

Hepatitis B and C Reactivation with Tumor Necrosis Factor Inhibitors: Synopsis and Interpretation of Screening and Prophylaxis Recommendations

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ABSTRACT: Information on reactivation of chronic viral hepatitis infection in patients who are candidates for tumor necrosis factor alpha inhibitors (TNFi) is in a constant state of flux. We retrieved the most updated guidelines (in English) of prominent rheumatological and gastroenterological professional societies for the management of chronic hepatitis B (HBV) and hepatitis C virus (HCV) infection in the context of treatment with TNFi. Subsequently, the major areas of uncertainty and absence of consensus in the guidelines were located and a secondary search for additional studies addressing those areas was performed. Based on our search we formulated a personal interpretation applicable to health care settings with virological laboratories capable of performing viral load measurements, and health systems that can support use of potent nucleoside/tide analogues in well-defined patient populations.

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During the last 15 years, tumor necrosis factor-alpha inhibitors have been approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthropathies and Crohn's disease. The entry of these drugs into clinical use generated the hope that they would present a less hepatotoxic alternative to disease-modifying anti-inflammatory drugs for patients with chronic viral hepatitis or preexisting liver disease. However, in the large pre-licensure controlled clinical trials with TNFi, patients with serious infections including viral hepatitis were excluded from participation and the effect of TNFi on viral hepatitis was unknown [1]. Since licensing became approved, elevated liver enzymes have been observed among patients treated with TNFi as a result of direct hepatotoxicity or secondary to reactivation of chronic viral hepatitis [2]. The infliximab package insert

The following serological profile should be performed in TNFi candidates: HBsAg, anti-HBcAg, anti-HBsAg and anti-HCV

specifically urges prescribers to exercise caution in prescribing the drug to patients identified as hepatitis B carriers [3]. A recent questionnaire sent to members of the American College of Rheumatology revealed that only 19–53% of responders were aware of manufacturers' warning regarding HBV reactivation during immunomodulatory therapy with infliximab, and only 69% performed screening prior to initiating therapy [4].

There are considerable variations in recommendations published by professional societies for screening, pretreatment vaccination and antiviral prophylaxis for HBV, and screening and management of hepatitis C virus prior to beginning therapy with TNFi. In this communication, we provide updated background data relating to the effects of TNFi on HBV and HCV infections. We then review selected currently used guidelines and expert opinion statements and highlight areas of uncertainty and absence of consensus. Finally, we propose patient management and screening recommendations that we believe will aid clinicians make timely and informed decisions for managing this challenging patient population.

We retrieved guidelines published by prominent hepato/gastroenterological societies for the management of HBV and HCV in the context of immunosuppression due to TNFi, or by rheumatological societies regarding the approach to screening for infectious diseases, and specifically viral hepatitis, before initiating TNFi. Key points necessitating decision making in screening, prophylaxis and management were identified in the guidelines and compared. Subsequently, secondary searches intended to locate original studies and case reports that addressed and expanded on the controversial points were carried out.

HEPATITIS C VIRUS

There is growing evidence that the pathogenesis of hepatocyte destruction and treatment resistance to interferon-alpha in chronic HCV infection may be mediated by up-regulation

TNFi = tumor necrosis factor-alpha inhibitor

HBV = hepatitis B virus
HCV = hepatitis C virus

of inflammatory cytokines such as TNF α [5]. In a number of patients, TNFi therapy has been associated with a fall in viral load, and occasionally it was associated with viral clearance even without concomitant antiviral therapy [6,7]. In a controlled trial, adding etanercept as adjuvant therapy to interferon/ribavirin was associated with a doubling rate of viral clearance at 24 weeks in naïve adult HCV-infected patients compared to treatment with interferon/ribavirin alone (63% vs. 32% respectively, $P < 0.05$), without apparent adverse effects [8].

Screening for HCV was recommended in a recent rheumatology consensus statement, but no clear contraindication for treatment or standard follow-up monitoring schedules were suggested [9]. A systematic literature review of more than 100 HCV-infected patients treated with TNFi between 1990 and 2010 identified only a single case of biopsy-confirmed HCV liver disease worsening during etanercept therapy. Improvement in liver enzyme levels was observed after withdrawal of etanercept therapy [10].

While these data are encouraging, case reports have indicated that treatment with TNFi may trigger the emergence of mixed cryoglobulinemia in patients with chronic HCV infection without affecting HCV viral load. Cryoglobulinemia appeared in two of six HCV patients treated with TNFi for active rheumatoid arthritis, and persisted in two others with active HCV replication [11].

Another unresolved issue pertains to combined treatment of IFN α and TNFi in HCV patients with rheumatic diseases. Autoimmune phenomena including exacerbation or induction of rheumatoid arthritis associated with IFN α treatment have been reported [12]. Conlon et al. [13] reported the development of a polyarthropathy in five patients undergoing IFN α therapy. Three of those five patients had a history of RA, suggesting an exacerbation of clinically silent disease. A recent case report of an RA patient receiving simultaneous TNFi and IFN α treatment for HCV reported no adverse effect on the patient's RA control. This patient achieved complete clearance of HCV viremia, suggesting that combined treatment with both agents may be safe, and potentially even beneficial, for both diseases [14]. Moreover, treatment with TNFi was suggested as a safe and effective way to treat patients with RA who would not otherwise be able to tolerate IFN α -based HCV treatment [15]. Recently oral direct-acting antiviral agents – telaprevir and boceprevir, serine protease inhibitors – have been approved for treatment of HCV genotype 1 [16]. These agents must be administered with peginterferon and ribavirin. Currently, there are not enough data to make a clear recommendation on the use of TNFi in patients treated with protease inhibitors for HCV infection.

IFN α = interferon-alpha
RA = rheumatoid arthritis

HEPATITIS B VIRUS

TNF α in HBV infection: Elevated levels of TNF α are observed in serum and hepatocytes of patients with chronic HBV infection. In contrast to HCV, TNF α in these patients may play a role in clearing and controlling HBV infection by synergizing with interferon in suppressing viral replication [17,18]. Inactivation of TNF α could theoretically lead to enhanced viral replication and therefore reactivate or worsen the liver disease [19].

Formal recommendations by leading professional associations for management of patients with inflammatory rheumatic disease and inflammatory bowel disease, infected with HBV, who are candidates for TNFi, are presented in Table 1.

Pretreatment screening: Pretreatment screening for HBV is a well-known requirement in patients who are candidates for treatment with DMARDS. Methotrexate is contraindicated in patients with serological evidence of infection irrespective of severity of liver disease and viral load. Severe cases of liver damage due to HBV reactivation have been reported following methotrexate administration [24]. Treatment with TNFi is not

contraindicated in HBV carriers; however, most guidelines support pretreatment screening for candidates. The ACR, the British Society of Rheumatology and the American Academy for the Study of Liver Diseases rec-

Treatment of HBsAg/HBV-DNA positive patients with TNF α inhibitors should be deferred until an adequate virological response is achieved as defined by hepatology guidelines

ommend screening only patients with high risk factors for HBV infection, namely, household contacts of HBV patients, injection drug users, patients with multiple sex partners in the previous 6 months, and health care personnel. The decision to conduct universal screening vs. screening based on risk factors should reflect the level of HBV endemicity in the country. The prevalence of hepatitis B surface antigen carriers in Israel is 1.5–2.0% (E. Zuckermann, personal communication). The specific serological markers to be tested should include HBsAg, anti-hepatitis B core and pretreatment HBV-DNA level in case the patient is HBsAg positive. Most guidelines subsequently recommend HBV vaccination for previously unvaccinated non-infected candidates for TNFi. Only the British Society of Rheumatology recommend testing anti-HBsAg titers in vaccinated individuals and considering a booster dose if titer levels are beneath acceptable cutoffs [23]. Anti-HBsAg antibody levels in rheumatoid patients have been shown to decline faster in those receiving DMARD therapy than in those who do not. This raises the question whether such patients should be given booster doses [25]. No data to support specific recommendations are yet available on this issue for patients on anti-TNFi therapy.

DMARDS = disease-modifying anti-inflammatory drugs
ACR = American College of Rheumatology
HBsAg = hepatitis B surface antigen

Table 1. Summary of guidelines from professional associations and expert consensus statements regarding vaccination, pretreatment screening and management of chronic hepatitis B in patients receiving TNF α inhibitors

Guideline/Consensus statement [ref]	Treatment approved for HBV active carriers with hepatological indication for treatment	Antiviral prophylaxis for HBsAg-positive inactive carriers without hepatological indication for treatment	Antiviral prophylaxis for HBsAg-negative/ Anti-HBc positive	Comments
AASLD Practice guideline update, 2009 [20]	Yes	At onset of the immunosuppressive course, and maintained for 6 months afterwards	Not enough data to recommend. Monitoring including HBV-DNA	Use prophylactic adefovir, tenofovir or entecavir when more than 12 months of therapy is needed
Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2010 [9]	No	Can be administered	Not assessed	
EASL guidelines for the management of chronic HBV infection, 2012 [21]	Yes	During immunosuppressive therapy and 12 months after cessation of therapy	No. Close follow-up	Patients with high HBV-DNA levels or prolonged immunosuppression should receive entecavir or tenofovir
Opportunistic infections in patients with inflammatory bowel disease: prevention and diagnosis, 2007 [22]	Not assessed	Consider lamivudine at least 3 weeks before immunosuppression. Other anti-HBV nucleosides should be considered	Not assessed	Testing for serological immunity Should be performed after hepatitis B vaccination
BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies, 2010 [23]	Yes	TNFi treatment may be safe if appropriate antiviral treatment is given	Serology monitored during therapy	
ACR 2008 recommendations for the use of non-biological and biological disease-modifying antirheumatic drugs in rheumatoid arthritis [24]	See comment	See comment	Not assessed	Contraindicated in both chronic hepatitis B and C, (treated or untreated) with significant liver injury (Child-Pugh B or C)*

*Child-Pugh severity of liver disease score based on presence of encephalopathy, ascites, bilirubin and albumin levels, and prothrombin time

AASLD = American Association for the Study of Liver Diseases, EASL = European Association for the Study of the Liver, BSR/BHPR = British Society of Rheumatology/British Health Professionals in Rheumatology, ACR = American College of Rheumatology

Chronic HBV-infected patients who need antiviral therapy irrespective of immunosuppression:

Patients with either HBeAg-positive or negative chronic hepatitis B, characterized by HBV-DNA levels \geq 2000 IU/ml and elevated liver enzymes or histological necroinflammatory activity (detected by a liver biopsy), require treatment with a potent nucleoside/tide analogue with the lowest rate of genotypic resistance [21]. Compliance should be reinforced. Recently Shale et al. [26] reported the outcome in 29 patients with HBV infection treated with TNFi. One of three patients with a pretreatment viral load > 2000 copies/ml experienced non-fatal worsening of liver enzymes. In addition, three patients developed acute hepatitis with one fatality. Their pretreatment viral load was not reported. The AASLD guidelines advise that patients with high level HBV-DNA continue antiviral therapy until they reach therapeutic endpoints for chronic HBV before undergoing cytotoxic chemotherapy [20]. Similarly, the European Association for the Study of the Liver guidelines support pre-emptive therapy with potent nucleoside/tide inhibitors during therapy with immunosuppressive agents for patients with high level HBV-DNA [21]. However, these guidelines do not address the question of the severity of the underlying liver disease. The

In HBV-DNA negative TNFi candidates potent nucleoside analogue prophylaxis should be offered and monitoring of aminotransferases and HBV-DNA should be performed every 3 months

ACR approves TNFi treatment only for HBsAg-positive well-compensated cirrhotic patients (Child-Pugh score A) [24]. Our personal interpretation and suggestion is that in HBV-infected patients with an indication for antiviral therapy, treatment with TNFi should be deferred until HBV-DNA becomes undetectable and aminotransferases have normalized. Patients with decompensated liver cirrhosis should not be treated with TNFi.

HBsAg-positive patients for whom antiviral treatment is not indicated for hepatological parameters:

Hepatitis reactivation in HBsAg-positive patients with undetectable HBV-DNA or low viral load (< 2000 IU/ml) has been described following chemotherapy, organ transplantation, and specifically hematopoietic stem cell transplantation [27]. In some cases the reactivation led to fulminant hepatitis [28,29]. Reactivation rates, without the use of antiviral prophylaxis, reached 54% [27]. Therefore, all candidates for chemotherapy, organ transplantation and rituximab therapy must be screened for HBV before initiating treatment, and lamivudine or telbivudine prophylaxis is administered if HBsAg is detected [20].

In contrast to oncology patients receiving chemotherapy or rituximab for limited periods (weeks to months), patients with inflammatory rheumatic disease and inflammatory bowel disease require immunomodulatory therapy for many years, raising

AASLD = American Academy for the Study of Liver Diseases

the risk of drug resistance. Viral resistance to lamivudine commonly develops with prolonged use and is detected in up to 17% of patients after 1 year and in 70% by 5 years. The emergence of resistance may be associated with hepatitis reactivation.

In a study involving patients scheduled to receive TNFi agents for treatment of rheumatic disease, the following groups of patients were given prophylactic lamivudine: all active HBV carriers, nine inactive carriers (HBsAg positive, HBV-DNA undetectable and aminotransferases normal), and potential occult carriers. All patients were treated with lamivudine for the duration of therapy (median 19 months). No cases of viral reactivation were observed [30]. In contrast, there have been published reports of inactive carriers who developed HBV reactivation after long-term infliximab therapy while receiving lamivudine prophylaxis [31,32]. These patients received lamivudine for chronic HBV, and lamivudine therapy was maintained while infliximab was administered. Undetectable HBV-DNA was reported before initiation of infliximab in both cases. During the reactivation, 3 and 2 years respectively after infliximab initiation, high levels of HBV-DNA were observed in both and increased aminotransferases were observed in one case. At reactivation, HBeAg was negative, suggesting emergence of a lamivudine-resistant precore mutant.

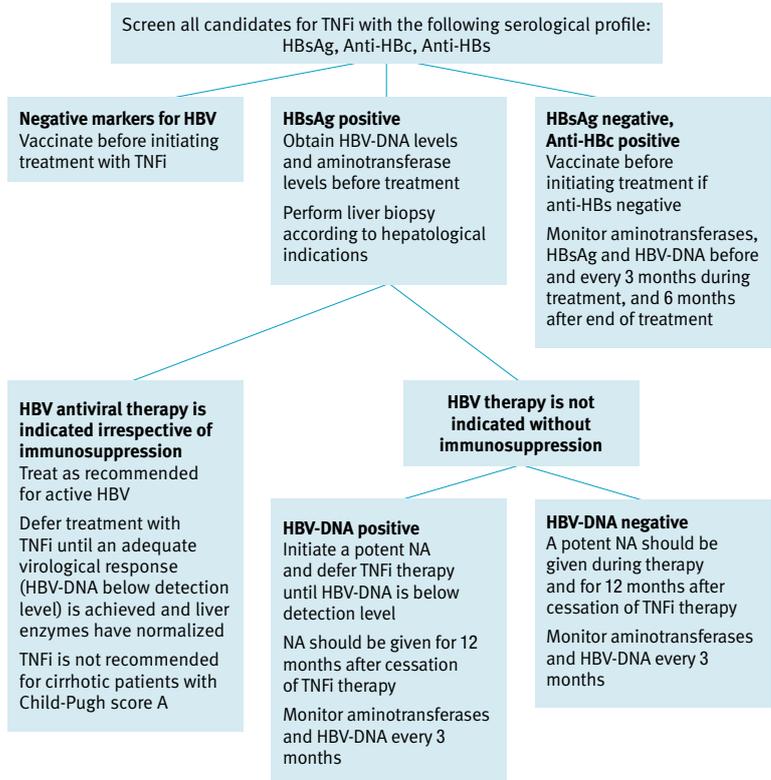
While the British guidelines still recommend antiviral

prophylaxis with lamivudine for inactive HBV carriers who need immunosuppression [Table 1], the 2009 AASLD practice guidelines and the 2012 European guidelines advocate the use of tenofovir or entecavir – nucleoside analogues with a high antiviral potency and high barrier to resistance – if long duration (> 12 months) immunosuppression is anticipated [20-23].

Occult HBV infection: Patients with occult HBV infection present a particularly challenging screening population [33]. These patients have detectable HBV-DNA in their serum or liver but are HBsAg negative. They either have HBsAg escape mutants not recognized by commercially available assays or very low levels of viremia with concentrations of HBsAg below detection level [34,35]. The most sensitive methodological approach to detect occult HBV infection is to analyze DNA extracts from liver tissue obtained by a liver biopsy. However, this cannot be performed as a clinical routine. Analysis of DNA extracts from blood samples by the polymerase chain reaction technique is not always sufficiently sensitive.

A lethal reactivation of HBV following rituximab administration has been reported in an HBsAg-negative/anti-HBsAg-positive patient [36]. Although the real magnitude of reactivation of disease in occult carriers receiving immunosuppression has not been adequately estimated, a number of reports indicate that it is probably not large. In HBsAg-negative patients with serological markers of past HBV infection (anti-HBc with or without anti-HBsAg) less than 5% developed HBV reactivation, after receiving chemotherapy for hematological diseases [37], while 1–5% developed HBV reactivation after solid organ transplantation [38,39]. Although a case report of HBV reactivation following infliximab treatment in an occult HBV carrier was recently published, overall it seems to be a rare phenomenon [40]. Currently all guidelines reviewed recommend close monitoring of these patients during treatment with TNFi. Since a serological profile of HBsAg negative, anti-HBs negative, and anti-HBc positive represents low grade immunity to HBV in some patients, we suggest HBV vaccination before TNFi therapy in these patients.

Figure 1. Algorithm for pretreatment screening, prophylaxis, and monitoring for HBV in candidates for TNFi therapy. NA = nucleoside/tide analogue



FINAL RECOMMENDATIONS

• **Suggested screening and management algorithm for HBV**
This algorithm, based on the guidelines reviewed and on relevant original studies, is intended to: a) indicate pretreatment serology testing for HBV, b) guide the clinician to decide if prophylaxis for HBV reactivation is warranted, and c) clarify intervals of laboratory monitoring during treatment with TNFi [Figure 1].

• **Suggested screening and management for HCV**
All candidates for TNFi should be screened for HCV. Based on published reports of viral loads of chronic HCV patients who received TNFi, it seems safe to infer that treatment with these

Anti-HBc = anti-hepatitic B core

biologics is safe in the short term. Close monitoring of HCV-RNA and liver enzyme levels at regular intervals, i.e., every 3 months, is warranted. In HCV-positive patients requiring treatment for hepatitis, simultaneous treatment with interferon and TNF α inhibitors may be attempted together with careful monitoring of clinical symptoms suggesting arthritis flares, as well as monitoring of viral levels and aminotransferases every 3 months. A high index of suspicion for cryoglobulinemia should be maintained.

Finally, the potential long-term effect of TNFi therapy on the risk of progression to advanced stages of fibrosis or cirrhosis, or the development of hepatocellular carcinoma associated with HCV or HBV awaits definition.

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