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

Eli Zuckerman MD

Liver Unit, Carmel Medical Center, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: reactivation, hepatitis B virus (HBV), hepatitis C virus (HCV), anti-tumor necrosis factor-alpha (anti-TNFα), preemptive treatment, immunosuppression

IMAJ 2013; 15: 366–368

Reactivation of chronic hepatitis B virus and hepatitis C virus infection is a well-known complication of immunosuppressive therapy in the setting of organ transplantation, hemato-oncological malignancy and solid cancer chemotherapy, occurring in up to 50% of patients if preemptive antiviral treatment is not used [1]. Although reactivation most commonly occurs upon restoration of the immune system following cessation of immunnosuppression, an accelerated course of HBV infection may accur with long-term immunosuppression. Such reactivation may lead to interruption of anti-cancer therapy, fulminant hepatic failure and hepatic decompensation, leading to a high rate of mortality [2]. As more experience and data begin to accumulate, risk factors for HBV reactivation are being identified. These predictors include the type of basic disease, the virological status, and the intensity and type of immunosuppression.

Over the last decade, biological therapies targeting B cells or tumor necrosis factor-alpha have become increasingly important agents in the management of hematological diseases, inflammatory bowel diseases, rheumatic diseases, and other refractory inflammatory conditions. As experience with the treatment with these agents accumulates, there is a growing body of evidence on viral reactivation, mainly with the use of rituximab and TNFα inhibitors. However, we are facing an absence of consensus and uncertainty regarding guidelines and expert opinion statements on many issues related to the screening and management of chronic HBV and HCV infection in patients receiving biological agents. However, the two viruses, HBV and HCV, differ in their response to immunosuppression and mechanism of reactivation and therefore should be discussed separately.

In this issue of *IMAJ*, Fuchs and colleagues importantly raise the concerns and uncertainty regarding the TNFi-induced viral reactivation and update the limited existent data in the recent literature [3].

HCV AND TNFI

Chronic HCV infection poses a potential hindrance to optimal therapy because of possible complications linked to immunesuppression, 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 fulminant hepatic failure is a rare event. In addition, the effect of TNFα blockade may be potentially beneficial in the setting of hepatitis C as TNFα 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, TNFα participates in the specific host immune response against HBV; therefore, inhibition of TNFα 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

HBV = hepatitis B virus

TNFα = tumor necrosis factor-alpha
HCV = hepatitis C virus
TNFi = TNFα inhibitors

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 uncommon 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 recommended that only patients at "high risk" for HBV infection be screened prior to initiation of immunosuppressive therapy [11]. The problem with this statement is that in areas with relatively high endemicity where the main route of infection is vertical or intrafamilial transmission a substantial number of HBV carriers will escape screening. The prevalence of hepatitis B surface antigen carriers in Israel is 1.75%, approaching 3% in the Arab population and anti-HBc 16% (Zuckerman E, unpublished data). In light of these observations it is reasonable to recommend routine universal screening for HBV, as appears in the guidelines of the Israel Association for the Study of the Liver, in all candidates for immunosuppressive treatment or cancer chemotherapy, including TNFi. The screening should include not only HBsAg but also anti-HBc and anti-HBsAg antibody (anti-HBs), as those with "past exposure" or "latent" HBV infection (HBsAg-negative, anti-HBc-positive) are at higher risk for reactivation than the general population and unvaccinated candidates should be vaccinated. However, it should be kept in mind that anti-HBs titers may decrease during long-term anti-TNF treatment in vaccinated patients as occurs with other immunosuppressive treatment or cancer chemotherapy [12], but there are insufficient data so far to recommend monitoring or boosting these patients.

PREEMPTIVE ANTIVIRAL THERAPY

During the last 20 years solid data have been accumulated showing that the rate of HBV reactivation may be extremely high, reaching more than 50% if prophylactic antiviral treatment was not administered [13]. The risk for reactivation depends mainly on the type of basic disease, the level of baseline HBV DNA, and the type, duration and intensity of the chemotherapy or immunosuppressive therapy [2]. A recent meta-analysis and systematic reviews of 14 studies showed that lamivudine prophylaxis in patients undergoing chemo- 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 aminotrasferases). In contrast to hemato-oncological or oncological 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

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 12–25% in patients on regimens containing corticosteroids and rituximab and in 14–50% in patients undergoing allogeneic bone marrow transplantation [2,14,18]. There are anecdotal reports of HBV reactivation in patients with occult HBV infection, but precise data on the safety of anti-TNF in these patients are not available. In a retrospective analysis of 62 psoriatic patients with occult HBV infection treated with anti-TNF biological agents over a period of approximately 4 years, only one patient experienced reappearance of HBsAg without detectable HBV DNA [19]. To date, there are no data to support prophylactic antiviral treatment in this setting and we should wait for the results of randomized controlled studies in order to address this issue. Close monitoring of liver enzymes and HBV DNA (every 3–6 months), especially in high risk patients, is mandatory as is vaccination of anti-HBs-negative patients .

The algorithm suggested by Fuchs et al. [3] is indeed reasonable but we have to wait until large controlled studies addressing all uncertainties can provide us with the missing answers.

Address for correspondence:
Dr. E. Zuckerman
Liver Unit, Carmel Medical Center, Haifa 34362, Israel
Phone: (972-4) 825-0053
Fax: (972-4) 825-0054
email: elizuc@clalit.org.il

References

1. Mindikoglu AL, Regev A, SchiffER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. *Clin Gastroenterol Hepatol* 2006; 4: 1076-81.
2. Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004; 90 (7): 1306-11.
3. Fuchs I, Abu-Shakra M, Sikuler E. Hepatitis B and C reactivation with anti-tumor necrosis factor inhibitors: synopsis and interpretation of screening and prophylaxis recommendations. *IMAJ* 2013; 15: 371-5.
4. Aslanidis S, Vassilladis T, Pyrpasopoulou A, Douloumpakas I, Zamboulis C. Inhibition of TNFα does not induce viral reactivation in patients with hepatitis C infection: two cases. *Clin Rheumatol* 2007; 26: 261-4.
5. Vauloup C, Krzysiek R, Greangeot-Keros L, et al. Effects of tumor necrosis factor antagonist treatment on hepatitis C-related immunological abnormalities. *Eur Cytokine Netw* 2006; 17: 290-3.
6. Brunasso A, Puntoni M, Guilia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology* 2011; 50: 1700-11.
7. Yeao W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009; 27 (4): 605-11.
8. Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; 53: 1363-5.
9. Herbein G, O'Brien WA. Tumor necrosis factor (TNF)-alpha and TNF receptors in viral pathogenesis. *Proc Soc Exp Biol Med* 2000; 223: 241-57.
10. Stine J, Khokhar O, Charalambopoulos J, Shaunmugam V, Lewis J. Rheumatologists' awareness of screening practices for hepatitis B virus infection prior to initiating immunomodulatory therapy. *Arthritis Care Res* 2010; 62: 704-11.
11. Lok A, McMahon B. AASLD Practice Guidelines Update. Chronic Hepatitis B: Update 2009. *Hepatology* 2009; 5 (3): 1-36 .
12. Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis G, Manolakopoulos S, Koskinas J. Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 2010; 69: 1352-5.
13. Xunrong L, Yan A, Liang R, Lau G. Hepatitis B virus reactivation after cytotoxic or immunosuppressive therapy – pathogenesis and management. *Rev Med Virol* 2001; 11: 287-99.
14. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. *Br J Hematol* 2007; 136: 699-712.
15. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy [Review]. *Ann Intern Med* 2008; 148 (7): 519-28.
16. Zingarelli S, Airo P, Frassi M, Bazzani, Scarsi M, Puoti M. Prophylaxis and therapy of HBV infection in 20 patients treated with disease modifying antirheumatic drugs or with biological agents for rheumatic diseases. *Reumatismo* 2008; 60: 22-7.
17. Esteve M, Loras C, Gonzalex-Huix F. Lamivudine resistance and exacerbation of hepatitis B in infliximab-treated Crohn's disease patient. *Inflamm Bowel Dis* 2007; 13: 1450-1.
18. Lau GK. Hepatitis B reactivation after chemotherapy: two decades of clinical research. *Hepatol Int* 2008; 2 (2): 152-62.
19. Cassano N, Mastrandrea V, Principi M, et al. Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: a retrospective analysis of 62 patients with psoriatic arthropathy. *J Biol Regul Homeost Agents* 2011; 25 (2): 285-9.

"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, physician, 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)