Italian consensus Guidelines for the management of hepatitis B virus infections in patients with rheumatoid arthritis **

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Abstract

Objectives. Hepatitis B (HBV) infection, which is prevalent worldwide, is also frequently seen in patients with rheumatoid arthritis (RA). The Italian Society of Rheumatology (SIR) and the Italian Society of Infectious and Tropical Diseases (SIMIT) endorsed a national consensus process to review the available evidence on HBV management in RA patients and to produce practical, hospital-wide recommendations.

Methods. The consensus panel consisted of infectious disease consultants, rheumatologists and epidemiologists and used the criteria of the Oxford Centre for Evidence-based Medicine to assess the quality of the evidence and the strength of their recommendations.

Results. A core-set of statements has been developed to help clinicians in the management of patients with RA and HBV infection. Vaccination and prophylaxis of RA patients treated with biological drugs have been also discussed.

Conclusions. HBV infection isn’t rare in clinical practice; a screening for HBV in all patients with early arthritis is not universally accepted, while it is considered mandatory before starting any immunosuppressive or hepato-toxic treatment. In fact, a specific risk, associated with the use of biologic treatments, exists for patients with HBV infection, although longitudinal studies of viral reactivation are generally reassuring.

RA patients with HBV infection should be referred to the hepatologist and correctly classified into active or inactive carriers. Patients with active hepatitis B should undergo antiviral treatment before starting immunosuppressive treatments. Occult HBV carriers should be monitored or receive prophylaxis on the basis of the risk of reactivation associated with the administered treatment.
Introduction

Hepatitis B virus (HBV) infection is a major public health concern in many countries. Approximately one-third of the world’s population has serological evidence of previous or current HBV infection, and 350-400 million people are chronic HBV surface antigen (HBsAg) carriers. HBV causes chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC), and is associated with more than 600,000 deaths every year (1). The prevalence of HBV infection varies significantly depending on geographical area: it is estimated to be around 1% in Western countries and more than 2% in most developing countries, with peaks higher than 8% in some Asian and African countries (1).

The host immunological response plays a key role in the natural history of HBV. Liver injury results from host immune cell cytotoxicity, rather than from viral cytopathic effect (1-3). Long-lasting persistence of viral genome in liver tissue, with or without detectable HBV DNA in serum, occurs also in anti-HBs and anti-Hepatitis B core (HBc) IgG positive subjects with resolved hepatitis B after HBsAg loss (2, 3) and the risk exists of HBV reactivation, mainly in the setting of immunosuppression (4) (table 1).

The prevalence of HBV infection in patients with rheumatic diseases is poorly known. The few studies that have investigated the prevalence of HBV infection in patients with rheumatoid arthritis (RA) were limited to small sample sizes, and specific populations or geographic areas; generally, the resulting prevalences were higher than or at least comparable to the HBV prevalence observed in the general population (5, 6). Nevertheless, the screening for HBV of all RA patients is not universally practiced, even if it is considered mandatory before starting any immunosuppressive or hepatotoxic treatment (7).

The widespread use of immunosuppressive drugs in RA patients and the prolongation of their life expectancy have increased the need to regulate the management on HBV infection in this disease. For this reason, the Italian Society of Rheumatology (SIR) and the Italian Society of Infectious and Tropical Diseases (SIMIT) endorsed a national consensus process to review the available evidence and produce practical, hospital-wide recommendations.

Methods

The recommendations for the management of HBV infections in RA patients included in this paper (table 2) are the product of a consensus procedure performed by the Italian group for the Study and Management of the Infections in patients with Rheumatic diseases (ISMIR group), promoted by the Italian Society of Rheumatology (SIR) and the Italian Society of Infectious and Tropical Diseases (SIMIT).
The consensus panel that was set up for this purpose consisted of infectious disease consultants, rheumatologists and epidemiologists who used the criteria of the Oxford Centre for Evidence-based Medicine (8) to assess the quality of the evidence and the strength of their recommendations.

We considered systematic reviews or observational studies, or case reports evaluating the risk of hepatitis infections or reacutization in patients exposed to biological disease modifying anti-rheumatic drugs (DMARDs).

**Risk of HBV reactivation in chronically HBV-infected RA patients**

HBV reactivation has been frequently reported in immunodeficient patients (9), included those with rheumatic disease treated with conventional or biological DMARDs, and/or high-dose prednisone (9, 10). A study at US Veterans Health Administration examined 556 patients with RA and presence of any HBV marker in serum, with normal or near normal ALT value at baseline, who were treated with biologic or non-biologic DMARD; among 959 episodes classified as adverse events, an ALT elevation at >100 IU/mL occurred in 2.7% of the cases within 12 months, without difference between those treated with biological or non-biological DMARD (2.6% vs. 2.8%, respectively, p = 0.87) (9).

**HBV and steroids.** It is known from 1980 that steroid treatment increases HBV replication in HBsAg chronic carriers (10). Besides, the use of steroids has been associated with HBV reactivation in rheumatic diseases in some of the studies (11). In particular, in occult and inactive carriers the risk of reactivating HBV infection resulted to be increased when prednisone was administered at a relatively high dosage (>20 mg/day for at least 2 weeks) (11); but also, in a prospective observational study, when the treatment is administered at lower dosage (≤10 mg daily) for a longer time (12).

**HBV and conventional DMARDs.** Methotrexate (MTX) is the most widely used DMARD in RA, but its safety in HBV infected patients is still undefined. Combined treatment with MTX and steroids can reactivate occult HBV infection, albeit less frequently and less severely than tumour necrosis factor (TNF)-α inhibitors (9-12). However, a cross-sectional study carried out in Thailand did not find any reactivation in 65 occult carriers treated with MTX over a period of 9 years (13). Leflunomide can interfere with liver function, and viral reactivations have been described in HBV chronic carriers with high baseline transaminase levels (14). Limited data are available on the use of sulfasalazine and hydroxychloroquine in RA patients with active or occult HBV infection, although a positive safety profile for the two drugs could be supposed, in particular for hydroxychloroquine (15). HBV reactivation was recently reported in a HBsAg negative/anti-HBc positive Japanese patient with RA treated with salazosulfapyridine monotherapy (16).
**TNF-α inhibitors.** There are currently five anti-TNF-α drugs approved for the treatment of chronic autoimmune arthropathies, skin psoriasis and chronic inflammatory intestinal diseases: three are monoclonal antibodies (infliximab [IFX], adalimumab [ADA], and golimumab [GOL]), one is receptor fusion protein (etanercept [ETA]); and one antibody fragment antigen-binding fragment conjugated with polyethylene glycol molecules (certolizumab pegol [CZP]).

Anti-TNF-α drugs indirectly favour HBV-DNA replication, because of the inhibition of cellular-, complement-, and antibody-mediated immunity. In a review including an heterogeneous series of patients receiving anti-TNFα (17) for various conditions (including IBD), without appropriate antiviral prophylaxis, hepatitis B reactivation was reported up to 39% of chronic carriers, particularly in those receiving infliximab; reactivation occurred in 1-3% of occult carriers (17). Anti-HBs negative occult carriers and those treated with monoclonal antibodies, steroids or conventional DMARDs resulted at significantly higher risk of reactivation (17). In a recent meta-analysis including patients with different rheumatic diseases the HBV reactivation rate was of 3.0% in occult infections, and of 15.4% in overt infection, without significant differences among anti-TNF-α drugs (18). On the other hand, no HBV reactivation was observed in 67 anti-HBc positive patients recruited in an Italian study (19).

**Rituximab.** Rituximab (RTX) is a chimeric murine/human monoclonal antibody that targets CD20-positive cells. When used alone or in combination with immunosuppressive drugs, it causes a long-lasting B lymphocyte depletion which has been associated with an increased risk of infection, including HBV reactivation (20). In fact, the use of this drug is associated with a five-fold increase in the rate of HBV reactivation and in 2013, the US Food and Drug Administration (FDA) added a new box warning regarding the risk of HBV reactivation in patients receiving RTX or ofatumumab (20); likewise, American Gastroenterological Association placed patients with rheumatoid arthritis treated with RTX, as lymphoma patients, in the high-risk group for HBV reactivation (30-60% of reactivations if HBsAg +,> 10% if anti-HBc-positive) (21).

Fulminant hepatitis has been described in inactive and occult HBV carriers treated with RTX, despite the presence of a protective titer of HBsAb (22). The presence in the serum of detectable HBV-DNA increases the risk of reactivation (23), which has been observed in more than 20% of HBsAg-/anti-HBc+ onco-hematological patients treated with RTX without concurrent antiviral prophylaxis (23). The data in rheumatic diseases are scarce and discordant. Two studies, including a total of 26 occult carriers, did not report an increased risk of HBV reactivation, (24, 25) while one case of inverse seroconversion (the appearance of HBsAg) has been described in a RA patient after 2 years of treatment with RTX and methotrexate (26). No HBV reactivations was seen in 33 HBsAg-negative/anti-HBc-positive RA patients with undetectable HBV DNA at baseline followed-
up for 34 months or more while receiving RTX combined with DMARDs. These data prompted the Authors to conclude that the risk of HBV reactivation in RA patients with resolved HBV infection treated with RTX+DMARDs is negligible, and that anti-HBV prophylaxis is not required in such cases, although serum HBsAg and/or HBV DNA monitoring are justified (27). On the other hand, three cases of HBV reactivation (two in chronic and one in past HBV infection) were recently reported in RA in a Greek multicentric study (28). It must be noted that HBV reactivation and hepatitis flare may occur months after stopping RTX and hence incidence data are influenced by the length of follow-up.

**Abatacept, tocilizumab.** HBV reactivation in patients treated with abatacept has been so far reported only in occult carriers and in four HBsAg positive RA patients treated with ABA and methotrexate without concurrent antiviral prophylaxis (29, 30). None of 72 RA patients (47 inactive carriers, 21 occult carriers, and 4 chronic active HBV carriers) treated with ABA intravenously in an Italian study experienced disease reactivation during a 24-month followup period. At baseline all of them had normal liver function tests and low or undetectable HBV DNA levels, except for those with chronic active hepatitis. Thirteen patients received prophylaxis with lamivudine, and 4 received treatment with adefovir or tenofovir. (31).

Only 2 cases of HBV reactivation have been reported in occult carriers treated with tocilizumab, but in both cases, HBV DNA and liver function spontaneously normalised in a relatively short time (32).

**Antiviral drug prophylaxis**

International guidelines consider the screening for HBsAg and anti-HBc as mandatory in all candidates for immunosuppressive therapy. In particular, HBsAg-positive patients should be tested for HBV DNA and, regardless of HBV DNA levels, should receive pre-emptive antiviral drugs during treatment and for 12 months after its discontinuation (2). However, a case of reactivation after rituximab discontinuation has been recently described with this schedule, (33). The screening for HBV infection (including HBsAg, anti-HBc, anti-HBs) and liver function tests should be performed in all patients with rheumatic diseases who are candidate to immunosuppressive therapies (2, 3).

Quantitative HBV DNA testing is mandatory for patients who are HBsAg positive; in anti-HBc positive/HBsAg negative patients detection of HBV DNA requires sensitive test, being present in plasma at low concentration (usually <200 IU/mL) and may fluctuate over time. Due to these shortcomings, there is general agreement to consider all anti-HBc positive/HBsAg negative patients as potential carrier of occult infection (2, 3). In HBsAg-positive patients, antiviral prophylaxis is
recommended before starting immunosuppressive therapy (biological DMARDs, MTX, leflunomide) independently from disease activity (2, 17, 21, 23).

In these latter patients, the risk of reactivation of HBV infection depends on the immunosuppressive drug used; rituximab entails the highest risk. There are no indications for starting antiviral treatment in occult HBV carriers who are candidates for biological drugs, with the exception of rituximab. The frequency of monitoring, by searching HBV DNA in plasma, in patients not receiving antiviral prophylaxis, can range from one to three months depending on the type of immunosuppressive therapy and comorbidities (2, 17, 21, 23).

In HBsAg positive patients, plasma HBV DNA concentrations repeatedly below 2,000 IU/mL, with normal ALT values and absence of significant liver disease, denote the condition of “inactive carrier”. In absence of adequate follow-up data, it may be difficult to characterize patients as inactive; HBsAg quantitative detection in plasma may help the diagnosis, since it is usually below 1,000 IU/mL in inactive carriers (34). True inactive carriers should receive prophylaxis with lamivudine, 100 mg/day, ideally starting from 1-4 weeks before DMARDs and continuing 6-12 months after stopping therapy. Patients with active HBV infection (HBV DNA >2,000 IU/mL, abnormal ALT and/or signs of liver disease) should be treated with entecavir or tenofovir, indefinitely, under specialist supervision. Entecavir or tenofovir should be also preferred in patients in whom the diagnosis of “inactive” carriers remains uncertain. (2, 17, 21, 23, 35).

Acute HBV infection in patients with RA

No data are available on acute HBV infection (AHB) in patients with RA on treatment with biological DMARDs or other immunosuppressive drugs. However, it can be presumed that new HBV infections might be more frequently asymptomatic in immunocompromised individuals than in the general population and more easily progress to chronicity.

In high-income countries with low prevalence of HBV infection, AHB occurs more frequently among immigrants or non-vaccinated older people in which, in particular when comorbidities coexist, it is associated with higher probability of severe presentation and mortality (1, 2).

AHB recovers spontaneously in 95% of immunocompetent adults (36). However death rates of 0.4-8.9% are still reported. The diagnosis of severe AHB is based on the presence of at least two among bilirubin levels higher than 10 mg/dl, international normalized ratio (INR) ≥1.6 or hepatic encephalopathy (38). In such patients, prompt and timely administration of antiviral treatment can shorten the duration of disease, promote recovery and improve survival (2). The administration of entecavir or tenofovir is recommended in such cases for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss, both of which
marking the transition to recovery and allowing to discontinue treatment quite safely (2). The employment of antivirals in AHB occurring in immunocompetent patients remains controversial, because the early suppression of HBV replication might reduce the efficiency of viral antigens presentation to immune system, inhibit the production of neutralizing antibodies and delay the seroconversion to either HBeAb and HBsAb (37). On the contrary, in patients with extrahepatic manifestations and comorbidities associated with immune alterations, antiviral treatment should be considered in case of AHB to prevent the progression in chronic infection and to reduce the duration of illness.

No data are available on AHB in patients with RA in treatment with biological DMARDs or other immunosuppressive drugs. However, it can be presumed that new HBV infections might be more frequently asymptomatic in immunocompromised individuals than in the general population and more easily progress to chronicity.

**Vaccination**

Routine HBV vaccination (HBVv) before biotherapy initiation in patients with negative screening tests has been questioned (2, 17, 21, 23) due to the theoretical risk of vaccine side effects and the possibility of a reduced effectiveness in patients already assuming immunosuppressants (7). Moreover, HBVv could delay the biotherapy initiation. It has been proposed that the need of vaccination should be weighted according to patient’s profile (age, family history, risk factors, etc.) and overall risk of infection (37). Accordingly, HBVv has been recommended only in patients with risk factors, such as intravenous drug abuse, health care personnel, persons having had multiple sex partners, or traveling or residing in high endemic countries (38). Moreover, due to some conflicting reports suggesting a reduced immunization rate after vaccination in patients with RA, as so as in inflammatory bowel disease (IBD), a schedule with a double dose of HBV vaccine has been proposed (39). On the other hand, the vaccination of immunocompromised HBV-seronegative patients is highly recommended by EASL and other international guidelines (2, 23).

HBVv should be ideally administered before treatment initiation; in RA patients already taking a DMARD or an anti-TNF agent vaccination should be offered preferably during a stabilized phase of the disease (2, 17, 21, 23). In patients, who are candidate to receive RTX treatment, HBVv should be preferably administered before starting therapy. When treatment with RTX is already ongoing, HBVv should be administered at least 6 months after the treatment initiation, or 4 weeks before the next course (38). Finally, no data are yet available suggesting a proper time of immunization in RA patients undergoing TCZ or ABA. According to the World Health Organization, an HBsAb concentration ≥10 IU/L is considered a reliable marker of protection against infection (40). Clinical
HBV infections has been documented in immunocompromised patients who did not maintain an anti-HBs concentration of ≥10 IU/L. Based on this evidence, seroprotection against HBV infections was redefined in such patients at ≥100 IU/mL (40).

Conclusions
Though relatively infrequently reported, reactivation of HBV infection needs to be carefully considered in RA patients on immunosuppressive therapy (8, 9). A serological screening for HBV at the time of diagnosis of RA is now universally accepted and strongly recommended (5). No significant differences in the risk of reactivation of overt or occult HBV infections was found among the different biological drugs used in RA patients, with the exception of RTX, for which experts agree that should be applied the precautionary principle, by administering full treatment in the HBs Ag positive cases and the antiviral prophylaxis to all the RA patients showing evidence of previous contact with HBV (2). In the absence of randomized controlled trials, which can not be implemented on this topic, much of this matter can only be regulated on the basis of expert opinion. This is the case of HBV vaccination, which should considered in all the serologically negative patients at RA diagnosis or as soon is possible before administering immunosoppressive treatments, and of acute HBV infections, that are suggested to be treated according to international guidelines (2).

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References


20. Mitka M. FDA: increased HBV reactivation risk with ofatumumab or rituximab. JAMA 2013; 310: 1664


<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>reference</th>
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<tr>
<td><strong>Chronic hepatitis B</strong></td>
<td>Chronic necro-inflammatory disease of the liver caused by persistent HBV infection</td>
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<tr>
<td><strong>Hepatitis B carrier</strong></td>
<td>Subjects who have hepatitis B surface antigen (HBsAg) in the blood for more than 6 months</td>
<td>2</td>
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<tr>
<td></td>
<td>Subjects with persistently normal serum alanine aminotransferase (ALT) and low (&lt;2000 IU/ml) serum HBV DNA levels</td>
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<tr>
<td><strong>Inactive carriers</strong></td>
<td>Persistence of HBV DNA in the liver of individuals negative for HBsAg</td>
<td>3</td>
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<tr>
<td><strong>Occult HBV carrier</strong></td>
<td>Abrupt increase in hepatitis B virus (HBV)</td>
<td>3</td>
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<tr>
<td><strong>HBV reactivation</strong></td>
<td>Replication in a patient with inactive or resolved hepatitis B</td>
<td>7</td>
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### Table 2. Recommendation of the ISMIR Consensus Group

<table>
<thead>
<tr>
<th>Nr</th>
<th>Statement</th>
<th>Level of evidence/grade of recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>All patients at the time of diagnosis of RA should be screened for HBsAg, anti-HBs, and anti-HBc IgG</td>
<td>2a B</td>
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<tr>
<td>2</td>
<td>In accordance with the international guidelines on HBV infection, HBsAg-positive patients should be referred to a specialist and undergo further evaluation, including quantitative HBsAg, HBeAg, anti-HBe, HBV DNA and anti-HDV IgG and liver function tests (AST, ALT, bilirubin, GGT, albumin, creatinine, INR, and a differential blood count) before starting immunosuppressive therapy</td>
<td>1a A</td>
</tr>
<tr>
<td>3</td>
<td>Anti-HBcIgG-positive, HBsAg-negative patients should also be referred to a specialist and undergo further evaluations, including HBV DNA and liver function tests (AST, ALT, bilirubin, GGT, albumin, creatinine, INR, and a differential blood count) before starting immunosuppressive therapy</td>
<td>2a B</td>
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<tr>
<td>4</td>
<td>Active HBV carriers should be treated with entecavir or tenofovir in accordance with the international guidelines before starting immunosuppressive therapy</td>
<td>1a A</td>
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<tr>
<td>5</td>
<td>ABH occurring in patients with RA, such as asymptomatic infections occurring in patients previously negative for HBV serology, should receive antiviral treatment according to international guidelines</td>
<td>5 B</td>
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<tr>
<td>6</td>
<td>Inactive HBV carriers treated with immunosuppressive therapies should receive prophylaxis with lamivudine. Prophylaxis with entecavir or tenofovir should be considered for patients with a baseline HBV DNA level of &gt;500 IU/mL</td>
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<td>5 C</td>
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<tr>
<td>7</td>
<td>Prophylaxis should be started 4 weeks before the immunosuppressive therapy and continued for 12 months after its discontinuation (24 months in the case of rituximab-treated patients)</td>
<td>3 C</td>
</tr>
<tr>
<td></td>
<td>Patients stopping prophylaxis should be closely monitored</td>
<td>5 C</td>
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|   | Occult HBV carriers should be monitored on the basis of the risk of reactivation associated with the administered treatment.  
- Low risk: HBsAg every six months  
- Medium-high risk (biological DMARDs and/or methotrexate and/or leflunomide and/or corticosteroids >7.5 mg/day): HBsAg every 3 months  
- High risk (RTX): consider prophylaxis with lamivudine when monitoring is not guaranteed | 5 C |
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<td></td>
<td>RA patients who are negative for HBV sero-markers at the time of diagnosis should be invited to undergo hepatitis B vaccination, preferably before undergoing immunosuppressive treatment. The anti-HBs titre of vaccinated patients should be evaluated before starting immunosuppressive treatment</td>
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