that careful monitoring of HBV DNA level is required in RA patients with resolved hepatitis B when receiving anti-rheumatic agents, especially biologic ones.

In Japan, HBV reactivation rates tend to differ regionally. A study from Aomori prefecture[49] in the northern part of Japan reported a relatively higher rate of de novo hepatitis stemming from TNF-alpha inhibitors than studies from Osaka[46] and Kumamoto[47] prefectures in the central and southern parts of Japan, respectively. It is speculated that these differences are attributed to variations in HBV genotype distribution; whereas genotype B is predominant in the former area, genotype C is more frequent in the latter areas.[50] Further studies are required to address this phenomenon.

In light of the above findings, it is evident that RA patients with past HBV infection who are treated with anti-rheumatic agents are at risk of developing HBV reactivation and ensuing de novo hepatitis B, especially those being treated with anti-rheumatic agents, such as TNF-alpha inhibitors, for an extended time. Spontaneous remission of HBV reactivation was observed in 1 of the 2 patients reported by Mori[47] and 2 of the 7 patients reported by Urata et al.[49], and so it should be noted that HBV reactivation does not necessarily result in the occurrence of de novo hepatitis B.

Prophylactic measures for de novo hepatitis B

Three measures are generally used to prevent de novo hepatitis B due to immunosuppressive therapy.[7] The first measure is to regularly check for serum HBV DNA during immunosuppressive therapy and administer NAs should it be detected.

The second measure is to administer NAs from the onset of immunosuppressive therapy. The third measure is to maintain circulating HBsAb titer using HB vaccines and/or HB immunoglobulins. Reports have suggested that regular evaluation of HBV DNA is effective in avoiding de novo hepatitis in patients treated with TNF-alpha inhibitors because HBV reactivation could be controlled by NAs when found at an early stage.[46, 49] It is still unclear how often and for how long patients should be tested to detect HBV viremia. Prophylactic administration of NAs is also an option to preempt de novo hepatitis B due to TNF-alpha inhibitors because NAs are normally used to prevent reactivation in carrier patients. However, the issue of cost-efficiency versus relatively low incidence of de novo hepatitis B needs to be reconciled. Lastly, maintenance of circulating HBsAb titer using HB vaccines may be effective in responders since several studies[44, 46] have shown that HBsAb titer decreases during TNF-alpha inhibitor therapy. As with HBV DNA monitoring and prophylactic NA administration, further studies are required to clarify the extent of HB vaccination effectiveness in preventing de novo hepatitis B due to TNF-alpha inhibitors.

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Table 1. Summary of references regarding reactivation hepatitis due to TNF-alpha inhibitors.

Category / Reference	Publication type
Case report and review in HBV carriers	
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Risk and prevention in HBV carriers	
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Case report of de novo hepatitis B	
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Risk of de novo hepatitis B	
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