Vital Hepatitis Reactivation with Anti-Tumor Necrosis Factor-Alpha: What Do We Know?

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**HCV AND TNFI**

Chronic HCV infection poses a potential hindrance to optimal therapy because of possible complications linked to immunosuppression, and because treatment with hepatotoxic drugs in patients with preexisting chronic liver disease may be challenging. Generally, the immune response towards the increased burden of infected hepatocytes upon withdrawal of the immunosuppression is usually blunted in hepatitis C compared with hepatitis B and thus severe hepatitis or fulminating hepatic failure is a rare event. In addition, the effect of TNFa blockade may be potentially beneficial in the setting of hepatitis C as TNFa appears to be involved in the pathogenesis of liver fibrosis through the stimulation of apoptotic pathways [4]. Finally, there is evidence that treatment with TNFi may lead to a decrease in HCV viral load, to a doubling of the rate of viral clearance with antiviral treatment, or even to HCV clearance without concomitant antiviral therapy [5]. A recent review of 37 publications with data on 153 chronically HCV-infected patients treated with TNFi showed only one case of histologically worsening liver disease [6]. In the remaining patients the liver disease and viral load were stable or even improved with concomitant antiviral treatment. Based on these data it seems that the safety profile of TNFi in the setting of HCV is acceptable, but in the absence of long-term and large controlled trials a definitive statement cannot be made. Until we have these data, screening for HCV infection and close monitoring of liver function tests and viral load is recommended, while being aware of the possible triggering of mixed cryoglobulinemia induced by TNFi.

**HBV AND TNFI**

Reactivation of HBV replication has been reported in 20–50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy. In contrast to HCV, TNFa participates in the specific host immune response against HBV; therefore, inhibition of TNFa can potentially enhance viral replication and worsen liver disease [7]. Although HBV reactivation is more common when chemotherapeutic regimens include corticosteroids or rituximab [8], the number of reports on reactivation in patients with rheumatoid arthritis or...
Crohn’s disease treated with TNFi has been persistently increasing [9]. Therefore, identifying patients at risk and prevention of such “flares” is extremely important. Since information regarding TNFi-induced HBV reactivation is still limited, many questions related to the management of HBV carriers receiving TNFi remain only partially answered or completely unresolved. Among them are: who to screen before treatment, what serological tests should be performed, and whether to vaccinate only unvaccinated subjects who are positive for anti-hepatitis B core antibody. Other issues are: who should receive preemptive treatment, when to start such treatment, what is the recommended therapy and for how long should it be used, who are the patients at specific risk of reactivation, and is there a specific TNFi that is safer than the others?

**PRETREATMENT SCREENING AND MANAGEMENT**

Unfortunately, despite most of the professional societies’ clear recommendations for HBV infection screening in patients (at least those at risk) who receive immunosuppressive therapy, it is still not common to observe patients with previously unrecognized HBV infection who experience severe HBV “flare” and hepatic decompensation that could be prevented if preemptive antiviral therapy was given. A recent survey reflects the problem of insufficient awareness to the risk of reactivation by showing that more than 30% of the members of the American College of Rheumatology do not screen for HBV infection prior to initiation of TNFi treatment [10]. The American Association for the Study of Liver Diseases and the American College of Rheumatology do not screen for HBV before initiation of TNFi treatment [10]. The American Association for the Study of the Liver recommends the use of lamivudine prophylaxis in patients undergoing chemo- or immunosuppressive therapy [2]. A recent meta-analysis and systematic reviews of 14 studies showed that lamivudine prophylaxis in patients undergoing chemotherapy or immunosuppressive therapy reduced the rate of reactivation by 87% (none of the 275 treated patients reactivated) and the rate of HBV-related mortality by 70% [14,15]. Based on these and additional solid data, all the relevant professional societies recommend prophylactic antiviral therapy. Thus, preemptive antiviral treatment should be administered to hepatitis B carriers, regardless of baseline HBV DNA level, at the onset of cancer chemotherapy or immunosuppressive therapy (including TNFi). HBsAg-positive individuals with baseline HBV DNA level > 2000 IU/ml should continue antiviral treatment until they reach the therapeutic endpoints for chronic hepatitis B (undetectable HBV DNA and normalization of aminotransferases). In contrast to hemato-oncological or oncolological patients where there is an urgent and immediate need to start chemotherapy or immunosuppressive therapy when HBV DNA level may still be high, in most patients treated with TNFi time allows an attempt to reduce the viral load to an undetectable level before initiating treatment with TNFi. Although there is consensus regarding the need for preemptive treatment in HBsAg-positive patients, the type of antiviral agent and duration of treatment are still debatable. 

As studies to date have focused on lamivudine (which was the first direct antiviral agent) for prophylaxis, the AASLD recommends the use of lamivudine (or telbivudine) if the duration of treatment is short (<12 months) and if baseline HBV DNA is not detectable. Lamivudine was shown to be as effective as prophylaxis in a few studies with a small number of patients using TNFi for more than 12 months [16]. However, the emergence of resistance during long-term treatment with lamivudine raises serious concern. Recently, anecdotal cases have been reported to experience reactivation while on lamivudine despite undetectable baseline HBV DNA [12,17]. These reports emphasize the need to use potent antivirals with a high barrier to resistance (tenofovir or entecavir) as prophylaxis, if the duration of immunosuppressive therapy is anticipated to be longer than 12 months, as was recommended in the 2009 AASLD and 2012 EASL (European Association for the Study of the Liver) guidelines. As

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anti-HBC = anti-hepatitis B core antibody  
HBsAg = hepatitis B surface antigen  
anti-HBs = anti-HBsAg antibody

AASLD = American Association for the Study of Liver Diseases
treatment with TNFi in the vast majority of patients with rheumatic diseases or inflammatory bowel disease is required for more than 12 months, entecavir or tenofovir should be the first choice. Prophylactic antiviral treatment should last as long as anti-TNFα is required. While considering the evidence that relapse of HBV can occur after cessation of immunosuppressive therapy, antiviral treatment should be continued for at least 6 months after the completion of treatment with TNFi; however, there are no data to specifically address this recommendation.

**“OCCULT” HBV INFECTION**

There is an increasing number of reports of reactivation in patients with “occult” HBV infection (HBsAg-/anti-HBc+), with or without anti-HBs; however, the rate is far lower than in HBsAg-positive patients. In hemato-oncological patients on conventional chemotherapy the rate of reactivation is 1.7%–3.5%. However, this rate may reach 12–50% in patients undergoing cytotoxic chemotherapy. Br J Cancer 2004; 90 (7): 1306-11. In patients with rheumatic diseases and chronic or resolved hepatitis B virus infection, prophylaxis of anti-TNF treatment is mandatory as is vaccination of anti-HBs patients. Antiviral treatment should last as long as TNFα does not induce viral reactivation in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis 2010; 69: 1352-5.

References

"May my silences become more accurate"
Theodore Roethke (1908-1963), American poet who published several volumes of influential and critically acclaimed verse

"I don’t know what your destiny will be, but one thing I do know: the only ones among you who will be really happy are those who have sought and found how to serve"
Albert Schweitzer (1875-1965), German theologian, musician, philosopher, physicist, and medical missionary in Africa. He received the 1952 Nobel Peace Prize for his philosophy of “Reverence for Life,” expressed in many ways, most famously in founding the Albert Schweitzer Hospital in Lambaréné (central Africa)

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