The safety of anti-TNF therapy in patients with hepatitis B and C virus infection

The use of anti-TNF agents over the last 15 years has revolutionized the treatment of various autoimmune diseases such as rheumatoid arthritis, spondyloarthropathies and inflammatory bowel diseases. Case reports of hepatitis B virus (HBV) reactivation in anti-TNF-treated patients in 2003 raised serious concerns about their safety in patients with chronic hepatitis B or C virus infection. More studies over the last decade have clearly shown that anti-TNF therapy can cause serious exacerbations of chronic HBV infection if no antiviral therapy is given, while more recent studies have indicated that prophylactic antiviral therapy significantly reduces that risk and should always be administered when a decision has been made for long-term anti-TNF therapy. By contrast, anti-TNF treatment appears to be safe when given for a short period of time (1–2 years) in patients with nonadvanced hepatitis C virus (HCV)-related liver disease. Future studies will address more specific questions regarding the optimal use of different oral anti-HBV agents (type of agents and duration of treatment) and the safety of anti-TNF agents when given for a long period in patients with chronic HBV or HCV infection, as well as the potential antiviral properties of anti-TNF agents in chronic HCV infection.

KEYWORDS: anti-TNF agents ■ hepatitis B virus ■ hepatitis C virus ■ inflammatory bowel diseases ■ rheumatoid arthritis ■ spondyloarthropathies

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Anti-TNF-directed therapies were introduced into clinical practice almost 15 years ago, heralding a new era in the treatment of various autoimmune or autoinflammatory diseases, such as rheumatoid arthritis (RA), spondyloarthropathies (ankylosing spondylitis and psoriatic arthritis), psoriasis and inflammatory bowel diseases (Crohn's disease and ulcerative colitis) [1]. This era – now referred to as the 'biologic's era' – has been based on the development of molecules (monoclonal antibodies and fusion proteins) that specifically target proinflammatory cytokines such as TNF, IL-1 and IL-6 or immune cells (B or T lymphocytes and antigen-presenting cells) that participate in the harmful immune response against the host [2]. Anti-TNF agents were the first to be developed, based on animal models showing the central role of TNF in the pathogenesis of inflammatory arthritides and inflammatory bowel diseases [1]. So far, more than two million people have received different anti-TNF agents for an expanding number of autoimmune or autoinflammatory diseases.

The overall safety profile of anti-TNF therapies has been proven to be excellent. Their safety in patients with coexisting chronic viral infections (active or latent) from viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and varicella zoster virus has been a matter of concern [3,4]. In this review, we will critically review the current evidence for the safety of these agents in patients with chronic HBV or HCV infection.

Hepatitis B virus

■ Phases: natural course of chronic HBV infection

HBV infection remains a global health problem with approximately 6% or 350 million people infected, despite the significant decrease in the rate of new infections that has been achieved by expanding vaccination programs worldwide [5]. Although the prevalence of chronic HBV infection remains low in industrialized countries of Europe and North America (<2%), its prevalence is moderate (2–8%) in several countries and more importantly is still high (>8%) in many crowded areas of the world (southeast Asia and Africa) [101]. Even among low prevalence countries, specific subgroups are at higher risk for chronic infection including immigrants from countries with intermediate-to-high HBV prevalence, users of injected drugs, household contacts of HBV carriers and persons with multiple sexual partners. Although data regarding the exact prevalence of HBV infection among anti-TNF candidates with autoimmune diseases are scarce, it is assumed that its prevalence is similar to that of the general population.

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The natural course of chronic HBV infection (defined by positive HBsAg for at least 6 months) has been well characterized over the last few decades [5,101]. It is now clear that the vast majority of chronically infected individuals have acquired the virus during the first few years of life either through vertical or perinatal transmission (from infected mother to child), as is the case for most patients in east Asia, or through intra-familial spread during childhood (<5 years of life) as has commonly occurred in Mediterranean countries. Chronic HBV infection, which may present with positive or negative HBeAg, usually runs through successive phases to end either in HBeAg positive or negative chronic hepatitis characterized by elevated aminotransferases (AST/ALT), serum HBV DNA (>2000 IU/ml) and liver necroinflammation (detected by liver biopsy), or in a chronic inactive carrier state evidenced by positive HBsAg, negative HBeAg and usually positive anti-HBe, persistently normal ALT/AST, low or undetectable HBV DNA (<2000 IU/ml), and absent or minimal liver inflammation. Long-term studies from Asia and Europe have shown that approximately 20–30% of untreated patients develop chronic liver inflammation (chronic hepatitis B – HBeAg positive or negative) and among them a significant proportion develop cirrhosis (2–5% per year) and/or hepatocellular carcinoma. The risk of progression to cirrhosis and hepatocellular carcinoma is much lower for patients who remain as chronically inactive carriers. Differentiating between chronic hepatitis B and the inactive carrier state is of significant clinical importance not only for assessing the prognosis of the individual patient, but also the risk for severe reactivation following immunosuppressive therapies.

HBV reactivation in anti-TNF-treated patients

HBV reactivation, defined by an increase of HBV DNA levels by >1 $\log_{10}$ compared with baseline with or without an associated increase in ALT levels, is a threatened complication of various immunosuppressive therapies including chemotherapy for hematologic diseases, solid tumors or after transplantation [6]. Although this risk has been discovered almost three decades ago, it was not until recently that various scientific organizations (mainly those associated with the study of liver diseases) clearly recognized this threat and recommended specific measures to prevent HBV reactivation [7,8,101].

The risk of HBV reactivation in chronically infected HBV patients (HBsAg positive) after immunosuppressive therapies without antiviral prophylaxis, ranges from 24 to 88% (combined rate: ~50%) [6]. Its incidence depends on the type of immunosuppressive therapy and the pre-therapy HBV replication rate. More specifically, a number of studies have shown that high-dose corticosteroids, high baseline levels of HBV DNA and the use of rituximab-containing regimens are associated with a higher risk for HBV reactivation in patients with hematological or neoplastic diseases, not receiving appropriate antiviral prophylaxis [6]. HBV reactivation can lead to severe clinical hepatitis and even death, especially in patients with underlying advanced liver disease. The mortality rate ranges 5 to 30% in different series.

The use of prophylactic antiviral therapy in patients receiving chemotherapeutic agents has been explored in a number of studies over the last two decades. Most data are available for the oral nucleoside analog, lamivudine, in this setting and clearly demonstrate that the pre-emptive use of this agent can decrease the rate of HBV reactivation and HBV-related mortality by more than 80% [9]. Based on these findings, different scientific societies recommend the prophylactic use of antiviral agents in all HBsAg-positive patients starting on chemotherapeutic agents [7,8,101].

The risk of HBV reactivation was acknowledged for the first time in the rheumatic literature shortly after the description of a few patients with rheumatic diseases who developed HBV reactivation during anti-TNF treatment [10–12]. Since then a number of case reports, retrospective case series and few prospective studies have clearly indicated that the use of anti-TNF agents is associated with HBV reactivation [13]. Although the exact risk of anti-TNF-induced HBV reactivation is not known, Ramos-Casals reviewed all of the HBsAg positive cases (n = 87) reported in the literature, estimated that risk at approximately 38% [13]. The baseline predictors for such reactivation have not been defined in this patient population. HBV reactivation in anti-TNF-treated patients, similarly to what has been reported in other immunosuppressed populations, can be quite severe leading to acute liver failure or even death. Based on these findings, a black box warning has been required by the US FDA in the Summary Product Characteristics of all anti-TNF agents.

The risk of HBV reactivation under anti-TNF treatment has also been reported in patients with inflammatory bowel diseases [4,14].

In a summary of studies in this setting, HBV reactivation seemed to develop practically at any time during anti-TNF therapy, as it was reported to occur just after the first infusion as well as after 2 years of anti-TNF therapy [4]. The majority of patients with inflammatory bowel disease and HBV reactivation associated with anti-TNF were receiving concomitant immunosuppressive agents, such as corticosteroids or thiopurines, suggesting that more profound immunosuppression clearly increases the risk of HBV reactivation [4,14].

The value of antiviral prophylaxis has been strongly supported by literature data showing a significant decrease in the rate of HBV reactivation under lamivudine therapy in anti-TNF-treated patients [15,16]. In a recent prospective study from our institution, only one patient (7%) among 14 HBsAg-positive patients developed viral reactivation during long-term combination therapy with anti-TNF agents and oral antivirals [16]. The reactivation in this case was due to the emergence of a lamivudine-resistant strain. Such strains usually arise during long-term lamivudine therapy in patients with chronic hepatitis B (up to 70% after 4–5 years of treatment) indicating the need for the use of oral antivirals with a low rate of resistance (entecavir and tenofovir) after prolonged therapy (>6 months) [17].

Guidelines for the use of anti-TNF agents in patients with chronic HBV infection

Currently there are no specific guidelines available for the use of anti-TNFs in patients with rheumatic diseases and coexisting chronic HBV infection. The American Association for the Study of Liver Diseases have included anti-TNF agents among the immunosuppressives that require concomitant antiviral prophylaxis (similar to chemotherapeutic agents) during short- or long-term treatment [101]. The American College of Rheumatology in its recommendations for the use of biologics in RA, suggested that anti-TNFs can be used in patients with nonadvanced liver disease (Child–Pugh class A) [18], while the European League against Rheumatism (EULAR) recommended against the use of anti-TNFs in patients with known hepatitis B infection [19]. Nevertheless, for those who are already on anti-TNF treatment and a chronic HBV infection is discovered, antiviral therapy is recommended [19].

In the absence of specific guidelines for the use of anti-TNFs in patients with chronic HBV infection, certain recommendations can be made. All patients who are scheduled or are already on anti-TNF treatment should be screened for HBV infection with standard serological assays (HBsAg, anti-HBs and anti-HBc) [19].

For patients found to be chronically infected with HBV (HBsAg positive), an individualized treatment approach, always in consultation with a hepatologist, should be followed. Treatment decisions should always take into account the serum-HBV DNA levels and the severity of HBV-related liver damage (mainly presence or absence of cirrhosis). Since for the majority of patients who require anti-TNF therapy, this will be a long-term treatment option, long-term therapy with oral antivirals will also be required. The most suitable antiviral agent in this setting has not been adequately studied. Both the American and the European Associations for the study of Liver Diseases recommend agents with low resistance rates for patients with chronic hepatitis B or cirrhosis such as tenofovir or entecavir [7,101]. As prophylaxis, however, for patients with low (<2000 IU/ml) or undetectable serum HBV DNA levels and no evidence of cirrhosis, lamivudine, which is a cheaper agent could also be used, particularly if the anti-TNF therapy may be given for ≤6–12 months. In all other HBsAg-positive patients treated with anti-TNF, tenofovir or entecavir may be safer prophylactic options. Regardless of the antiviral that is finally chosen, close monitoring of ALT and HBV DNA levels is mandatory. There are no widely accepted recommendations for such monitoring which may be based on ALT and HBV DNA determinations every 3–6 months or even closer particularly during the first months. For patients who demonstrate HBV reactivation while on antiviral/anti-TNF therapy, HBV sequencing looking for the specific drug-related resistant HBV strain needs to be performed, and that will dictate the choice of the appropriate antiviral agent.

Patients with past HBV infection (HBsAg negative but positive for anti-HBc) should be tested for HBV DNA. If they are found to have detectable serum HBV DNA, they should be treated similarly to HBsAg-positive patients. If they have undetectable serum HBV DNA, they should be followed carefully with 3-monthly ALT and HBV DNA testing during anti-TNF therapy and for 6–12 months after anti-TNF discontinuation and should be treated with an antiviral upon confirmation of HBV reactivation before ALT elevation.

Hepatitis C virus

Natural course of chronic HCV infection

HCV infection typically results from parenteral transmission either through infected syringes (as it commonly occurs among intravenous drug users) or through transfusion of blood or blood-derived products before 1992 [20]. Its worldwide prevalence is almost half of that of HBV (~3% or 180 million infected people), with certain countries showing a much higher rate (2.5–10%).

In contrast to HBV, the majority of chronic HCV infections occur during adulthood with a high chronicity rate (60–85%) after viral exposure [20]. The natural course of HCV infection is rather unpredictable, with an estimated rate to progression to advanced liver disease (cirrhosis) ranging between 5 and 30% after three decades. Factors that have been clearly associated with an increased rate of fibrosis progression include long duration of infection, excessive alcohol use, age >40 years at the time of initial infection, coexisting viral infections (such as HIV or HBV) and male sex [20].

HCV reactivation in anti-TNF-treated patients

The role of immunosuppression in the natural history of chronic HCV infection is less clear compared with chronic HBV infection [3]. From a number of observational studies, mainly in patients with HCV-associated mixed cryoglobulinemia (with or without associated non-Hodgkin's lymphoma), as well as in patients with various hematologic or neoplastic diseases who had received immunosuppressive or chemotherapeutic regimens, no signs of an increased risk for short-term HCV-related liver damage were observed [3]. For example, the short-term use of medium-dose corticosteroids has been temporally associated with an increase in serum HCV RNA levels but without any significant adverse effect on liver function. Similar data are available for chemotherapeutic agents showing no evidence of HCV reactivation and liver decompensation. Based on these data, there is no need for concomitant anti-HCV therapy in patients receiving immunosuppressive or chemotherapeutic agents.

There are limited data available for the effect of disease-modifying antirheumatic drugs commonly used in rheumatic diseases, such as methotrexate, leflunomide or cyclosporine. Overall, their administration appears to be safe in small series where carefully selected patients without significant underlying liver fibrosis were treated. Interestingly there are now more data available for the use of anti-TNF agents in patients with chronic HCV infection compared with other immunosuppressive agents [21,22]. In a recent study, Brunasso *et al.* systematically reviewed all published cases of patients with various autoimmune diseases (n = 153) who had been treated with anti-TNF agents for a mean period of approximately 1 year [21]. The majority of these patients had received etanercept (110/153, 72%). During treatment, serum HCV RNA and ALT levels did not change significantly and more importantly only two cases with confirmed or probable worsening of HCV-related liver disease were noted (1.3%) [21]. Although these data appear reassuring it should be noted that liver biopsies were rarely performed in these patients, the status of the underlying liver disease (mild-to-severe fibrosis or cirrhosis) was not always carefully evaluated and the follow-up period was rather short (~1 year).

Collectively these data emphasize that anti-TNF agents are the best studied immunosuppressive agents in patients with rheumatic diseases and concomitant chronic HCV infection and that their short-term administration does not raise any specific safety concerns. Furthermore, there are preliminary human [23] and animal [24] data that suggest that anti-TNF therapy may have an antiviral effect in HCV-infected humans or animals.

Guidelines for the use of anti-TNF agents in patients with chronic HCV infection

There are no specific recommendations for the use of anti-TNF agents in rheumatic patients with chronic HCV infection. The American College of Rheumatology in its recommendations for RA suggests, similarly to chronic HBV infection, that anti-TNFs can be used in nonadvanced HCV-related liver disease (Child–Pugh class A) [18]. In the most recent EULAR recommendations it was noted that there was "no increased incidence of toxicity associated with TNF-α blocking agent therapy" in patients with chronic HCV infection, but no specific recommendations about their use were made [19].

Future perspective

HBV

Treating patients with chronic HBV infection and a coexisting rheumatic/autoimmune disease with anti-TNF agents remains a challenging task with many unanswered questions.

Prospective studies that will address the issue of antiviral resistance in patients on long-term treatment with different oral antivirals are clearly needed in order to formulate specific guidelines. Furthermore, specific guidelines for the appropriate monitoring of these patients in a cost-efficient way are needed since the cost of HBV DNA measurement remains high.

HCV

Anti-TNF therapy appears to be safe when given for a short period of time in patients with nonadvanced HCV-related liver disease. Unanswered questions that need to be addressed in future studies include their safety during long-term administration as well as in selected patients with more advanced liver disease. Results from ongoing studies in patients with chronic HCV infection (without concomitant rheumatic disorders), where a combination of antiviral (IFN-α-based regimens) and anti-TNF therapies were tested, will provide definite evidence about the safety and potential antiviral efficacy of anti-TNF agents.

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Executive summary

- Chronic hepatitis B or C infection affects 3–6% of the general population worldwide including patients with various autoimmune diseases that require chronic anti-TNF therapy.
- Anti-TNF therapy can cause hepatitis B virus (HBV) reactivation in approximately 40% of treated patients without antiviral prophylaxis. This reactivation can be associated with severe morbidity and increased mortality.
- Recent studies have shown that oral antiviral therapy when administered in combination with anti-TNF agents can significantly decrease HBV reactivation. These data suggest that under close monitoring, anti-TNFs can be safely used in patients with chronic HBV infection.
- The administration of anti-TNF agents has not been associated with hepatitis C virus reactivation or worsening of hepatitis C virus-related liver disease in chronically infected patients. Anti-TNF agents can be given in these patients without the need for antiviral therapy but under close monitoring.

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