

## Continuing medical education

### How does one manage patients with rheumatoid arthritis and positive serology to hepatitis B, hepatitis C, human immunodeficiency virus?☆

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#### ABSTRACT

Chronic viral infections in rheumatic patients are a diagnostic and therapeutic challenge. Some of the disease-modifying antirheumatic drugs (DMARD) commonly used in rheumatoid arthritis, such as methotrexate and leflunomide, are hepatotoxic. With biological therapy, which is now widely used in patients refractory to these and other DMARD, some cases of reactivation of hepatitis B, even fulminant cases, have been reported, especially when employing TNF antagonists and rituximab, so their use must be carefully assessed and usually accompanied by antiviral therapy. However, there have not been reports of reactivation of hepatitis C after immunosuppressive therapy. In patients with HIV infection, administration of immunosuppressive therapy carries a high risk of opportunistic infections, although the new highly active antiviral therapy allows the use of some drugs in selected cases.

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### ¿Cómo manejar al paciente con artritis reumatoide y serología virus de hepatitis B, hepatitis C, virus de la inmunodeficiencia humana?

#### RESUMEN

Las infecciones virales crónicas en un paciente reumático constituyen un reto diagnóstico y terapéutico. Algunos de los fármacos antirreumáticos modificadores de la enfermedad (FAME) más utilizados en la artritis reumatoide, como el metotrexato y la leflunomida, presentan riesgo de hepatotoxicidad. Con la terapia biológica, que es hoy en día ampliamente utilizada en pacientes refractarios a estos y otros FAME, se han descrito casos de reactivación de hepatitis B, incluso fulminante, especialmente con los antagonistas del TNF y rituximab, por lo que su utilización ha de ser cuidadosamente valorada y, generalmente, administrada junto con tratamiento antiviral. Sin embargo, no se han descrito casos de reactivación de hepatitis C tras terapia inmunosupresora. En los pacientes con serología VIH la administración de tratamiento inmunosupresor conlleva un elevado riesgo de infecciones oportunistas, aunque la nueva terapia antiviral altamente activa permite utilizar algunos fármacos en casos seleccionados.

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#### Introduction

Rheumatoid arthritis (RA) is a progressive chronic autoimmune disease, characterised by chronic inflammation of the joints, which affects 0.5%-1% of the adult Spanish population. The coexistence

of a viral infection in a rheumatic patient environment sometimes supposes a diagnostic dilemma. This is because the viral infection can present rheumatological manifestations and a therapeutic challenge due to the hepatotoxicity risk of the drugs used for RA treatment and, above all, in the probability of reactivating an underlying viral infection. In clinical practice these patients can be often undertreated due to the risk, with the progression risk of their joint disease.

There are currently no guidelines in Rheumatology on how to treat these patients, only prevention strategies that are mainly based on information seen in patients.

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## Rheumatoid arthritis and positive serology to hepatitis B

From an epidemiological point of view, Spain has been classified as a country of a hepatitis B virus (HBV) lower middle endemic infection rate, with a prevalence rate of approximately 2%, although its incidence has decreased notably since compulsory vaccination against HBV. Although there are endemic areas, transmission is mainly vertical. In Spain, transmission is greater sexually and intravenously, so infection is commonly seen in certain risk groups, among which are included: patients from endemic areas, with sexual risk behaviour (history of many sexual partners, with a sexually-transmitted disease or homosexual relationships), family or sexual contact with a person infected with HBV, co-infection by hepatitis C virus (HCV) or human immunodeficiency virus (HIV), patients who are intravenous drug addicts and those receiving haemodialysis or immunosuppressive therapy.<sup>1</sup>

### Natural history of chronic infection by hepatitis B virus

There are approximately 2,000 million people infected with HBV throughout the world, with a world prevalence of 5%. Chronic HBV infection is the leading cause of liver cirrhosis (CH) and hepatocellular carcinoma (HCC). Approximately 500,000 people die each year through HBV infection complications.

Although nearly 95% of infections are resolved in the acute stage, 5% become chronic.<sup>2</sup> Chronicity is defined by the persistence of HBsAg positivity in serum for more than 6 months. Patients who present persistence of positive HB surface antigen (HBsAg) can in turn be subdivided into two groups: those with chronic HBV hepatitis and those shown to be asymptomatic HBV carriers. In patients with chronic HBV, hepatic enzymes are higher, there is inflammation in the hepatic histology, HBV DNA is  $>10^5$  copies/l and there is a greater risk of progression to CH and HCC, as well as greater risk of HBV transmission. In contrast, asymptomatic carriers do not have elevated hepatic enzymes, have minimum hepatic inflammation and their viral DNA is  $<10^4$  copies/l.<sup>2</sup>

Although it was traditionally thought that patients with a history of hepatitis B with HBsAg negative serology (-) were cured, recently cases have been reported with these characteristics that can have an occult HBV infection. In both cases HBsAg is negative, but in the cured infection the hepatic enzymes are normal, the HBV DNA is negative and the HB antibodies Ac and HbCac are positive. In cases of occult infection, hepatic enzymes could be slightly altered, viral DNA is positive, although with low titres (sometimes much lower than the technique used, which is why identification depends on the sensitivity and specificity of the trials used) and the antibodies HbCac and HBsAc may be positive or not<sup>2,3</sup> (Figure 1). Occult HBV infection has been reported mainly in patients presenting co-infection by HCV or HIV, HCC and cryptogenic liver fibrosis. These patients overlap those previously thought cured and are patients who should be closely monitored due to the risk of viral reactivation when immunosuppressive treatment is started. In fact, cases of reactivation of occult infection by biological agents, including rituximab, have been reported.<sup>3</sup>

### Reactivation of HBV

HBV is a hepatotropic, noncytotoxic virus that infects hepatocytes, with hepatitis B being an immune-mediated disease, so that the host response depends primarily on the state of immunosuppression. In an immunocompetent patient, there is a humoral and cytotoxic response against infected hepatocytes, producing its cytolysis and resulting in hepatitis. In contrast, in an immunocompromised patient (e.g., in immunosuppressive therapy), no cytolysis takes place, so viral replication and viraemia increase. When the immune system is restored (for example, by immunosuppressive therapy), an immune hyper-responsiveness occurs against the infected hepatocytes, resulting in hepatitis, which in many cases can be fulminant.

The tumour necrosis factor (TNF) is the main cytokine involved in HBV infection. It inhibits viral replication and stimulates the immune response, producing cytolysis and inducing apoptosis of infected hepatocytes. When biological drugs inhibit TNF, they produce an inhibition of the autoimmune system, creating a favourable environment for viral replication.<sup>4</sup>

### Reactivation of infection by hepatitis B virus and disease-modifying anti-rheumatic drugs

Reactivation of infection by HBV is the reappearance of inflammation and hepatic necrosis in people who were known healthy carriers or who presented an apparently resolved infection. It is characterised by high levels of hepatic enzymes, fluctuations in viral DNA levels and HBsAg positive.<sup>1</sup>

Cases of HBV reactivation have been reported in RA patients in relation to DMARD administration, mainly methotrexate (MTX), with the first being described by Flowers et al in 1990.<sup>5</sup> This reactivation has been observed in RA patients with HBsAg (+) who were receiving MTX, generally with low doses ( $\leq 10$  mg/week) and usually 15-60 days after the decrease in MTX dose or after its withdrawal.<sup>6</sup> Its evolution can be serious, with cases of hepatic failure and even death being reported.<sup>6</sup>

### Reactivation of the infection by HBV and anti-TNF

There have been HBV reactivation cases reported with the 3 anti-TNF agents, the majority in cases related to infliximab, after the 3rd or 4th infusion. However, the fact that infliximab was the first biological agent approved for RA treatment could give the false impression that it is responsible for reactivation in the majority of cases. In addition, due to its treatment schedule (approximately 8 weeks pass between the 3rd and 4th infusions), there is sufficient time to re-establish the immune system and produce HBV reactivation, while with other biological agents there is a shorter interval between doses.<sup>4</sup>

### Reactivation of the hepatitis B virus and rituximab

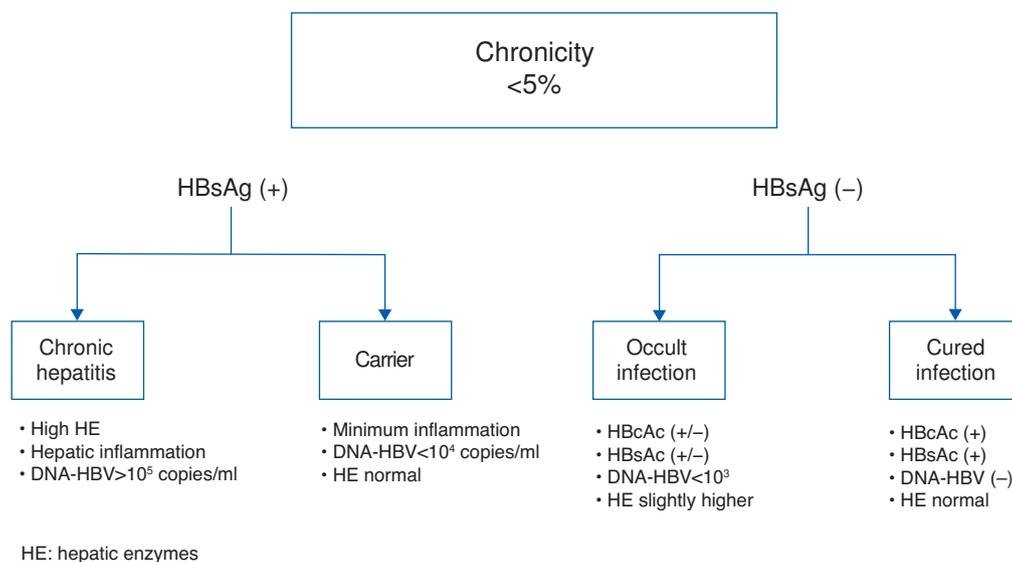
There have been cases reported on HBV reactivation, even fulminant hepatitis, after rituximab (RTX) treatment not only in patients with HBsAg (+) but in patients with occult HBV infection (HBsAg [-]), mainly in the onco-haematological field.<sup>7</sup> We therefore do not recommend RTX treatment for patients with HBsAg (+) due to the high risk. In patients with HBsAg (-), it should be nearly compulsory to discount an occult HBV infection before starting RTX. Basal HBV DNA should be determined and followed up every 1-3 months, as well as carrying out a strict monthly hepatic enzyme control.<sup>7</sup>

### Hepatotoxicity

Currently, the most frequently used DMARDs in RA are MTX and leflunomide (LFN), which are hepatotoxic. Cases of high hepatic enzymes have been reported, especially in the first 6 months, although hepatic failure is exceptional. Despite the fact that in these cases there were other possible hepatotoxic drugs (NSAIDs) used together and many patients had other risk factors (excessive consumption of alcohol), the use of MTX and LFN is not recommended in patients with HBV. In these cases, the toxic effect of treatment would be added to the viral effect on the hepatic tissue, causing a synergic effect and increasing the risk of liver damage.<sup>8</sup>

### Action strategy for a patient with rheumatoid arthritis and positive serology to hepatitis B

At present, there is no consensus or handling guidelines for patients with RA and HBV serology in the Rheumatology field.



**Figure 1.** Chronicity of hepatitis B. Subtypes: chronic hepatitis, asymptomatic carrier, occult infection and infection cured.

However, there are other prevention strategies, the most noted being that of Calabrese et al,<sup>2</sup> who divides patients into high risk HBV groups, as previously mentioned, and those who will receive high risk treatment (high doses of corticoids, immunosuppressive or biological treatment).

Firstly, they advise carrying out HBV serology including HBsAg, HB core antibody (HBcAb) and HB surface antibody (HBsAb). If the HBsAg is positive, prophylactic treatment should be carried out with antivirals (lamivudine); this should be started 2-4 weeks before starting immunosuppressor treatment and maintained for 6 months after stopping the treatment. Cases of resistance to lamivudine have been reported when immunosuppressor treatment is maintained long term, which is why we should consider other antivirals (adefovir, tenofovir, entecavir). If all HBV serology is negative, patient vaccination should be considered. In a patient with HBsAg (-), HBcAb (+) and HBsAb (+/-) a strict monitoring should be carried out and in case of reactivation, anti-viral treatment added<sup>2</sup> and be assessed by the hepatologist (Figure 2).

### Rheumatoid arthritis and positive serology to hepatitis C

Infection caused by HCV is also a worldwide problem. It has a global prevalence of 2.2%, with the prevalence in Spain being 1.2%-1.9%. It is different to HBV, given that 70% to 80% of HCV infection becomes chronic.<sup>7</sup>

Hepatitis C virus is hepatotropic and lymphotropic. There is a possible pathogenic link, mediated by immune complexes, between chronic HCV infection and polyarthralgia/polyarthritis symptoms that can sometimes mimic RA; that is why a differential diagnosis should be carried out. Patients with HCV can also present myalgias, vasculitis, cryoglobulinemia and, frequently, positive rheumatoid factor and antinuclear antibodies.<sup>9</sup>

#### Pathophysiology of infection by hepatitis C virus

Unlike HBV, the main cytokine involved in viral clearance in HCV is interferon gamma (INF- $\gamma$ ). Although TNF does not have a direct effect on the pathogenesis of the infection by HCV, it produces an INF- $\gamma$  inhibition and indirectly decreases viral clearing. The persistence

of high TNF levels have been associated with HCV recurrence, so it might be involved as refractory to treatment with INF- $\gamma$ .<sup>10</sup> In this way, TNF antagonists could produce an improvement in HCV infection by blocking the inhibition produced by the TNF.

#### Hepatitis C virus and disease-modifying anti-rheumatic drugs

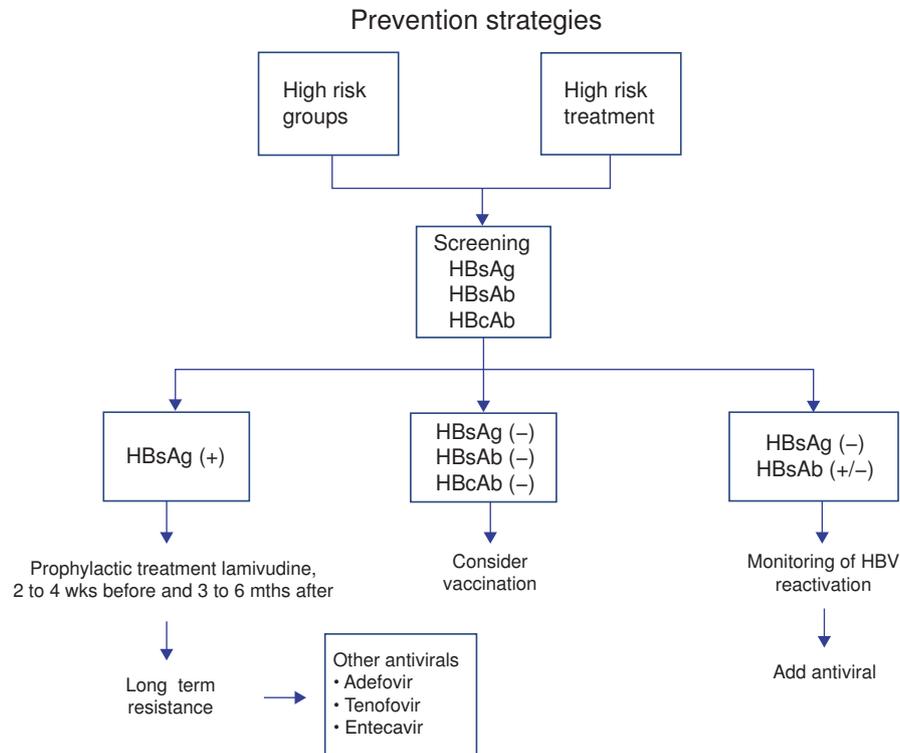
With regards to DMARDs, MTX and LFN could aggravate the hepatic damage due to their potential hepatotoxicity, in the same way as HBV. Other DMARDs could be used on patients with HCV such as gold salts, sulfasalazine or antimalarials, although they do not always achieve disease control. Cyclosporine A also has an inhibitory effect on viral replication, mediated by the inhibition of cyclophilin B.

#### Hepatitis C virus and biological therapy

The antagonists of TNF are not hepatotoxic and, as we have previously seen, produce a decrease in the viral load. That is why, unlike in HBV, there would be no risk of viral infection activation. In these cases, antiviral prophylaxis would not be necessary. In addition, studies in patients with HCV and antiviral treatment (ribavirin, interferon) showed that addition under treatment with TNF antagonists obtained better results regarding the improvement of viral infection.<sup>10</sup> Despite these good results and there being no contraindications, we advise that hepatic enzymes should be monitored monthly, and if these increase, viral RNA should be determined.<sup>10</sup> There are few cases with abatacept, although no reactivation of HCV has been reported.<sup>11</sup>

### Rheumatoid arthritis and positive serology to the human immunodeficiency virus

Infections caused by HIV affect nearly 40 million people throughout the world. From a rheumatological point of view, HIV infection could be associated with different rheumatic diseases such as Reiter syndrome, psoriatic arthritis, inflammatory myositis, Sjögren's syndrome, necrotizing vasculitis, monoarticular, polyarticular or oligoarticular arthropathies and fibromyalgia. There has been a lesser incidence rate of RA reported in these patients due to greater immunosuppression



**Figure 2.** Prevention strategies for HBV reactivation in rheumatic patients.

from the HIV infection. With the introduction of highly active anti-retroviral therapy (HAART), there have been dramatic changes in the natural history of HIV: a lower level of immunosuppression and a greater survival rate have been achieved in these patients. An increase in the incidence of rheumatic diseases has also been observed.

Treatments with certain DMARDs such as gold salts, anti-malarials or salazopyrin are allowed in these patients.

With respect to biological therapy, it is known that TNF plays a role in the pathogenesis of infection due to HIV, as it favours its spread, lymphocyte depletion and increased apoptosis and thus contributes to the progression of the immunodeficiency.<sup>10</sup> In this way, anti-TNF treatment could be beneficial, although an increase in opportunistic infections has been reported.<sup>12</sup> However, in certain cases, especially in patients who are less immunosuppressed, biological therapy could be considered if RA control is not obtained with DMARDs. It has been proposed that these patients should present: figures of CD4 > 200/mm<sup>3</sup>, a viral load < 60,000 copies/mm<sup>3</sup> and not present a concomitant infection before starting biological therapy.<sup>10</sup>

### Consensus update of the Spanish Society of Rheumatology

In the latest update by the Spanish Society of Rheumatology on RA therapy, a risk of hepatotoxicity by LFN and MTX is indicated. In relation to biological agents, it is suggested that HBV and HCV serology should be determined before beginning treatment and a strict hepatic function control should be undertaken, as well as assessing HBV vaccination in patients without infection.<sup>13</sup>

### Recommendations from the American College of Rheumatology

The latest recommendations of the American College of Rheumatology contraindicate the treatment with MTX and LFN in all

patients with HBV and/or HCV. With regards to biological therapy, its contraindication depends on the functional state of the liver disease. Anti-TNFs, RTX and abatacept are thus contraindicated in patients with HBV and/or HCV who present Child-Pugh class B or C (regardless of prophylactic antiviral treatment), with those with Child-Pugh A being allowed.<sup>14</sup>

### Recommendations from the European League Against Rheumatism

The latest recommendations from the European League Against Rheumatism on RA treatment advise undertaking HBV and HCV serology before starting biological therapy in all patients. They recommend that anti-TNFs not be administered to patients with HBV infection. A HBV serology should be carried out before starting RTX; if this is positive, RTX treatment would be contraindicated. Should HBV infection be diagnosed during treatment with anti-TNF, prophylactic anti-viral treatment should be added.<sup>15</sup>

### Conclusions

#### *Rheumatoid arthritis and the hepatitis B virus*

- The DMARDs MTX and LFN would not be recommended. Gold salts, antimalarials and salazopyrin would be allowed.
- Biological drugs are not hepatotoxic, but there is a risk of HBV reactivation. In patients with HBsAg (+), we recommend antiviral prophylaxis (lamivudine) before and during anti-TNF treatment, and treatment with RTX would not be recommended. In patients with HBsAg (-), we would recommend close monitoring of hepatic enzymes and viral DNA.

*Rheumatoid arthritis and the hepatitis C virus*

- The DMARDs MTX and LFN present risk of hepatotoxicity. Other DMARDs would be allowed.
- Anti-TNF drugs and RTX are effective and safe in patients with RA and chronic HCV infection, with antiviral prophylaxis not required. There are few cases with abatacept, although no reactivation of HCV has been reported.

*Rheumatoid arthritis and human immunodeficiency virus*

- Treatment with salazopyrin and antimalarials is allowed.
- Biological treatment could be considered in selected cases.

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