

EDITORIAL

HBV and targeted synthetic (ts)
DMARDs: what have we learned from
bDMARDs and tsDMARDs?Elisa Gremese,¹ Antonio Gasbarrini,² Gianfranco Ferraccioli ³

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Hepatitis B virus (HBV) infection is one of the most complex and fascinating viral infections. The resolution of HBV infection is shown by the disappearance of HBV DNA from serum, by hepatitis e and hepatitis B surface antigen (HBsAg) seroconversion, and by a full normalisation of liver transaminases. These biological laboratory tests should characterise a full clearance of the virus. This is not the case with HBV. The complexity of the infection resides in the very long immunological response that can continue for years, after the acute phase, and as demonstrated by several studies by the positivity of HBV DNA in serum, peripheral mononuclear cells and liver, years after the apparent recovery.¹ Therefore, only the absence of DNA in the liver means a cure. Even though there are no clear-cut data showing that low levels of HBV DNA can cause a progression of liver damage, it is pretty clear that either spontaneously or after immunosuppressive therapy, HBV can reactivate (rHBV).^{2,3} Once HBV DNA still is detectable, yet there is no detectable HBsAg, the biology claims there is occult hepatitis B virus infection (OBI). OBI is defined as the presence of replication-competent HBV DNA (ie, episomal HBV covalently closed circular DNA (cccDNA) in the blood and/or in the liver of people who test negative for HBsAg by currently available assays.^{4,5} It has been demonstrated that HBV DNA is only intermittently detected in serum/plasma, and when detectable, the concentration is low, usually less than 200 IU/mL (about 1000 copies/mL).⁶ From a molecular point of view, OBI is characterised by the stability and long-term persistence of cccDNA in the nucleus of infected hepatocytes, with a strong suppression of overall replication activity and viral protein expression exerted by the host's defence mechanisms. The presence of replication-competent HBV DNA and

the long half-life of hepatocytes imply that HBV infection, once initiated, may continue for life even if efficient immune control is achieved.⁷⁻⁹

In these cases, the absence of HBsAg is counterbalanced by the presence of hepatitis B core antigen and by the presence of the immunological response anti-hepatitis B core antibody (HBc Ab) positivity. Detection of anti-hepatitis B virus core protein (HBc) antibody, as a surrogate marker of OBI, is useful when an HBV DNA test is not available or when intermittent viraemia is suspected, but it should be kept in mind that a negative anti-HBc Ab, still with OBI, may occur. In fact, not all anti-HBc-positive subjects are HBV DNA positive, and the absence of an anti-HBc antibody does not completely exclude seronegative OBI.

Therefore, OBI can be classified into two groups, seropositive OB+ (80%–99% of the OBIs are anti-HBc and/or anti-hepatitis B surface (anti-HBs) positive) and seronegative OBI- (1%–20% are anti-HBc and anti-HBs negative), on the basis of the HBV antibody profile.⁴ In people with seropositive OBI, HBsAg may have become negative either following the resolution of acute hepatitis B or after decades of HBsAg-positive chronic HBV infection. Otherwise, people with seronegative OBI might have progressively lost the hepatitis B antibodies.

Why does this happen? Because in the liver, the episomal HBV cccDNA exists as a chromatinised viral minichromosome, and since hepatocytes have a very long half-life, this means that HBV infection, once initiated, may continue for life even if efficient immune control is achieved. In fact, cccDNA in OBI cases is fully replication competent and can reactivate.^{4,5} In the vast majority of cases, OBI does not appear to lead to any clinical sequelae, and so detection of HBV DNA

in serum/plasma is not reasonable for all subjects who are anti-HBc positive and/or anti-HBs positive. Detection of HBV DNA should be reserved to patients with OBI receiving chemotherapy or immunosuppressive therapy, including the established and emerging new biological response modifiers. Indeed, if viraemic, they should be treated similarly to HBsAg-positive patients. Indeed a subset of people with OBI are infected with HBV S variants carrying mutations in the S gene ('S-escape' mutations), resulting in the production of modified HBsAg that is not recognised by some commercially available HBsAg assays. Circulating HBV DNA levels in these people may be comparable with those detected in HBsAg-positive individuals.

This is especially important when donors of liver transplants need to be evaluated. In a recent study, out of 100 transplant liver donors with OBI+ (anti-HBc+), cccDNA was found in 52% (27/52) of the OBI positive, with a median of 13 copies/10⁵ cells (95% CI 5 to 25). More importantly, using an assay specific for anti-HBc of IgG class, the median antibody level was significantly higher in HBV cccDNA-positive than HBV cccDNA-negative donors (17.0 (95% CI 7.0 to 39.2) vs 5.7 (95% CI 3.6 to 9.7) cut-off index (COI), respectively, *p* = 0.007). By multivariate analysis, an anti-HBc IgG value above 4.4 COI was associated with the finding of intrahepatic HBV cccDNA.¹⁰ This explains why, in addition to other risk factors like gender (male) and age (elderly), coinfection with hepatitis C virus, which should deserve a specific analysis,¹¹ immunosuppressive therapies can lead to acute (sometimes fatal) HBV reactivation.

OBI AND RHBV

Reactivation of HBV is defined as HBsAg seroreversion and/or an increase of serum HBV DNA by at least 1 log above the lower limit of detection in a person who had previously undetectable HBsAg and HBV DNA or as an increase of more than 1 log increase in people who had detectable HBV DNA at baseline.⁵ The risk of reactivation can be divided into high risk (if the rate of HBV reactivation is >10%), moderate risk (if the risk of reactivation is between 1% and 10%) and low risk (if the risk of reactivation is <1%) based on the type of immunosuppressive therapy.¹²⁻¹⁴ Because of high risk of reactivation, all HBsAg-positive candidates for chemotherapy and immunosuppressive should start potent nucleos(t)ide analogue with high barrier to resistance (entecavir (ETV), tenofovir disoproxil (TDF) or tenofovir alafenamide (TAF)) as a treatment (ie, patients with chronic hepatitis) or as prophylaxis (patients with chronic infection, without chronic hepatitis). Since HBV reactivation ranging from 20% to 30% in lamivudine-treated patients with lymphoma was seen, third-generation antiviral drugs (ETV or tenofovir) are recommended in all the patients regardless of HBV DNA levels^{12 13} (table 1).

OBI AND BIOLOGICAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs)

Immunosuppressive agents by inhibiting host immune responses lead to enhanced replication of HBV in the liver and to enhanced expression of the viral antigenic epitope. Among the immunosuppressive treatments, while conventional synthetic disease-modifying

Table 1 Differential group risk and treatment strategies in patients with rheumatoid arthritis with occult hepatitis B virus infection

	Targets of treatment	HBsAg negative, anti-HBc positive
High risk (>10%)	Prophylaxis should start 1 week before beginning immunosuppression therapy B-cell-depleting anti-CD20-directed monoclonal antibodies (eg, rituximab, epratuzumab, ocrelizumab, obinutuzumab and ofatumumab) Glucocorticosteroids>20 mg/day+csDMARDs	Prophylaxis with lamivudine or TDF/TAF/ETV
Moderate risk (1%–10%)	Glucocorticosteroids>10<20 mg/day for >4 weeks TNF-I, tocilizumab, JAK 1–2, 1–3, 1-TYK-2 inhibitors	Prophylaxis with lamivudine or TAF, TDF/ETV if therapy lasts >12 months
Low risk (<1%)	Glucocorticoid<10 mg/day Methotrexate Leflunomide Sulfasalazine Hydroxychloroquine Abatacept	Monitor HBsAg, ALT and HBV DNA every 3 months

Modified from Perrillo *et al.*¹²

csDMARD, conventional synthetic disease-modifying antirheumatic drug; ETV, entecavir; HBc, hepatitis B virus core protein; HBsAg, hepatitis B surface antigen; JAK, Janus kinase; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; TNF, tumour necrosis factor; TYK, Tyrosin Kinase.

antirheumatic drugs (csDMARDs) are all considered at low risk, the glucocorticoids (GCs) may be at various risk depending on the doses. GCs are often used for the shortest possible period of time, along with methotrexate (MTX) to control an active disease. If the patient is HBsAg positive, there is a pretty high risk of reactivation with a treatment longer than 4 weeks and a dose above 20 mg/day of prednisolone or its equivalent, a dose considered clinically significant to induce immunosuppression.¹⁵ It is well known that GC represents a risk factor for infections. In the literature, there are cases of patients with dermatomyositis or Systemic Lupus Erythematosus (SLE), HBsAg+ treated with GC alone, who did not receive prophylactic antiviral therapy, in whom HBV reactivation occurred after 5–9 months.¹⁶ With a dose of 50 mg/day in a nephrotic syndrome reactivation of an OBI– was seen after 2 months, and 1 year later under lamivudine HBsAg and HBeAb were positive. In this particular patient, the genotype was C and no HBV mutations were observed in the precore or core promoter regions.¹⁷ The GC can upregulate GC-responsive transcription regulatory elements contained in HBV genome, leading to HBV increased viral replication, and can directly suppress cytotoxic T cells which are involved in HBV control. Single case reports of reactivation have also been described in OBI+, with MTX and low doses of GC,¹⁸ though the risk with csDMARDs alone is considered very low. Therefore, GC, not csDMARDs, is considered a key risk factor especially at moderate–high doses.

With targeted bDMARDs the biology is even more complex. B cell depletion therapy in HBsAg+ (rituximab (RTX), ofatumumab and obinutuzumab (OBINU)) is thought by the medical agencies (Food and Drug Administration and European Medicines Agency) to be a high risk factor for possible reactivation. It has even been suggested that almost all will develop reactivation at some point.^{12–13} In 326 HBeAb+ (OBI+) receiving RTX or OBINU as part of chemotherapy for non-Hodgkin's lymphoma, 27 patients had reactivation (8.2%), of whom 17 were on OBINU and 10 were on RTX. Depletion of B cells producing protective antibodies (ie, anti-HBs), along with other not well-defined mechanisms, is thought to be the most likely explanation.

Targeting T cells with CTLA-4Ig (abatacept (ABA)) raises the biological concern of the T-cell response to HBV. Persistent HBV infection results in the upregulation of CTLA-4 on hepatic CD8+ T cells. This prompts CD8+ T-cell apoptosis, and the activation of cytotoxic T lymphocytes (CTLs) is blocked. On the other hand, HBV infection can induce a variety of inhibitory molecules and upregulate their expression on CD4+ Th cells. For example, HBe induces PD-1 upregulation through activation of the c-Jun N-terminal kinase, extracellular signal-regulated kinase and phosphoinositide 3-kinase/AKT pathways.¹⁹ Targeting CTLA-4 might then influence the cytotoxic response to HBV. In an interesting study, eight patients with rheumatoid arthritis (RA) and chronic hepatitis B (all HBsAg+) received ABA for active RA. Four

patients started on prophylaxis (three on entecavir and one on tenofovir) with the initiation of ABA, and none of them experienced HBV reactivation, while the remaining four patients without antiviral prophylaxis developed viral reactivation. The patients who underwent prophylaxis improved significantly, while those who did not undergo prophylaxis did not improve and developed hepatitis, defined as a 10-fold increase in DNA.²⁰ Of note, three of these patients had previously received anti-tumour necrosis factor (TNF). In a further study, 72 patients, 47 inactive carriers, 21 occult carriers and 4 chronic active carriers of HBV were all treated with ABA. The status of inactive carrier was defined as having persistent HBsAg positivity, anti-HBe positivity, HBV DNA levels, 2000 IU/mL and normal liver function tests (LFTs). The status of occult HBV carrier was defined as HBsAg negativity in serum with HBeAb reactivity or anti-HBe reactivity. Thirteen underwent prophylaxis with lamivudine, and four underwent treatment with adefovir or tenofovir. Before ABA, 23.6% had received one bDMARD; 45.8% had been previously treated with two bDMARDs; and 19.4% had been treated with three bDMARDs. At the end of 2 years of follow-up, 68% were still on ABA (discontinuation for primary and secondary failures or adverse events (AEs)), and none of the patients had to stop ABA for HBV-related reactivations.²¹ Therefore, targeting B cells is considered at high risk, and targeting T cells is considered at low–moderate risk. Targeting immune-inflammatory proteins represents a low challenge in the real world.

TNF has biological activity and an amino acid sequence similar to lymphotoxin, which inhibits HBV replication, and infected cells are also reported to be selectively killed by TNF. In addition, TNF acts to suppress HBV DNA replication by reducing intracellular HBV transcription and that IFN and TNF–, produced by T cells, reduce levels of HBV cccDNA in hepatocytes by inducing deamination and subsequent cccDNA decay.²² On the other hand, interleukin (IL)-6 promotes T-cell proliferation and CTL differentiation and antibody production by B cells. More importantly, IL-6-gp130-STAT3-dependent gene expression in hepatocytes mediates the IL-6-triggered protection in immune T cell-mediated hepatitis.²³ Specifically, two proteins, KC (also known as Gro–) and SAA2 (serum amyloid A2), mediate liver protection. Therefore, both IL-6 and TNF contribute to HBV clearance and liver protection. Among other bDMARDs, in 135 patients with RA HBeAb+, HBeAb–, treated with csDMARDs or bDMARDs and followed up for 12 months with DNA tests (sensitivity 2 log/copies/mL) every 3 months, 7 patients became positive (5.2%–3.64 log/copies/mL). Of these, five had received etanercept, one had received tocilizumab (TOCI), and one had no bDMARD. Though the numbers were small, when comparing patients who received targeted biologic Disease Modifying Anti Rheumatic Drugs (tbDMARDs) or only csDMARDs, the risk in those taking bDMARDs was more than twofold higher (85.7 vs 36.0%, respectively; $p=0.008$).¹⁸ The literature suggest that the estimated proportion of patients

experiencing HBV reactivation in patients with RA with resolved HBV infection during TNF- α treatment was 1.7%,¹⁹ while the risk of HBV reactivation in resolved HBV infections in TOCI-treated patients was estimated around 8.6%.^{24–26}

OBI AND JANUS KINASE (JAK) INHIBITORS

HBV is thought to be a weak inducer of the innate immune response. The adaptive immune response is considered the major player in the resolution of acute infection. The transcriptional template of HBV is the cccDNA, which resides inside the hepatocyte nucleus as a minichromosome. Recovery from acute HBV infection has strong T-cell responses to several epitopes of different regions of the HBV genome, while patients chronically infected with HBV have weak T-cell responses to a few epitopes. In contrast with the 90% persistence of infected children, in adults, only 5% of infected people become chronic carriers or had occult infections.²⁷ This depends on the non-recognition of the ‘stealth virus’ by the immune system. Normally, interferon (IFN)- α and IFN- β , collectively known as type I IFNs, are the major effector cytokines of the host immune response against viral infections. In these cases, the IFN response to the infections is blunted. Type I IFNs activate several JAK-signal transducer and activator of transcription (STAT) signalling pathways, which regulate the transcription of target genes. The activated JAKs are mainly JAK-1 and Tyrosin Kinase 2 (TYK-2), and the phosphorylated STATs are STAT-1, STAT-2 and STAT-3 in most cells and in lymphocytes STAT-4 and STAT-6.²⁸

Once JAKs are inhibited, the immune response to the virus is even weaker, and this can lead to reactivation of the stealth virus that resides inside the hepatocytes. This means that weak IFN effects are downregulated even further by JAK inhibition, especially JAK-1 and TYK-2 inhibition. Ruxolitinib (RUXO, a selective JAK-1–2 inhibitor) has been reported to be associated with reactivation of occult HBV (first patient, HBsAg negative, anti-HBc positive, HBV DNA 39 UI/mL; second patient, HBsAg negative, anti-HBc positive, HBV DNA <10 UI/mL). In the first patient, after 2 months, HBV reactivation occurred (HBsAg positive, HBV DNA 840 UI/mL); in the second patient, reactivation with HBsAg (HBcAg positive, HBV DNA 42 200 000 UI/mL) occurred after 5 months.²⁹ Whether these effects relate to the downregulation of IL-1, IL-6 or TNF (which mediates the positive clinical benefits in myelodysplasia) secondary to JAK-2–1 preferential inhibition needs to be defined.

In a cohort of 106 Taiwanese patients with RA treated with tofacitinib (TOFA JAK-1–3 inhibitor), 69.8% were HBc Ab positive; of these, six patients were HBsAg positive. Of note, all six patients were also on steroids. Of four carrier patients not receiving nucleotide analogues (NUCs), two had a reactivation defined by a 10-fold rise in HBV DNA. Two others received NUCs and did not reactivate. Among those who had occult HBV, no reactivation

was seen despite NUCs not being given.³⁰ From these preliminary data, it seems that the risk associated with TOFA mainly occurs in carriers, less in the occult infection, whereas with RUXO, reactivation may occur also in occult. Therefore, targeting JAK-2 may represent a higher risk, yet no real data are available, and we need real-world data to define the risk.

Along this line, it appears very important to have data on baricitinib (BARI JAK-1–2 inhibitor) because of the similarity with RUXO, less with TOFA. In the paper by Harigai *et al*,³¹ which collected four trials and one long-term extension, the authors (AA) did analyse retrospectively patients with RA treated with BARI either after MTX, as well as after non-reponse to TNF-incomplete responders. They state that in these trials, at baseline, patients were excluded if they were (1) HBsAg+, (2) HBcAb+/HBsAb– (in Japan, could enrol if HBV DNA–) or (3) HBsAb+ and HBV DNA+. Among the 215 patients who had evidence of occult carriers (HbcAb+) and who underwent a postbaseline DNA test, 32 (14.9%) were HBV DNA+ at some point following treatment initiation. Of these patients, 17 were concomitantly receiving GC. Four patients met the definition of clear reactivation of HBV (HBV DNA level of ≥ 100 IU/mL). BARI was permanently discontinued in four patients and temporarily interrupted in two patients. No patient developed clinical evidence of hepatitis, and in five of eight patients, antiviral therapy was not used. The take-home messages of the study are (1) BARI therapy can lead to rHBV infection; (2) BARI suspension in these patients prevents the occurrence of hepatitis; and (3) we have no answer on whether antiviral therapy can allow pursuing of BARI therapy without hepatitis relapses.

HOW TO DEAL WITH HBV REACTIVATION: HEPATOLOGIST VIEWPOINT

The hepatology community suggests pre-emptive therapy (monitoring HBsAg and/or HBV DNA every 1–3 months during and after immunosuppression and starting ETV, TDF or TAF treatment in cases of detectable HBV DNA or HBsAg seroreversion) rather than prophylaxis for patients with chronic infection (typically HBV DNA <2000 UI/mL and normal ALT) and low risk of reactivation (ie, subjects being treated with MTX, leflunomide, azathioprine and intra-articular steroid injections). Among HBsAg-negative, anti-HBc-positive subjects in the high-risk group (patients treated with RTX in the oncohaematological setting or those undergoing stem cell transplantation), antiviral prophylaxis is recommended.^{12 13} Lamivudine may be used safely in this setting.³² In HBsAg-negative, anti-HBc-positive subjects with moderate (1%–10%) risk of HBV reactivation, prophylaxis is generally recommended.¹³ According to this rule with JAK inhibitors, the last approach should be recommended, yet in the Harigai *et al* study, those who had reactivation were mainly on concomitant GC. Therefore, even though more data are needed and no clear-cut suggestions can

be made at this time on how to treat all OBIs, we believe one suggestion should be accepted: if JAKs are used at baseline along with GC, even at low doses, a prophylactic therapy should be started. If no GCs are given, then a strict watch-and-see algorithm may be adopted.

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