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REVIEW

Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: Extending perspective from old to newer drugs

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Abstract

Hepatitis B virus (HBV) reactivation in rheumatoid arthritis (RA) patients undergoing biological therapy is not infrequent. This condition can occur in patients with chronic hepatitis B as well as in patients with resolved HBV infection. Current recommendations are mainly focused on prevention and management strategies of viral reactivation under tumor necrosis factor-α inhibitors or chimeric monoclonal antibody rituximab. In recent years, growing data concerning HBV reactivation in RA patients treated with newer biological drugs like tocilizumab and abatacept have cumulated. In this review, epidemiology, pathogenesis and natural history of HBV infection have been revised first, mainly focusing on the role that specific therapeutic targets of current biotechnological drugs play in HBV pathobiology; finally we have summarized current evidences from scientific literature, including either observational studies and case reports as well, concerning HBV reactivation under different classes of biological drugs in RA patients. Taking all these evidences into account, some practical guidelines for screening, vaccination, prophylaxis and treatment of HBV reactivation have been proposed.

Key words: Rheumatoid arthritis; Hepatitis B virus; Biologics; Anti-TNF; Rituximab; Tocilizumab; Abatacept

Core tip: Hepatitis B virus (HBV) infection represents a major issue in patients with rheumatoid arthritis (RA) undergoing biological disease-modifying anti-rheumatic drugs (bDMARDs). While several observational studies and trials deal with the risk of HBV reactivation under anti-TNF agents, there is limited experience with newer drugs as tocilizumab (TCZ) and abatacept (ABA). In this paper, literature concerning the risk of HBV reactivation in RA patients undergoing different classes of bDMARDs, including ABA and TCZ, has been revised. Finally, some evidence-based practical suggestions for the management of this condition are proposed.

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INTRODUCTION

Over the last decade, the introduction of biologic drugs for the treatment of rheumatoid arthritis (RA) led to significant improvements in clinical and radiographic disease outcomes. From available scientific evidences, low disease activity or even clinical remission resulted more frequently achievable with biologic and conventional synthetic disease-modifying antirheumatic drugs in combination (bDMARDs and csDMARDs, respectively) rather than with therapeutic regimens including csDMARDs only[1]. According to the current recommendations for RA management[2-6], bDMARDs may be initiated in patients who have failed to respond to at least one csDMARD, including methotrexate (if not contraindicated). Table 1 summarizes the principal bDMARDs currently licensed for RA treatment. The first generation of biological drugs targeting specific effector molecules in RA pathogenesis is represented by tumor necrosis factor alpha (TNF-α) inhibitors (TNFI). Five agents of such class of bDMARDs are currently approved for RA: three monoclonal antibodies [infliximab (IFX), adalimumab (ADA), and golimumab (GOL)], one modified antibody Fab fragment [certolizumab pegol (CZP)] and one soluble receptor [etanercept (ETN)]. Moreover, B-cell targeted therapy with rituximab (RTX), a chimeric monoclonal antibody against CD20, a B-lymphocyte antigen that specifically depletes mature B-cells, is another well-established therapeutic option for RA treatment. Recently other therapeutic agents targeting molecules involved in RA pathogenesis have been approved: tocilizumab (TCZ), a humanized monoclonal antibody against interleukin 6 (IL-6) receptor which selectively blocks IL-6 biological effects, and abatacept (ABA), a soluble CTLA4-Fc fusion protein, that, by mimicking the cytotoxic T-lymphocyte antigen 4 (CTLA4), a negative regulator of T-cell costimulation, mainly prevents the activation of the T-cell compartment. Either anti-TNF, anti-IL-6 or costimulation blockade agents can be prescribed as first-line biologic therapies, while RTX is usually indicated as a second-line treatment option, that means for patients who failed and/or are intolerant to a first bDMARD, even if under certain circumstances, it can be considered as a first-line drug[4]. The combination therapy of a biologic agent with methotrexate (or another equivalent csDMARD such as leflunomide[7,8]) is generally more effective than monotherapy, as shown for TNFI[9], RTX[10] and TCZ[11]. Nevertheless, bDMARD monotherapy might be considered in case of contraindications for csDMARDs[12]. Biologic therapy is more effective than csDMARDs in achieving clinical response (measured by validated composite indexes) and in preventing radiographic damage as well. For instance, randomised controlled trials on TNFI show a remission rate of 50% *vs* 28% with ETN + methotrexate over methotrexate alone respectively[13]; similarly, ADA + methotrexate resulted in a remission rate of 34%, against 17% for methotrexate alone[14]. Furthermore, most evidences support the superiority of bDMARDs over csDMARDs in preventing structural and functional deterioration, even for long-term periods[14-17]. Compared to TNFI, newer bDMARDs, like TCZ and ABA, showed similar efficacy profiles, even if slight differences have been reported in specific contexts[18,19]. Despite their recognised therapeutic effects in most treated patients, biologic therapy with TNFI might result inadequate in approximately 30% of cases, thus carrying on the risk of further joint damage[20]. After TNFI failure, no particular bDMARD seems to be better than the others as second line choice[18-21].

All these drugs carry a potential for serious infective complications, especially involving the reactivation of latent infections with intracellular pathogens. This is particularly the case for latent tuberculosis, or latent infection with viruses such as Herpes Simplex Virus, hepatitis C and hepatitis B virus (HBV). The prevalence of HBV infection in patients affected by rheumatic diseases is similar to the one of the general population. In the last decade, increasing attention has been paid to the possibility of HBV reactivation in RA patients undergoing treatment with bDMARDs. Growing evidences, coming first from oncology, then from gastroenterology and rheumatology fields, suggest that HBV reactivation can occur not only in hepatitis B surface antigen (HBsAg) carriers, but also in HBsAg negative individuals presenting liver HBV-DNA with detectable or undetectable serum HBV-DNA [occult HBV infection (OBI)], during or eventually after immunosuppression. Among the available bDMARDs approved for RA, the risk of HBV reactivation under TNFI has been well-described in several observational studies. Moreover, the evidences about the well-established risk of HBV reactivation in hematological patients treated with RTX, have been replicated in several reports on RA patients. In contrast, for this topic, observational data for newer bDMARDs with different targets like ABA and TCZ are still lacking, with only a few reports published. Consequently the existing practical guidelines for the prevention and management of viral reactivation are mostly targeted to the "older" rather than to the newer bDMARDs.

In this paper, literature concerning the risk of HBV reactivation in RA patients undergoing different classes of the most commonly prescribed bDMARDs has been revised. Finally, some evidence-based practical suggestions for the prevention and the treatment of this condition are proposed.

Table 1 Four classes of immunotherapies licensed to treat rheumatoid arthritis

Class	Mode of action	Drug	Mechanism of action	Route of administration	Therapeutic regimen	Half-life	Major approved indications (FDA)
TNF inhibitors	TNF-α neutralization	Adalimumab (fully human monoclonal IgG1 antibody)	Binding to TNF	SC	40 mg every 2 wk	13 d	RA, JIA, PsA, AS, CD, UC, PP, non radiographic axial SpA
		Golimumab (fully human monoclonal IgG1 antibody)	Binding to soluble and membrane bound TNF	SC	50 mg every 4 wk	13 d	RA, PsA, AS, UC
		Certolizumab (pegilated FabI fragment of a human monoclonal antibody)	Binding to TNF	SC	200 mg every 2 wk or 400 mg monthly	14 d	RA, CD, PsA, AS, non-radiographic axial SpA
		Etanercept (p75 TNF receptor - IgG1 Fc fusion protein	Works as a decoy receptor. It binds to soluble TNF, blocking the binding to its receptor	SC	50 mg weekly or 25 mg twice a week	3-6 d	RA, PsA, AS, poliarticular JIA, PP
		Infliximab (chimeric mouse-human monoclonal IgG1 antibody)	Binding to soluble and membrane bound TNF	IV	3 mg/kg (up to 7.5 mg/kg if not effective) every 8 wk after loading at 0, 2 and 6 wk	9 d	RA, PsA, AS, CD, pediatric CD, UC, pediatric UC, PP
B-cell depletion	B-cell lysis	Rituximab (chimeric mouse-human monoclonal IgG1 antibody)	Binding to CD20 and depletion of $CD20^+$ B cells	IV	Two infusions of 1000 mg 2 wk apart. This can be repeated every 6 mo if symptoms return. Infusions are preceded by IV methylprednisolone to reduce the incidence of infusion reactions	18 d (range 5-76)	BNHL, CLL, RA, GPA, MPA
T-cell inhibition	T-cell costimulation blockade	Abatacept (extracellular domain of CTLA4-IgG1 Fc recumbinant human fusion protein)	Binding to CD80/ CD86, blocking T-cell co-stimulation	IV	500-750-1000 mg infusions (for body weight < 60, between 60 and 100 or > 100 kg) every 4 wk following three loading infusions at 0, 2 and 4 wk	13 d (range 8-25)	RA, poliarticular JIA
				SC	125 mg weekly		
IL-6 inhibition	IL-6 receptor blockade	Tocilizumab (humanized monoclonal IgG1 antibody)	Binding to soluble and membrane bound IL-6 receptor	IV	8 mg/kg every 4 wk	10-13 d	RA, poliarticular JIA, sistemic JIA

FDA: Food and Drug Administration; CTLA-4: Cytotoxic T-lymphocyte associated-antigen 4; IL-6: Interleukin 6; IV: Intraveneous injection; PEG: Polyethylene glycol; SC: Subcutaneous; TNF: Tumour necrosis factor; JIA: Juvenile Idiopathic Arthritis; PsA: Psoriatic arthritis; AS: Ankylosing spondylitis; SpA: Spondiloarthritis; CD: Chron's disease; UC: Ulcerative colitis; PP: Plaque psoriasis; BNHL: B-cell non-Hodgkin lymphoma; CLL: Chronic lymphocytic leukemia; GPA: Granulomatosis with polyangiitis (Wegener's disease); MPA: Microscopic polyangiitis.

HBV: EPIDEMIOLOGY AND NATURAL HISTORY

Chronic infection with HBV is still a significant global health problem: about 2 billion people worldwide have been infected with HBV and approximately 5% of the world population is affected with chronic HBV infection, which is the leading cause of HBV-related complications such as chronic hepatitis, HBV-related cirrhosis, and hepatocellular carcinoma (HCC), accounting for 500000 to 700000 deaths per year[22]. The geographic distribution of HBV infection can be described as follows: 88% of global population lives in areas of intermediate ($HBsAg^+$ prevalence 2%-7%) or high endemicity (> 7%) corresponding to African and East-Asian territories where most infections occur from vertical transmission; whereas the remaining 12% lives in low endemicity areas ($HBsAg^+$ prevalence < 2%), roughly corresponding to North Europe and United States, where HBV infection usually primarily occurs in adulthood[23]. In western countries the incidence of HBV infection has been furtherly diminished by widespread vaccination programs since the 1980s[24]. HBV is a partially double-stranded DNA

Table 2 Nomenclatures and definitions used in hepatitis B virus infection

Markers	Chronic inactive carrier	HBeAg positive CHB	HBeAg negative CHB	"Resolved hepatitis B"
HBsAg	+	+	+	-
HBeAg	-	+	-	-
Anti-HBe	+	-	+/-	+/-
Anti-HBs	+	-	+/-	+/-
Anti-HBc	+	+/-	+	+/-
ALT	-	+/-	+	-
Serum HBV-DNA	Undetectable/< 2000 IU/mL	Persistent/intermittent ↑ (> 20000 IU/mL)	Persistent/intermittent ↑ (> 2000 UI/mL)	Detectable or undetectable
Liver injury	+/-	Moderate/severe CHB	Minimal to severe CHB	-
Necroinflammation	No (> 90%)	Yes (> 90%)	No (> 90%)	No

CHB: Chronic hepatitis B; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; anti-HBe: Antibodies to hepatitis B e antigen; anti-HBs: Antibodies to hepatitis B surface antigen; anti-HBc: Antibodies to hepatitis B core antigen; ALT: Alanine aminotransferase.

virus transmitted by percutaneous or permucosal exposure to infected body fluids and perinatally from mother to infant. The virus genome is able to convert into a covalently closed circular form (cccDNA) that can persist lifelong into the nuclei of infected cells, leading to the likelihood of viral reactivation during or after immunosuppression[25].

Natural history of HBV infection is a dynamic process and runs throughout 4 distinct phases[26].

The immune tolerant phase is characterized by positive serum hepatitis B e antigen (HBeAg), serum HBV-DNA >10^5 copies/mL, and normal aminotransferase levels. In this phase cellular response is absent, with consequent minimal liver inflammation. After vertical infection this phase may last > 40 years (possibly leading to HBV genome integration, with decreased likelihood of viral eradication), while it is usually short-term in adults.

The HBeAg-positive immunoactive phase is characterized by a weak cellular response against infected hepatocytes, expressed by elevated aminotransferase levels (hepatitis), HBV DNA levels > 10^5 or between 10^4-10^5 copies/mL, and histological evidence of liver inflammation. As serum viral load falls, *HBe seroconversion* (from HBeAg to anti-HBe) can occur at a rate of 4%-10% per year.

Most people after HBeAg seroconversion enter the so-called HBV inactive phase, associated with a more effective cytotoxic T-cell response leading to normalization of aminotransferases and undetectable or < 2000 UI/mL serum viral load (inactive carrier state). During this phase, which may last lifelong, liver inflammation improves along with a lower risk of serious complications. Nevertheless, an estimated 20% of patients will reactivate, possibly leading to HBV-related complications: this condition, known as *HBeAg-positive* or HBeAg-negative chronic hepatitis B (CHB), is defined as HBsAg serum positivity for > 6 mo, along with serum HBV-DNA between 2000 and 20000 IU/mL or > 20000 IU/mL as well as elevated aminotransferases[26,27].

A proportion of patients develops HBsAg clearance at a rate of 0.5%-0.8% per year[28] (resolution phase). Generally in these patients only anti-hepatitis B core antigen (anti-HBc) antibodies are detectable, because protective anti-HBs antibodies can be lost in time. The concept of occult HBV infection (OBI, defined with detectable liver HBV-DNA with serum undetectable or < 200 IU/mL HBV-DNA in $HBsAg^-$ individuals) has been recently introduced to describe the underlying risk of HBV reactivation under immunosuppressive therapy[29-31]. In this phase the risk of development of cirrhosis is minimal, whereas the risk of HCC is reduced but still significant[32]. Definitions of HBV status in virological, biochemical and serological terms are summarized in Table 2.

CURRENT MANAGEMENT OF CHRONIC HEPATITIS B

Antiviral therapy is generally recommended for CHB patients who have HBV DNA levels > 2000 IU/mL, serum aminotransferases above the upper limit of normal (ULN) and moderate to severe active liver necroinflammation and/or at least moderate fibrosis[33]. Patients with alanine aminotransferase (ALT) > 2 times ULN and serum HBV-DNA > 20000 IU/mL may start treatment even without liver biopsy. The ideal endpoints of antiviral therapies are long-term suppression of viral replication, sustained HBeAg seroconversion for $HBeAg^+$ individuals, and HBsAg clearance. Long-term viral suppression can now be achieved in > 95% cases with oral nucleic acid analogues (NAs), although HBsAg loss remains a hard to achieve target (< 10%). Drugs available for the treatment of CHB include interferon-α (IFN), pegylated-INF-α2a (PEG-IFN) and six NAs, that can be classified into nucleosides (lamivudine, telbivudine, emtricitabine, entecavir) and nucleotides (adefovir and tenofovir) analogues. While IFN-based regimens, despite a good efficacy profile, lead to frequent side effects and contraindications[33,34]; oral NAs show a better safety profile. Though inexpensive, the first generation agents (such as lamivudine) are associated with a high rate of viral resistance (about 70% after 5 years), which limit their use in clinical practice. Entecavir and tenofovir are

potent HBV inhibitors with a high barrier to resistance, and they are currently recommended as first-line monotherapies. These agents have to be given either indefinitely (HBeAg$^-$ CHB) or for 12 mo following HBeAg seroconversion in HBeAg$^+$ CHB[35].

HBV REACTIVATION: DEFINITION AND RISK FACTORS

HBV reactivation in patients with chronic inactive/resolved HBV infection undergoing immunosuppressive treatment is defined as the combination of two findings: a > 1 log10 IU/mL increase in serum HBV-DNA level or the detection of previously undetectable HBV-DNA; and serum ALT elevation > 2-3 times the ULN[36,37]. The increase in liver function tests (hepatitis) usually follows viral reactivation[36]. Reactivation clinically ranges from a subclinical and transient event to severe hepatitis; in a limited proportion of patients acute liver failure and death have been reported, with a higher risk for patients affected by CHB and advanced histological injury[36].

The host serological status and HBV-DNA levels are major risk factors for HBV reactivation: HBsAg carriers are at greater risk, and the risk increases with HBV-DNA load[36,37]. For HBsAg negative patients, the risk of reactivation is considerably lower in individuals with both anti-HBc and anti-HBs antibodies[38]. The risk may be higher in the event of concomitant methotrexate therapy[38]. A variety of immunosuppressive drugs may lead to HBV reactivation: corticosteroids, cytotoxic agents, cs- and bDMARDs. In most cases reactivation occurs after treatment withdrawal, as a result of the restored immunity[39]. The liver damage due to HBV reactivation is a two-stage process: initially during intense immunosuppression an enhanced viral replication occurs as reflected by increased serum and liver HBV-DNA; then, during the subsequent immune restoration after treatment withdrawal a rapid immune-mediated destruction of HBV-infected hepatocytes overcomes, clinically manifested with hepatitis, hepatic failure and even death. In a recent retrospective study of 35 cases of HBV reactivation in patients undergoing immunosuppressive treatment for immune-mediated inflammatory disease, reactivation appeared a median of 35 wk (2-397) after treatment start, with earlier occurrence in RTX-treated and in HBsAg$^+$/HBV-DNA$^+$ patients[38]. However, earlier appearance was not associated with an increased clinical severity. Factors significantly associated with HBV-related serious complications (death and/or fulminant hepatitis) were identified in Asian ethnicity, delay from immunosuppressive therapy initiation to HBV reactivation diagnosis, HBV-DNA load and aminotransferases at HBV diagnosis. The use of specific TNFI/antiviral molecules did not differ between patient who experienced or not serious events, but patients with a poor outcome tended to receive IFX, ADA or 1st-generations NAs as compared with those with a favorable outcome (P = 0.07 and P = 0.03)[38].

ROLE OF PRO-INFLAMMATORY CYTOKINES IN HBV INFECTION

RA is a chronic inflammatory disease affecting 1% of adult population that predominantly involves the synovial membrane of diarthrodial joints. The disease is characterized by the activation of resident synovial macrophages in association with a massive synovial infiltration of lymphocytes and neutrophils, and by the local development of an inflammatory milieu, which in turn promotes the proliferation of synoviocytes and fibroblasts, and neoangiogenesis: all this leads to the production of an aberrant, hyperplastic tissue, the so-called rheumatoid pannus, and to the differentiation and activation of chondrocytes and osteoclasts and subsequent cartilage and bone destruction. Apart from macrophages and other innate immunity "effector" cell types (dendritic cells, neutrophils, synoviocytes, osteoblasts, osteoclasts, and chondrocytes), three major pathways of RA immunity response have become recognized as pivotal: B-cells, T-cells, and a wide range of inflammatory cytokines that, acting as an intricate and redundant network both systemically and locally, shift the balance towards a proinflammatory state[40]. Synovitis is ultimately driven by a number of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1. TNF-α is overexpressed in the synovial fluid of patients with RA. Moreover, TNF-α transgenic mice spontaneously develop arthritis[41]. IL-6, a typical cytokine featuring redundancy and pleiotropic activity, also plays a key role in the development of RA[42], promoting an imbalance between Th17 and regulatory T (Treg) cells and the production of autoantibodies, such as rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPA). IL-6 also promotes synovial inflammation and cartilage and bone destruction and exerts systemic effects leading to cardiovascular, psychological, and skeletal disorders.

RA was historically considered a T-cell driven disease, although adaptive humoral immunity also plays a pivotal role in its pathogenesis, as shown by the production of RF and ACPA, that are considered to be the serological hallmarks of RA. It has long been recognised that activated CD4 and CD8$^+$ T-cell subsets, B-cells, plasmablasts and plasma cells are abundant in rheumatoid synovial tissue. A substantial proportion of patients show ectopic germinal centres that may support B cell maturation and class switching and thereby promote autoantibody production[43].

HBV infection causes acute and chronic necroinflammatory hepatitis. The pathogenesis of HBV infection, similarly to that of RA, is still largely unknown. Massive hepatic injury occurring during CHB seems to be immune-mediated and depends on HBV-specific cytotoxic T-cells[44]; moreover, an efficient

control of HBV infection requires the synergic actions of both innate and adaptive immunity[45].

Innate immunity induces in HBV infected cells the production of type I interferons and several proinflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-10, some of which are reported to suppress viral replication and/or to exert non-cytolytic viral clearance. In HBV infected patients TNF-α is produced by intrahepatic leukocytes in a HBc-dependent fashion[46]. Several reports show intrahepatic and serum TNF-α elevation in patients with acute or chronic hepatitis B, suggesting a potential role in inhibiting viral replication[47]. The persistence of HBV infection may be associated with $CD8^+$ T-cell loss of the ability to secrete enough TNF-α to kill infected hepatocytes (the so-called "exhausted phenotype")[48]. Genetic polymorphisms leading to lower TNF-α expression associate with an increased risk of HBV chronicization[49]. It has been recently demonstrated that in TNF-α knockout mice and in ETN-treated mice HBV infection persists, with subsequent increase in HBV-specific $CD8^+$ T-cells, serum and liver HBV-DNA, and antigen expression. Thus in this animal model TNFI may be able to suppress HBc-dependent viral clearance effects[49]. However, in patients with CHB this cytokine may contribute to liver injury[50]. Other cytokines, like IL-1, might be involved in the natural history of HBV infection but data concerning their real role and meaning are still most elusive[51,52].

Cellular immunity is critical for the outcome of HBV infection, too: HBV-specific T-cells are involved in the control of viral infection, whilst non-specific NK cells infiltrate the liver leading to hepatocellular injury[53]. In humans, IL-6 in combination with TGF-β and IL-1β drive naive $CD4^+$ T-cell to differentiate into Th17 cells in a HBc-dependent fashion[54]. Th17 cells can produce multiple cytokines that trigger the recruitment and activation of neutrophils leading to massive tissue inflammation[55]. Recent reports showed that in CHB patients antigen non-specific Th17 response is increased and that the peripheral Th17 frequency is associated with the degree of liver damage[56,57]. A recent study revealed that the increased Th17 response in CHB patients correlates with the enhanced IL-6 receptor (IL-6R) expression on $CD4^+$ T-cells, suggesting IL-6R as a potential novel target for CHB immunotherapy[58]. In addition, several studies demonstrated that IL-6 facilitates *in vivo* and *in vitro* HBV infection[59] and might be able to predict the development of HCC in HBV infected patients[60]. However, conclusive data are still lacking and the immunosuppressive action of the anti-IL-6R antibody TCZ might actually play a detrimental role.

CTLA-4, an inhibitory receptor expressed by activated T-cells that acts as a negative regulator of T-cell responses seems to be involved in HBV infection: studies in humans suggest an influence of CTLA4 polymorphisms in HBV clearance, HBV-related carcinogenesis and HBV reactivation after immunosuppression, but the underlying mechanisms are still unclear[61-63].

Recent reports suggest that humoral immunity plays an important role in the immune response to HBV. HBcAg is able to directly activate B-cells to produce specific antibodies in the absence of regulatory T-cells[64]. In patients with $HBeAg^-$ CHB, $CD20^+$ B-cells infiltrate the liver and correlate with histologic necroinflammation and fibrosis[65]. However, immunosuppression and B-cell suppression are associated with viral reactivation. B-cells are thus involved in liver inflammation in HBV infected patients, but whether their influence on disease progression is harmful or beneficial is still unknown.

SAFETY OF BMARDS IN PATIENTS WITH COMORBID HBV INFECTION

While in the last decade an amount of data has been cumulated regarding the effect of TNFI and RTX on RA patients with CHB or even OBI; the likelihood of HBV reactivation in patients undergoing newer bDMARDs TCZ and ABA has been more recently described. Available evidences stratified by bDMARDs about this topic will be exposed in the following sections.

ANTI-TNF AGENTS

It has been 11 years since the first reports of HBV reactivation after TNF-α blockade have been reported[66,67]; since then, a cumulative evidence from case reports and small retrospective or prospective studies has been collected[68-81]. TNFI-induced immunosuppression is able to decrease HBV antigen presentation: the abrupt increase in viral presentation at treatment discontinuation induces an acute cytotoxic response, which can cause extremely severe hepatitis. Table 3 summarizes the observational studies of HBV reactivation in RA patients undergoing TNFI. A distinction has to be made between CHB patients ($HBsAg^+$) and patients with resolved infection ($HBsAg^-$/anti-HBc^+).

Patients with chronic HBV infection ($HBsAg^+$)

In a 2011 review of 87 published cases of TNFI-treated CHB patients, Perez-Alvarez et al reported an HBV reactivation rate of 38%[76], similar to that observed under chemotherapy (50%)[36]. Half of the patients had received IFX, 33% ETN and 17% ADA. In most cases (about 75%), viral reactivation was accompanied by an increase in aminotransferase levels. Among patients with severe reactivation, 5 developed liver failure and 4 died from HBV-related complications. Interestingly, only 25% of the patients who developed HBV reactivation had received antiviral prophylaxis, compared to 62% of those who didn't experience viral reactivation. Apart from potential publication bias, these data indicate an increased risk of HBV

Table 3 Hepatitis virus B reactivation in rheumatoid arthritis patients receiving tumor necrosis factor-α inhibitors: studies in patients with markers of chronic or remote hepatitis virus B infection

Ref.	Study design	Target population	No. of patients	Treatment	Antiviral Prophylaxis	HBsAg$^+$	Anti-HBc$^+$ and anti-HBs$^-$	Anti-HBc$^+$ and anti-HBs$^+$	HBV-DNA$^+$	Anti-HBs$^+$/ anti-HBc$^-$	Reactivation
Carroll *et al*[69]	Case series	Rheumatic pts or pts with IBD with CHB	13	11 treated with IFX, 2 treated with ETN	Lamivudine	13 pts (100%)	-	-	-	-	7 cases with IFX, 2 cases with ETN
Charpin *et al*[70]	Prospective	RA (12)/SpA (9) pts with resolved HBV infection	21	4 treated with IFX, 14 with ETN, 3 with ADA	0 pts	0 pts	0 pts 100% (with 3 pts < 100 UI/mL)		0 pts	-	Mean decrease in anti-HBs titre 8%; no cases of HBV reactivation
Chung *et al*[71]	Retrospective	RA (41), SpA (60), JIA (2) pts	103	TNFα inhibitors	0 pts	8 pts	-	-	0 pts	-	1/8 HBsAg$^+$ (12.5%) after 6 wk of IFX
Caporali *et al*[72]	Prospective	RA (59), SpA (8) pts with resolved HBV infection	67	25 treated with IFX, 23 with ETN, 19 with ADA	0 pts	0 pts	46 pts	28 pts	0 pts	-	No cases of HBV reactivation
Vassillopoulos *et al*[73]	Prospective	RA (66), SpA (64), other (1) patients with actual/remote HBV infection or vaccinated for HBV	131	43 treated with IFX, 64 with ETN, 62 with ADA	14 pts (100% of CHB group): 11 with lamivudine, 2 with entecavir, 1 with telbivudine	14 pts	19 pts		0 pts among CHB group	19 pts (vaccinated)	No cases of HBV reactivation in pts with resolved HBV infection. In vaccinated pts, slight decrease in anti-HBs titres (median 163 > 105 IU/mL, $P = 0.01$). Among CHB pts, 1 (7%) treated with Lamivudine + ETN developed HBV reactivation due to a resistant mutant strain
Mori *et al*[74]	Prospective	RA pts with actual/remote HBV infection	239	9 treated with IFX, 18 with ETN, 2 with ADA, 5 with TCZ, 28 with csDMARDs	2 (100% of HBsAg$^+$ pts) with entecavir	2 pts	60 pts		0 pts	-	2 cases of HBV reactivation in anti-HBc$^+$ pts (3.3%), 1 with csDMARDs and 1 with ADA
Tamori *et al*[75]	Prospective	RA pts with positive anti-HBc	50	22 treated with IFX, 20 with ETN, 2 with ADA	Entecavir	5 pts	45 pts		-	-	2/5 (40%) cases of HBV reactivation among HBsAg$^+$ pts; 1/45 (2%) cases of HBV reactivation among HBcAb$^+$/HBsAg$^-$ pts, not under TNFI
Pérez-Alvarez *et al*[76]	Systematic review	TNFI-treated pts	257	Anti-TNF (not specified)	Not specified	89 pts	168 pts		-	-	HBV reactivation in 35 (39%) pts among HBsAg+ group, fatal in 4 cases. Lower risk if pre-emptive NAs (23% *vs* 62%, $P = 0.003$). Higher risk with IFX *vs* ETN. Nine cases (5%) of HBV reactivation in HBcAb$^+$/HBsAg$^-$ pts, fatal in 1 pt
Lan *et al*[77]	Prospective	RA anti-HBc$^+$ pts	88	40 pts treated with ETN, 48 with ADA	10 HBsAg$^+$ pts treated with lamivudine	18 pts	12 pts	58 pts	0 pts	22 pts (vaccinated)	Among HBsAg+ pts, no cases of HBV reactivation if pre-emptive NAs; mean decrease in HBV-DNA = 153 IU/mL ($P < 0.001$); 5/8 cases of reactivation without antivirals. 1 case of HBV reactivation in the HBsAg-/anti-HBs- group
Lee *et al*[78]	Systematic review	HBsAg$^+$ rheumatic disease-positive pts	122	14 pts treated with IFX, 56 with ETN and 25 with ADA	48 pts (drug not specified)	122 pts	-	-	Not specified	-	15 cases (12.3%) of HBV reactivation, including 1 SpA patient treated with pre-emptive lamivudine
Lee *et al*[79]	Systematic Review	HBsAg$^-$/anti-HBc$^+$ rheumatic disease-positive (RA 327, SpA 121) pts	468	100 pts treated with IFX, 269 with ETN and 95 with ADA	Not specified	0 pts	Not specified	Not specified	Not specified	-	8 cases (1.7%) of HBV reactivation, 7 with ETN and 1 with ADA; satisfactory clinical outcomes with antiviral therapy

Droz *et al*[38]	Retrospective	Pts with immune-mediated inflammatory diseases (RA 14, CTD 7, vasculitis 5, other 9) developing HBV reactivation	35	7 pts treated with TNF-α inhibitors (not specified), 4 with RTX, 1 with ABA, 1 with TCZ, the others with steroids and/or other immunosuppressants	5 pts (drug not specified)	23 pts	12 pts		Not specified	-	Reactivation occurred a median of 35 wk after therapy start. 88.6% were asymptomatic; 25.7% had severe hepatitis. Management were NAs in 91.4% cases and decrease/withdrawal of immunosuppressants in 45.7%. Pooling these data with literature, earlier reactivation for RTX and HBsAg/HBV-DNA$^+$ pts
Ye *et al*[80]	Prospective	Inflammatory arthritis pts (50 RA, 37 SpA)	87	TNFα inhibitors: 56 treated with IFX, 31 with ETN)	4 pts among CHB group , 9 pts among inactive carriers (not specified)	37 (6 HBV-DNA+, 31 HBV-DNA-) pts	50 pts		Not specified	-	2 cases of HBV reactivation among CHB pts not receiving pre-emptive NAs, none in those receiving it. Among inactive HBsAg carriers, 6 cases of reactivation in pts who didn't receive NAs, none in those who did. No cases in HBsAg$^-$ pts
Nakamura *et al*[81]	Retrospective	RA	57	48 treated with TNFα inhibitors (including 9 receiving also TCZ); 7 with TCZ alone and 2 with TCZ and ABA	0 pts	0 pts	11 pts	38 pts	0 pts	8 pts (not vaccinated)	HBV-DNA detected in 3 pts (5.3%), 2 receiving TCZ and 1 receiving ETN, with serum HBV-DNA < 2,1 log copies/mL, and subsequent undetectable HBV-DNA within months

Pts: Patients; CHB: Chronic hepatitis B; IFX: Infliximab; ETN: Etanercept; IBD: Inflammatory bowel disease; SpA: Spondyloenthesoarthropaties (psoriatic arthritis included); csDMARDs: Conventiona Synthetic disease-modifying antirheumatic drugs; JIA: Juvenile idiopathic arthritis; TCZ: Tocilizumab; NAs: Nuclet(s)ide analogues; CTD: Connettive tissue disease; RTX: Rituximab; ABA: Abatacept. Adapted from Lunel-Fabiani *et al*[82] *Joint Bone Spine* 2014.

reactivation in TNFI-treated CHB patients, particularly without proper antiviral prophylaxis. In a 2010 prospective study 14 HBsAg$^+$/anti-HBc$^+$/anti-HBs$^-$ patients, 8 classified as inactive HBsAg carriers and 6 suffering from active CHB, were treated with combination therapy with oral NAs and TNFI: antiviral prophylaxis could prevent viral reactivation in > 90% of cases[73]. Only one active CHB patient developed HBV reactivation (7%) after 3-year prophylactic lamivudine: viral sequencing indicated a resistant mutant strain, as frequently happens during long-term lamivudine administration. Lee *et al*[78] have recently reported 15 HBV reactivation cases (12.3%) in a systematic review of 122 HBsAg$^+$ rheumatic patients undergoing TNFI or csDMARDs. 10/15 patients provided clinical data: 4 cases occurred in RA patients (none treated with TNFI) and no HBV-related complication occurred. Percent of 39.3 patients had received pre-emptive NAs. Similarly, a recent prospective study reported in a cohort of 37 HBsAg$^+$ patients with inflammatory arthritis a reactivation rate of 33.3% without pre-emptive antiviral prophylaxis with no cases in patients treated with NAs. Of the 6 CHB patients (HBV-DNA > 10^5 copies/mL, elevated ALT), both of the 2 patients not receiving oral NAs developed viral reactivation; and the other 4 treated with pre-emptive NAs showed no viral replication. In the 31 inactive HBsAg carriers (HBV-DNA < 10^4 copies/ml, normal ALT), out of the 22 patients not receiving NAs, a transient HBV-DNA increase was detected in 4 cases, with a gradual viremic normalization after therapy withdrawal. No cases were detected in the 9 inactive carriers receiving antiviral prophylaxis[80]. It is currently unknown whether different TNFI affect HBV reactivation to different extents. The risk may be lower with ETN, whose affinity for TNF-α is lower; whilst IFX seems to be more frequently associated with HBV reactivation[70]. A possible explanation could be that IFX administration scheme at intervals of 8 wk may result in a cytokine wash-out leading to a possible "immune-reconstitution" effect[82].

Patients with resolved HBV infection (HBsAg-/anti-HBc$^+$)

Data from oncology and hematology indicate that HBV reactivation occurs in < 5% of patients with resolved HBV infection treated with chemotherapy[83,84]. Similar data among rheumatic patients have cumulatively been published in recent years. In two prospective studies from Southern Europe no cases of HBV reactivation among 88 TNFI-treated patients with remote HBV infection were described[70,72] although none of these patients had detectable HBV-DNA at baseline. Similarly, in a retrospective taiwanese study[84] no reactivation was observed among 58 HBsAg$^-$/anti-HBc$^+$/anti-HBs$^+$ patients under TNFI, although one case of HBV reactivation was recorded between 12 HBsAg$^-$/anti-HBc$^+$/anti-HBs$^-$ patients, involving a patient with detectable baseline HBV-DNA. These data suggest that the risk of HBV reactivation is rather low in anti-HBc$^+$/anti-HBs$^+$ patients, although the likelihood of this event could be higher for HBV-DNA$^+$ and/or for anti-HBs$^-$ patients. A chinese prospective study did

not report any reactivation case in 50 TNFI-treated patients with resolved HBV infection and inflammatory arthritis[77]. Lee *et al*[79] have recently reported in a systematic review of 468 anti-HBc$^+$/HBsAg$^-$ rheumatic patients undergoing TNFI a reactivation rate of 1.7%. Out of 8 cases, 7 were RA patients, and in all cases clinical outcome was satisfactory. In a japanese prospective study of 50 RA HBcAb$^+$ patients treated with csDMARDs and/or TNFI, reactivation occurred in only 1 out of 45 HBsAg$^-$ patients (2.2%), treated with csDMARDs only. Interestingly, in TNFI-treated patients, anti-HBs titres decreased significantly in the middle- and low-titer groups (P = 0.032 and P = 0.007), remaining high in high-titer group (P = 0.875), but did not became negative in any patient[75]. It remains to be clarified whether a long period of TNFI therapy in RA patients induces the disappearance of anti-HBs leading to viral reactivation as well as in hematological field. A recent japanese retrospective study of 244 HBsAg$^-$/anti-HBc$^+$ RA patients, HBV-DNA was detected in three patients (5.3%), only one receiving a TNFI, particularly ETN (out of a total of 48 TNFI-treated patients indicating a 2.1% reactivation rate). Reactivation consisted in a subclinical, transient HBV-DNA elevation, subsequently turning undetectable within months[81]. Even if limited by a possible publication bias, these data indicate that HBV reactivation in patients with serological markers of past HBV infection is a quite rare event and that for these patients no specific prophylaxis is required.

Vaccinated patients

As suggested by a prospective study, a possible decrease in anti-HBs titer in TNFI-treated patients with remote HBV infection can occur[70], but this might not be systematically followed by viral reactivation such as in hematological field[85]. Similarly, in a prospective study of 19 HBV vaccinated patients a slight decrease in anti-HBs levels during TNFI treatment was reported[73], although a comparable decrease was observed in patients treated with methotrexate alone, indicating no specific effect of TNFI on HBV protective immunity.

RTX

A growing scientific literature indicates high rates of HBV reactivation in patients undergoing RTX for hematological diseases not receiving proper antiviral prophylaxis, ranging from 27% to 80% in HBsAg$^+$ patients[39] and from 3% to 25% in HBsAg$^-$/anti-HBc$^+$ patients, with higher risk for anti-HBs$^-$ individuals[86,87]. Reports of HBV reactivation in rheumatic patients treated with RTX are summarized in Table 4. There are limited data regarding the safety of RTX in rheumatic CHB patients[68]; although, the efficacy of pre-emptive NAs (mainly lamivudine) in preventing reactivation in HBsAg$^+$ patients treated with RTX appears to be similar to that observed in patients under chemotherapy, with a reactivation rate of 0%-13%[68]. Three recent reports from Southern Europe have described HBV reactivation in RA patients undergoing RTX, occurring not only in HBsAg carriers but also in two patients with resolved HBV infection. The first patient experienced HBV reactivation 1 mo after RTX administration, even though she had been receiving pre-emptive lamivudine for CHB. Lamivudine was thus switched to tenofovir with aminotransferases and HBV-DNA normalization[88]. In the second report, a RA patients with resolved HBV infection experienced HBV reactivation following 2 years of therapy, 3 mo after the last RTX infusion. RTX was then withdrawn and entecavir initiated, with a gradual amelioration of aminotransferase levels and HBV-DNA normalization[89]. The third report involved a HBsAg$^-$/anti-HBc$^+$/HBV-DNA- RA patient that developed HBV reactivation with subsequent acute hepatitis after 2 years of RTX + methotrexate combination therapy. Discontinuation of immunosuppressive treatment and antiviral therapy with entecavir resulted in the control of HBV infection within a few months[90]. A 2013 prospective study did not report any case of HBV reactivation under RTX neither in a series of 2 HBsAg$^+$/HBV-DNA$^-$ rheumatic patients treated with antiviral prophylaxis nor in a series of 12 HBsAg$^-$/anti-HBc$^+$ rheumatic patients, indicating a quite safe profile[91]. Interestingly, in the 4 patients with history of HBV vaccination, a slight decrease in antibody titers that did not reach statistical significance was noted. However, antibody titers did not fall below protective levels[92]. Droz *et al*[38] reported other 4 cases of HBV reactivation under RTX in patients affected with inflammatory diseases; indicating an earlier timing of viral reactivation for patient receiving anti-CD20 treatment.

NEWER BDMARDS

TCZ

There is limited experience with TCZ, a humanized anti-IL-6 receptor antibody, among HBV-infected RA patients (Table 5). Nagashima *et al*[92] reported that TCZ was administered safely and effectively in a RA patient affected with CHB, not recognised at baseline since serological screening for HBV had not been performed. In another case report, a patient with active RA stopped IFX due to HBV reactivation (pre-treatment viral status unknown). She was then treated with lamivudine until HBV-DNA turned undetectable, and later started TCZ; this resulted in a prompt disease control together with persistently normal serum aminotransferases and undetectable HBV-DNA[93]. A similar report regarding a CHB patient with adult-onset Still's disease indicates an excellent disease control with no viral reactivation by introducing TCZ after complete viral control with entecavir[94]. A recent retrospective study from Nakamura et al described 2 cases of HBV reactivation in RA patients undergoing TCZ without pre-emptive antivirals (out of a total of 18 TCZ-treated HBsAg$^-$/anti-HBc$^+$ patients, with a

Table 4 Case reports and studies of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing rituximab

Ref.	Study design	Patients charachteristics	Therapy	Baseline virological status	Timing of HBV reactivation	Antiviral Therapy	Results	Comments
Pyrpasopoulou *et al*[88]	Case Report	56-year-old female RA pt starting RTX after 3 anti-TNF (ETN, IFX, ADA) and ABA. Previous diagnosis of CHB	RTX Antiviral prophylaxis with lamivudine	$HBsAg^+$, $anti\text{-}HBe^+$	1 mo after first RTX administration	Tenofovir + lamivudine RTX withdrawal	Good clinical, serological and virological response	-
Ghrénassia *et al*[89]	Case Report	78-year-old with RA test+ and erosive RA starting RTX after IFX because of a concomitant diagnosis of lymphoma	RTX monotherapy	$HBsAg^-$/$anti\text{-}HBc^+$	9 mo after RTX starts	Entecavir RTX withdrawal	Good clinical, serological and virological response	-
Gigi *et al*[90]	Case Report	64-year-old female RA pt starting RTX as a first-line bDMARD	RTX + methotrexate	$HBsAg^-$/$anti\text{-}HBc^+$	2 yr after RTX start	Entecavir RTX withdrawal	Good clinical, serological and virological response	-
Mitroulis *et al*[91]	Prospective study	41 rheumatic pts (34 RA; 7 others) who had received ⩾ 1 cicle of RTX and had ⩾ 6 mo of follow-up	17 pts treated with concomitant methotrexate, 35 with concomitant steroids. 2 pts treated with NAs without HBV reactivation	23 pts not HBV exposed; 4 vaccinated pts; 12 $HBsAg^-$/$anti\text{-}HBc^+$ (9 $anti\text{-}HBs^+$); 2 pts $HBsAg^+$ $anti\text{-}HBc^+$. HBV-DNA undetectable in all pts	No cases of viral reactivation observed	-	-	Slight decrease in anti-HBs titres in vaccinated pts ($P = 0.29$), never under protective levels
Droz *et al*[38]	Retrospective (subgroup analysis)	4 pts affected with immune-mediated inflammatory disease treated with RTX	Not specified	Not specified	4 cases of HBV reactivation a median of 35 wk after therapy start (global data)	Not specified	No cases of fulminant hepatitis	Early reactivation with RTX and in $HBsAg^+$/$HBV\text{-}DNA^+$ pts (global data)

Pts: Patients; ETN: Etanercept; IFX: Infliximab; ADA: Adalimumab; ABA: Abatacept; CHB: Chronic hepatitis B; bDMARD: Biological disease-modifying antirheumatic drug; NAs: Nucleot(s)ide analogues; RTX: Rituximab; HBsAg: Hepatitis B surface antigen.

reactivation rate of 11.1%): in both patients HBV-DNA rised but remained below quantitation limits (< 2.1 log copies/mL), and then it spontaneously turned undetectable, along with normal aminotransferases throughout the entire period of follow-up: such data might suggest the possibility of a transient HBV-DNA fluctuation during the first 3-6 mo of TCZ, which doesn't necessarily lead to *de novo* hepatitis and possibly resolves within a few months[81]. This evidence suggests that TCZ, if co-administred with pre-emptive NAs, could be a treatment option for RA HBV carrier patients when disease activity is uncontrolled with csDMARDs. However, periodic monitoring of liver function tests and HBV-DNA is mandatory.

Abatacept

Studies regarding HBV reactivation in rheumatic patients undergoing ABA are summarized in Table 6. A recent monocentric retrospective study has been performed including 8 ABA-treated RA patients showing active CHB ($n = 2$) or inactive HBsAg carriers ($n = 6$)[95]. All patients not receiving antiviral prophylaxis ($n = 4$), which were all inactive HBsAg carriers at baseline, experienced viral reactivation, with a > 10 fold increase of HBV-DNA. None of the NAs-treated patients (3 with entecavir and one with tenofovir) had viral reactivation. Moreover, patients who had been receiving both ABA and NAs showed a statistically significant improvement in DAS28 compared to those without prophylaxis ($P = 0.025$). This is the first study suggesting that the use of ABA in RA/CHB patients appears to be safe and efficacious as long as pre-emptive antiviral prophylaxis is properly given. A case of severe hepatitis due to HBV reactivation has been reported in a RA patient with resolved HBV infection ($HBV\text{-}DNA^-$) previously

Table 5 Case reports of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing tocilizumab

Ref.	Study design	Patient charachteristics	Therapy	Basal virological Status	Timing of HBV reactivation	Antiviral Therapy	Results	Comments
Nagashima *et al*[92]	Case Report	60-year-old female RA pt, RA test and ACPA positive with erosive disease, starting TCZ after IFX and methotrexate	TCZ + steroids	HBsAg-10 yr before TCZ start, basal serological screening not performed	6, 5 years after TCZ start	Entecavir Ongoing TCZ	Subclinical, good serological and virological responses	Diagnosis made by detection of persistently high serological markers in an asymptomatic pt without liver function tests' alterations
Tsuboi *et al*[93]	Case Report	59-year-old female RA pt initially treated with IFX thus withdrawn for HBV reactivation	IFX and then TCZ (after HBV reactivation)	Serological screening not performed before IFX. At 5th IFX infusion $HBsAg^+/HBV\text{-}DNA^+/HBeAg^+$	32 wk after IFX start	Lamivudine Ongoing TCZ	Good clinical, serological and virological response until 2 years after TCZ start	-
Kishida *et al*[94]	Case Report	Adult-onset Still's disease pt affected with CHB	TCZ + ongoing entecavir	$HBsAg^+$	No reactivation observed	-	Good clinical, serological and virological response until end of follow-up	-
Nakamura *et al*[81]	Retrospective	Among 9 RA pts treated with TCZ (7 with TCZ alone and 2 with TCZ and ABA in sequence), 2 cases of HBV reactivation were detected: (a) 75-year old male pt starting TCZ as a first line therapy	TCZ monotherapy	$HBcAb^+$ Undetectable HBV-DNA	4 mo after TCZ start	-	Subclinical, subserological, good virological response	HBV-DNA fluctuated always < 2, 1 log copies/mL throughout 4 mo until it became persistently undetectable, even after switch to ETN (due to lack of efficacy)
		(b) 55-year-old female pt starting TCZ after IFX and ETN	TCZ + methotrexate	$HBcAb^+$ Undetectable HBV-DNA	2 mo after TCZ start	-	Subclinical, subserological, good virological response	HBV-DNA fluctuated always < 2, 1 log copies/mL throughout 5 mo until it became persistently undetectable, even after switch to ADA (due to lack of efficacy)
Droz *et al*[38]	Retrospective (subgroup analysis)	1 pt affected with immune-mediated inflammatory disease treated with TCZ	Not specified	Not specified	median of 35 wk after therapy start (global data)	Not specified	No cases of fulminant hepatitis	Early reactivation in $HBsAg^+/HBV\text{-}DNA^+$ pts (global data)

Pts: Patients; ACPA: Anti-citrullinated peptide antibodies; IFX: Infliximab; CHB: Chronic hepatitis B; ABA: Abatacept; ETN: Etanercept; HBsAg: Hepatitis B surface antigen; TCZ: Tocilizumab; HCV: HCV: Hepatitis B virus.

treated with a TNFI without antiviral prophylaxis and then with ABA, leflunomide and steroids. Nine month after the first ABA infusion, she experienced viral reactivation with liver function tests increase; this led to suspension of biological therapy. As expected, liver function tests continued to increase along with the gradual T-cell immune reconstitution, with a time lag of 2 mo between ABA withdrawal and viral flare. She was then treated with tenofovir with gradual amelioration of aminotransferases and undetectable HBV-DNA[96]. Another case of HBV reactivation in a RA patient with resolved HBV infection (basal HBV-DNA unknown) undergoing ABA was lately reported: 10 mo after treatment start, HBsAg turned positive along with a rise in HBV-DNA; treatment was then stopped and tenofovir was started, with a gradual amelioration of liver function tests and HBV-DNA within a few months[97]. In a recent italian case series of 9 RA patients treated with ABA (8 with resolved HBV infection and 1 chronic inactive carriers), one patient with comorbid HCV chronic infection started lamivudine for liver function tests elevation (< 2-fold ULN) occurring 2 mo after ABA initiation, with a gradual amelioration of lab levels

Table 6 Case reports of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing abatacept

Ref.	Study design	Patients characteristics	Therapy	Basal virological status	Timing of HBV reactivation	Antiviral therapy	Results	Comments
Kim *et al*[95]	Retrospective	8 RA pts affected with CHB	ABA + pre-emptive NAs (4 pts: 3 with entecavir and 1 with tenofovir) ABA without antiviral prophylaxis (4 pts)	$HBsAg^+$ Detectable HBV-DNA in 3/8 pts	Not specified	Not specified	Among pts receiving NAs, no cases of HBv reactivation. Among pts without antiviral prophylaxis, all pts experienced HBV reactivation	Among pts receiving NAs, a statistically significant improve in DAS28-ERS was detected; which was not noted in the control group
Germanidis *et al*[96]	Case Report	72-year-old female RA pt starting ABA after ADA	ABA + leflunomide	$Anti\text{-}HBc^+$/ $HBsAg^-$/$anti\text{-}HBs^+$/$anti\text{-}HBe^+$	6 mo after ABA start	ABA and leflunomide withdrawal Consequent anviral treatment with tenofovir (12 about 1 yr later)	Good clinical, serological and virological response to tenofovir	2 mo time lag between ABA withdrawal and liver tests flare, suggesting that HBV reactivation evolved in parallel with T cell immune reconstitution
Fanouriakis *et al*[97]	Case report	68-year-old female RA pt with erosive disease	ABA + methotrexate	$HBsAg^-$/$anti\text{-}HBc^+$ Basal HBV^- DNA unknown	10 mo after ABA start	Tenofovir ABA withdrawal	Good clinical, serological and virological response	-
De Nard *et al*[98]	Case series	9 RA pts treated with ABA	ABA 8/9 pts treated with concomitant methotrexate Lamivudine in 2 pts (1 $HBsAg^+$ and 1 $HBsAg^-$) from baseline, and in 1 pt with comorbid HCV infection after ABA start	8 $HBsAg^-$/$anti\text{-}HBc^+$ 1 $HBsAg^+$/$HBV\text{-}DNA^-$	1 pt with comorbid HCV infection experienced aminotransferases elevation (< 2 x ULN) 2 mo after ABA start 1 pt with resolved HBV infection not receiving NAs developed HBV-DNA positivation 12 mo after ABA start	Lamivudine Ongoing ABA Ongoing ABA No prophylaxis	Subclinical, gradual amelioration of liver function tests, persistently undetectable HBV-DNA ConsecutiveHBV-DNA fluctuations; no flares in liver function tests even after entecavir initiation at 24 mo while switching to ADA (unpublished data)	No cases of HBV reactivation among pts receiving pre-emptive NAs
Droz *et al*[38]	Retrospective (subgroup analysis)	1 pt affected with immune-mediated inflammatory disease treated with ABA	Not specified	Not specified	median of 35 wk after therapy start (global data)	Not specified	No cases of fulminant hepatitis (global data)	Early reactivation in $HBsAg^+$/$HBV\text{-}DNA^+$ pts (global data)

Pts: Patients; CHB: Chronic hepatitis B; NAs: Nucleot(s)ide analogues; ADA: Adalimumab; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis B virus.

along with persistently undetectable viral load. Other 2 patients (1 chronic inactive carrier and 1 with resolved infection) underwent lamivudine before ABA with no HBV-related adverse event, whilst among the other 6 HBsAg- patients not receiving antiviral prophylaxis only 1 developed HBV-DNA positivity (85 UI/mL) without aminotransferase elevation at 12 mo[98], with subsequent fluctuations of viral load, turning initially negative at 18 mo and then rising again at 24 mo (290 UI/mL) without liver function tests alterations and without specific antiviral treatment. After infectivologist consult the patient thus started entecavir, concomitantly with switch to adalimumab for arthritis flare, with undetectable HBV-DNA 3 mo after TNFI start (unpublished data).

CONCERNS ABOUT HBV VACCINATION

Hepatitis B vaccine (HBVv) is a recombinant DNA vaccine that provides protection against HBV infection and its complications, including cirrhosis and HCC[99]. As more than 1 billion doses of vaccine have been used

since 1982, it is considered to be safe[100]. Vaccination scheme usually involves 3 booster injections and is currently indicated for high risk patients: newborns, health care workers and adults presenting conditions of immunosuppression or behavioral risk factors (multiple sexual partners, drug abusers, travelers to endemic areas)[100].

Some concerns have been raised on the possible development of autoimmune adverse events after HBVv: cases of multiple sclerosis, Guillain-Barre syndrome, idiopathic thrombocytopenic purpura, optic neuritis, glomerulonephritis, transverse myelitis, vasculitis, systemic lupus erythematosus diagnosis or flare-up[101,102] and even the so-called autoimmune/inflammatory syndrome induced by adjuvants[103] have been reported[104]. Conflicting data about a possible association with HBVv and arthritis (RA or other) diagnosis or flare-up have been reported in 32 cases and 3 controlled studies. In one study HBVv, compared to rubella vaccination, showed an increased risk of chronic arthritis incidence (attributable risk 5.1-9.0)[105]; whilst two studies comparing the risk of RA flare following HBVv with RA controls[106] or with RA prevalence in the same community[104] did not find a significant association between HBVv and the risk of arthritis. Interestingly, in one of these studies a decreased efficacy of HBVv in RA patients was noticed[106]. These results do not provide solid scientific data to support the existence of a causal link between arthritis and HBVv: the most likely explanation still remains the coincidental temporal association. However, in a panorama of decreasing worldwide incidence of hepatitis B, mainly due to immunization programs, a recent "anti-vax" misconception is concentrating public attention and the media on vaccine adverse events rather than on prevention and control, which may lead to lower vaccine coverage and subsequent community wide outbreaks.

Routine vaccination before biotherapy initiation in patients with negative screening tests seems to be obviously appropriate; nevertheless, in patients affected with autoimmune diseases some precautions should be taken[78]: the risk of infection must be weighed against the theoretical risk of vaccine side effects, according to each patient's profile (age, family history, risk factors, *etc.*)[107]. On the other hand, HBVv administration may delay biotherapy initiation, and the immune response may be blunted in patients affected with chronic arthritis taking immunosuppressants[107]: if we consider that a single injection is insufficient to induce protective immunization, if the following injections are administered under TNFI (most of all IFX and to a lesser degree ETN), they often fail to generate an immune response[108]. Since the risk of contracting HBV during adulthood is low, except for high-risk situation, HBVv might be postponed. In contrast, in high risk patients, particularly the younger ones, HBVv should be administered before treatment initiation[109]. In patients with resolved HBV infection and insufficient antibody protection (anti-HBc$^+$/anti-HBs$^-$), a booster injection might be given to strengthen immunization[109] and to induce the production of protective anti-HBs, whose titer should be then measured.

RECOMMENDATIONS FOR CLINICAL MANAGEMENT OF RA PATIENTS WITH CHRONIC/RESOLVED HBV INFECTION UNDERGOING BDMARDS

Since proper prospective studies comparing different screening and treatment options for HBV-infected RA patients starting bDMARDs therapy are lacking, only expert-opinion-based suggestions can be made[2-4,6,33,38,68,82].

Screening

As stated by all the recent recommendations, all patients starting bDMARDs should be screened for HBV infection with HBsAg, anti-HBc and anti-HBs antibodies, as well as HBV-DNA load and liver function tests in patients found to be positive[2-4,6,68,82]. Considering the cost of chronic bDMARD therapy and the potential for serious HBV-related complications, such screening results to be cost-effective. Recent studies have shown that only 69% of US rheumatologists routinely performs universal HBV screening before biologic therapy[110]. When the results indicate active/remote HBV infection, a full battery of liver tests must be obtained, and it is appropriate to consult an hepatologist to evaluate whether antiviral treatment or prophylaxis is indicated before starting bDMARDs therapy[68].

Vaccination

As stated before, a careful risk-benefit assessment should be made concerning HBVv administration before bDMARD treatment. According to current recommendations[111], HBVv is only recommended in patients "at risk" (*e.g.,* travel to or residence in endemic countries, medical profession, infected family member; only if protective antibodies against HBV are absent. Grade of evidence Ⅱ-Ⅲ; strength of recommendation B-D) and should ideally be administered during stable disease. Nevertheless, vaccination could also be considered in selected patients with active disease for whom the benefits of HBVv outweight the risks[99]. HBVv can be administered during the use of csDMARDs and TNFI but should ideally be administered before starting RTX (or, when treatment with RTX is already ongoing, at least 6 mo after the start but 4 wk before the next course[111]). Further studies are needed to establish indication and proper time of immunization in RA patients undergoing TCZ or ABA.

Antiviral pre-emptive therapy and follow-up

Given the risk associated with IFN-based schemes in patients with autoimmune diseases, only NAs are recommended for these patients. To date, no consensus or recommendations are available regarding the specific bDMARD that should be preferentially chosen according to HBV infection profile. Pre-emptive treatment must be started (at least 1 mo) before the biotherapy, and must be prolonged (as well as virological monitoring) until at least 6 mo after its discontinuation. The efficacy of pre-emptive lamivudine has been retrospectively assessed in 88 RA patients treated with TNFI showing markers of recent/remote HBV infection[77]: for $HBsAg^+$ patients, 5 of 8 untreated patients underwent HBV reactivation versus none of 10 treated patients. Regarding the 70 $HBsAg^-$/anti-HBc^+ patients, without antiviral prophylaxis, a single case of HBV reactivation was reported in a patient with OBI ($HBV\text{-}DNA^+$, anti-HBs^-). Nevertheless, newer NAs such as entecavir and tenofovir are considered the first choice for patients at high risk of HBV reactivation, due to lower risk of drug resistance. However, comparative data between lamivudine and newer NAs for pre-emptive therapy of HBV reactivation are lacking. In addition, the potential side effects of entecavir and tenofovir must be weighed against the excellent safety profile of lamivudine. The current recommendations are summarized below.

For $HBsAg^+$ patients, antiviral therapy should be initiated before any bDMARDs therapy[68]. The choice of the appropriate NA mainly depends on the duration of the scheduled therapy and on HBV serology status (CHB *vs* inactive carrier). In general, patients receiving long-term immunosuppression (> 12 mo) and/or suffering from CHB are placed on the newer NAs[34]. For patients with HBV-DNA < 2.000 IU/mL who are scheduled for short-term immunosuppression (< 12 mo) treatment with lamivudine should be considered. Biotherapy should not be started until the HBV-DNA levels become undetectable, and thus frequent (after 1 mo, then every 3-6 mo) monitoring of HBV-DNA and liver function tests is mandatory[35,81]. This recommendation might safely be applied to patients undergoing TCZ and ABA.

For $HBsAg^-$/anti-HBc^+ patients undergoing bDMARDs, additional risk factors should be taken into account: HBV-DNA positivity, presence of anti-HBs (which should protect against reactivation, although this effect is controvertial, mostly with RTX), and the degree of immunosuppression induced by different bDMARDs, particularly for RTX. Baseline screening for HBV-DNA is always recommended, and if found to be positive, it is appropriate to start newer NAs[34]. In patients with resolved HBV infection (undetectable HBV-DNA) undergoing TNFI, simple monitoring without pre-emptive treatment is recommended (particularly if also anti-HBs+): liver function tests, HBsAg and HBV-DNA should be assessed 1 mo after treatment start, and then every 3-6 mo. Pre-emptive treatment should also be strongly considered, regardless of HBV-DNA status, for patients undergoing RTX. Moreover, although there are few data concerning newer bDMARDs, we suggest that also for ABA-treated patients, regardless of HBV-DNA status, antiviral prophylaxis should be taken into account; whilst TCZ is relatively safe. In these cases, regular monitoring of aminotransferases, HBsAg and/or HBV-DNA every 3-6 mo of follow-up is mandatory.

When HBV reactivation is diagnosed, as soon as HBV-DNA becomes detectable and before hepatocellular damage starts, antiviral therapy must be promptly initiated and immunosuppressive therapy must be discontinued. If HBV-DNA becomes positive during lamivudine therapy, the patient should be switched to tenofovir, since cross-resistance has been reported between lamivudine and entecavir.

CONCLUSION

HBV infection is a relevant worldwide condition, affecting also rheumatologic patients. Immunosuppressive treatment with bDMARDs might interfere with HBV natural history, leading to an increasing risk of viral reactivation, with consequent liver damage, up to possible fulminant hepatitis and death. Rheumatologists should be well-aware about such risk in RA patients undergoing different classes of bDMARDs, in order to define drug by drug proper preventive and therapeutic strategies. More robust evidences about newer bDMARDs (TCZ and ABA) are still needed in order to better define their specific drug-related risk in HBV infected RA patients and to draw univocal recommendations. An integrated management of this subset of patients should be encouraged between rheumatologists and virologists.

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