

Profilaxia da Reactivação do Vírus da Hepatite B na Terapêutica Imunosupressora em Doenças Reumáticas. Orientações para a Prática Clínica

Prophylaxis of Hepatitis B Reactivation with Immunosuppressive Therapy in Rheumatic Diseases. Orientations for Clinical Practice

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RESUMO | A reactivação da infecção pelo vírus da hepatite B (VHB) é uma complicação potencialmente grave da imunossupressão, que pode ser identificada e prevenida de modo eficaz. Tem-se verificado um número crescente de casos de reactivação do VHB em doentes sob imunossupressão no contexto de doenças reumáticas, como a artrite reumatóide ou o lúpus eritematoso sistémico. As recomendações nesta área devem ser individualizadas, tendo em conta dois aspectos: os esquemas imunossupressores utilizados (alto ou baixo risco de reactivação) e as diferentes fases da infecção pelo VHB, como seja a hepatite B crónica, o portador inactivo do VHB, ou mesmo a infecção oculta (por exemplo AgHBs negativo com anti-HBc positivo). Nos doentes com doenças reumáticas que vão iniciar terapêutica imunossupressora de alto risco, propomos o rastreio universal com testes serológicos da hepatite B com o antígeno de superfície do VHB (AgHBs), anticorpo anti-HBs e anti-HBc. Os doentes com hepatite B crónica (AgHBs positivo, ADN VHB ≥ 2000 UI/ml) devem iniciar terapêutica antivírica; os portadores inactivos do VHB (AgHBs positivo, ADN VHB < 2000 UI/ml, aminotransferases normais) expostos a terapêutica imunossupressora de alto risco devem realizar igualmente profilaxia da reactivação do VHB. A profilaxia deve ser iniciada 2 a 4 semanas antes do início da terapêutica imunossupressora e mantida pelo menos durante 6 a 12 meses após a sua suspensão. Recomenda-se a utilização do entecavir ou tenofovir como antivíricos de primeira linha. Nos portadores inactivos do VHB sob terapêutica imunossupressora de baixo risco nos doentes AgHBs negativo / anti-HBc positivo (infecção a VHB no passado ou infecção oculta), a estratégia deve ser monitorização da reactivação viral através da determinação das aminotransferases e do ADN-VHB a cada 6 meses). *GE – J Gastroenterol 2011;18:123-130*

PALAVRAS-CHAVE: Doenças reumáticas, reactivação da hepatite B, imunossupressão, entecavir, tenofovir.

ABSTRACT | Reactivation of infection with hepatitis B virus (HBV) is a potentially serious complication of immunosuppression, which should be identified and efficiently prevented. There have been an increasing number of cases of HBV reactivation in patients receiving immunosuppression in the context of rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus. The recommendations in this area should be individualized taking into account two aspects: immunosuppressive regimens used (high or low risk of reactivation) and the different stages of HBV infection: chronic hepatitis B, inactive HBV carrier, occult hepatitis B infection defined by HB surface antigen (HBsAg) negative and antibody anti-HB core (anti-HBc) positive. In patients with rheumatic diseases that will start high risk immunosuppressive drugs, we propose a universal screening with serological tests for hepatitis B (HBsAg, anti-HBs and anti-HBc). Patients with chronic hepatitis B (HBsAg positive, HBV DNA ≥ 2000 IU / ml) should initiate antiviral therapy. Inactive HBV carriers (HBsAg positive, HBV DNA < 2000 IU / ml, normal aminotransferases) exposed to high risk immunosuppressive therapy should undergo prophylaxis of HBV reactivation.

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Prophylaxis should be started 2 to 4 weeks before the beginning of immunosuppressive therapy and maintained for at least 6 to 12 months after its suspension. It is recommended to use entecavir or tenofovir as first line antiviral agents. In inactive HBsAg carriers under low-risk immunosuppressive therapy and patients with HBsAg negative / anti-HBc positive (HBV infection in the past or occult infection), the strategy should be monitoring of viral reactivation with aminotransferases and HBV DNA determination in every 6 months. *GE – J Gastroenterol 2011;18:123-130*

KEYWORDS: Rheumatic diseases, hepatitis B reactivation, immunosuppression, entecavir, tenofovir.

INTRODUCTION

Hepatitis B virus (HBV) chronic infection is the leading cause of liver cirrhosis and hepatocellular carcinoma (HCC) in the world¹. It is estimated that almost one third of the world population has been infected with the virus and about 350 million people are chronically infected². In Portugal, about 1% of the population has a chronic carrier of HBsAg³. Hepatitis B infection is easily prevented by vaccination⁴.

HBV infection is a heterogeneous disease with distinct phases, depending on age of infection, viral replication, immune response against the virus and liver damage. The evolution for chronicity is unusual in adults, with more than 99% clearing effectively the virus⁵. However, in most of these patients viral particles remain in the nucleus of the hepatocytes, and may be used as copies for viral replication under some circumstances, like immunosuppression⁶. If not detected and treated, viral reactivation can be severe and sometimes fatal. Given the increasing use of immunosuppressant, the potential serious effects of HBV reactivation and efficacy of prophylaxis, it is important to identify patients at risk and implement appropriate measures.

The aim of this paper is to review hepatitis B virus reactivation in patients under immunosuppression therapy for rheumatic diseases and to propose prophylactic measures. This was made considering recent data available in the literature of rheumatic diseases and taking into account the experience obtained in other areas where there is more extensive knowledge on this subject, like hematology and oncology^{7,8}.

HEPATITIS B VIRUS INFECTION

1) The natural stages of chronic hepatitis B virus infection

The natural history of chronic hepatitis B (CHB) infection is determined by the interplay between the virus and the host immune response^{9,10}. According to this, it is possible to distinguish five phases:

- immune tolerant phase. The immune system is not reacting against the virus. The virus replicates freely, hepatitis B e antigen (HBeAg) is positive, with very high levels of HBV DNA, (more than 10^8 IU/ml) but there is no liver damage and aminotransferases are normal.

- immune reactive phase. The immune system controls the virus. Low serum HBV DNA levels are present, with increased or fluctuating levels of aminotransferases and moderate to severe liver necroinflammation.

- inactive HBV carrier phase. Represents immunological control of the infection and is characterized by very low or undetectable serum HBV DNA levels, antibody against HBeAg (anti-HBe) positivity and normal aminotransferases. These patients have a very low risk of cirrhosis or HCC. HBV DNA is less than 2 000 IU/mL.

- HBeAg negative CHB phase. This represents a later phase in the natural history of CHB infection, with the development of HBeAg negative variants. It is characterized by active hepatitis, with fluctuating levels of HBV DNA and aminotransferases.

- HBsAg negative phase. This is the closest to cure of CHB infection and it is characterized by the presence of antibody against HBcAg (anti-HBc) with or without antibody against HBsAg (anti-HBs). In these patients, low-level of HBV replication occurs in the liver, but HBV DNA is generally not detectable in the serum (termed occult HBV infection)¹¹. This occurs because during viral replication copies of covalently closed and circular DNA (cccDNA) are produced, and these remain in the nucleus of the hepatocytes, integrated in host DNA. It is considered that all HBsAg negative anti-HBc positive individuals are potential HBV occult carriers. Although they have generally an excellent prognosis, an increasing number of viral reactivation cases have been reported in concomitantly immunosuppressed patients¹² or in the setting of organ transplants¹³.

This late phase is indistinguishable from the recovery of an acute hepatitis B.

2) Diagnostic markers in hepatitis B virus infection

The diagnosis of HBV infection typically is based on the evaluation of serologic markers of HBV infection. The serologic markers allow the distinction between active (including acute or chronic hepatitis B) and past infection. It also identifies vaccinated and susceptible persons for acquiring HBV infection (Table 1).

3) Definitions and diagnostic criteria used in HBV infection

In clinical practice, it is useful to classify patients with the following definitions: chronic hepatitis B, inactive HBsAg carrier and “resolved” hepatitis B^{14,15}.

- chronic hepatitis B (active carrier of HBV) is defined as the presence of HBsAg (two determinations, 6 months apart) with or without concomitant HBeAg and HBV DNA ≥ 2000 IU/ml (the immune reactive phase and the HBeAg

negative CHB phase). This condition is characterized by chronic necroinflammatory liver disease (elevated ALT and histological lesions in liver biopsy) related with persistent viral replication. Chronic hepatitis B can be subdivided into HBe-positive chronic hepatitis B and HBe-negative chronic hepatitis B. Hepatitis B e-negative chronic hepatitis B is the most common, representing nowadays about 70 to 80% of chronic hepatitis¹⁶. Therapy for HBV is indicated. When HBV DNA levels are above 2000 IU/ml and/or the serum ATL levels are above the upper limit of normal and liver biopsy shows moderate to severe active necroinflammation and/or fibrosis.

- inactive HBsAg carrier is defined as the presence of HBsAg without HBeAg, normal aminotransferases and low viral load (< 2000 UI/ml). These patients have persistent liver HBV infection without significant ongoing necroinflammatory disease (they have HBV “infection” without “hepatitis”). There is no indication for therapy in this group but they may be candidates for prophylaxis of HBV reactivation.

- “resolved” hepatitis B (the HBsAg-negative phase described above) is characterized by previous history of acute or chronic hepatitis B or the presence of anti-HBc (with or without anti-HBs). HBV DNA is usually undetectable in the serum, but may be detectable in hepatocytes. It is considered as potential occult hepatitis B infection (OBI). These concepts are outlined in table 2.

HEPATITIS B INFECTION AND IMMUNOSUPPRESSIVE THERAPY

1) The mechanism of HBV reactivation

The immunosuppressive schemes used in several diseases and in the transplantation field may influence HBV infection, accelerating the course of liver disease or reactivating it¹⁷. In most situations, reactivation of hepatitis B leads to an asymptomatic flare, but cases of decompensated liver disease, fulminant hepatitis and death have been described^{12,18}.

Table 1. Interpretation of hepatitis B virus serology

SEROLOGY	INTERPRETATION
HBsAg – Anti-HBc – Anti-HBs –	Susceptible for HBV infection
HBsAg – Anti-HBc + Anti-HBs +	Previous HBV infection
HBsAg – Anti-HBc + Anti-HBs –	Previous HBV infection (more rarely, false positive or chronic HBV infection without HBsAg, i.e occult B infection)
HBsAg – Anti-HBc – Anti-HBs +	Immunization to HBV infection due to vaccination
HBsAg + Anti-HBc + / IgM anti-HBc + Anti-HBs –	Acute HBV infection (could also be a chronic infection/reactivation)
HBsAg + Anti-HBc + / IgM anti-HBc – Anti-HBs –	Chronic HBV infection

Table 2. Definition and diagnostic criteria of chronic hepatitis B, inactive HBsAg carrier state and resolved hepatitis B infection/occult B infection

BsAg	Chronic hepatitis B	hepatitis	“Resolved” hepatitis B (anti-HBc positive)
HBeAg	+	+	-
anti-HBs	+ / -	-	-
anti-HBc	-	-	+ / -
ALT	+	+	+
HBV DNA blood	Persistent or intermittent increase	Persistently normal	Persistently normal
HBV DNA tissue	+ (≥ 2000 UI/ml)	+ (< 2000 UI/ml)	- (> 90%)
Liver injury	+	+	+* / -
(necroinflammation)	Yes (> 90%)	No (> 90%)	No

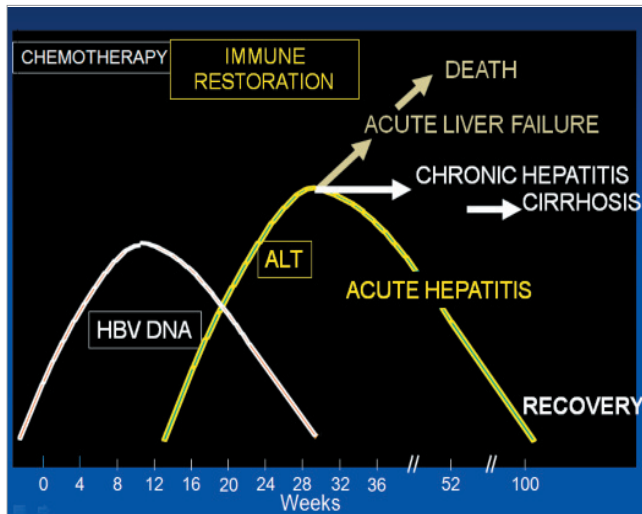


Fig. 1. Hepatitis B reactivation and immunosuppressive therapy

Liver damage in HBV reactivation occurs in two main occasions (Fig. 1): massive viral replication during immunosuppression or in the immune restoration phase, immediately after the withdrawal of immunosuppression, which is characterized by an enhanced host immune response against HBV infected hepatocytes. This latter mechanism is the most implicated in liver damage, which can vary from a mild hepatitis to hepatic failure and death.

The rate of reactivation is higher in the context of hemato-oncological diseases (14 to 70%)^{18,19}. HBV reactivation can also occur in patients receiving chemotherapy for solid organs²⁰, and this complication can become more frequent due to the increasingly aggressive immunosuppressive regimens.

Severe cases of hepatitis flares have been described during treatment with anti-tumor necrosis factor (anti-TNF) agents in patients with rheumatoid arthritis^{21,22} and inflammatory bowel disease (IBD)^{23,24} with chronic HBV infection. With the widespread use of this class of drugs, more cases of reactivation of HBV infection in inactive HBsAg carriers²⁵ and also in individuals with occult infection²⁶ have been reported. The long term follow-up of HBsAg negative/anti-HBc positive patients treated with anti-TNF suggests that the reactivation rate is low. In fact, in a cohort of 72 patients followed for 43.5 ± 21.3 months no reactivation has occurred²⁷. The issue of HBV reactivation has been included in review articles and consensus on the management of IBD patients^{28,29}. The evidence seems to support that if HBV infection is properly diagnosed and treatment or prophylaxis is adequately begun the use of anti-TNF in hepatitis B patients is safe³⁰⁻³².

Other biological therapies, particularly rituximab (anti-CD20)^{12,33-35} and alemtuzumab (anti-CD52)³⁶ have been involved in cases of HBV reactivation of HBsAg positive individuals and of HBsAg negative/anti-HBc positive patients with hemato-oncologic diseases. The risk of HBV reactivation with

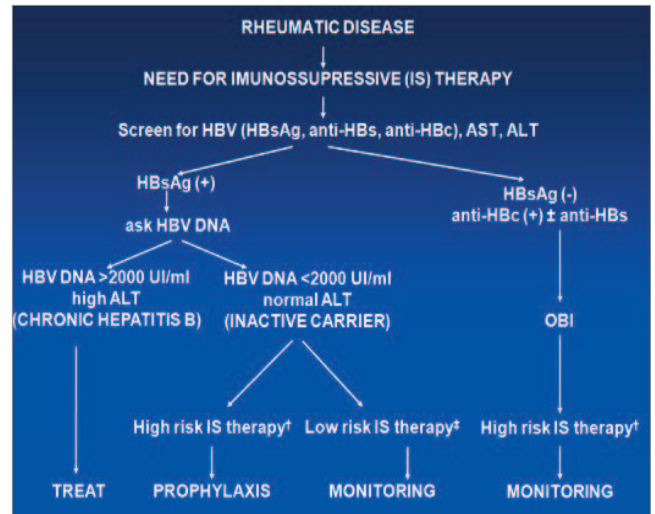


Fig. 2. Algorithm to manage HBV infected patients undergoing immunosuppressive therapy for rheumatic diseases

*OBI – Occult B Infection

† glucocorticoids > 7.5 mg / day for long periods, anti-TNF, rituximab, cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, mycophenolate mofetil and azathioprine

‡ glucocorticoids < 7.5 mg / day, sulphasalazine, hydroxychloroquine and gold compounds

rituximab is higher when it is used in combination with chemotherapy, but it can occur with rituximab alone³⁵. Reactivation of HBV seems to be less frequent in rheumatic patients treated with rituximab but some cases have been reported³⁷.

There are no reported cases of HBV reactivation in the context of the use of abatacept, anakinra and tocilizumab.

Apart from the use of biologics attention should be also paid to the use of other immunosuppressors for rheumatic diseases treatment. Of particular relevance is the use of moderate to high dose of corticoids for systemic lupus erythematosus management which have been clearly associated with HBV reactivation³⁸. In addition, treatment of rheumatoid arthritis with low dose methotrexate (MTX) has been associated with fatal HBV reactivation in HBsAg negative/anti-HBc positive patients and the immunological reconstruction after MTX withdrawal has been also associated with fatal HBV reactivation³⁹⁻⁴².

Beyond the risk of a serious hepatic event, HBV reactivation associated with immunosuppression has a negative impact on their disease, delaying or hindering treatments that would be needed for remission induction or maintenance, with a significant impact on social and familiar aspects and in the quality of life of these patients.

There are some trials, including two randomized trials, showing that prophylactic therapy with lamivudine can reduce the rate of viral reactivation and mortality⁴³⁻⁴⁵. However, in the field of rheumatology, there are no national or international recommendations for the prophylaxis of HBV reactivation, despite some previous discussions published in the context of case reports and reviews^{21-28,46}.

2) WHO SHOULD BE SCREENED FOR HBV INFECTION?

There is no consensus on which patients should be screened before the institution of an immunosuppressive therapy. There are two main strategies: screening patients considered at high risk for HBV infection or universal screening. The European Association for the Study of the Liver (EASL) guidelines¹⁵, recommend universal screening of all candidates for immunosuppressive therapy. Given the absence of risk factors in many patients with HBV infection, the risk of HBV reactivation and the possibility of adequate prevention, we defend that screening should be universal. Thus, and referring to patients with rheumatic disease, all patients who will start or are assumed to require immunosuppressive therapy should be screened for HBV infection.

3) HOW TO SCREEN?

The screening for HBV chronic infection should be done with the determination of HBsAg, anti-HBc and anti-HBs. It is further recommended that patients with negative serological tests (HBsAg, anti-HBs and anti-HBc all negative) should be vaccinated as soon as possible, preferably with a rapid scheme, consisting of four doses at 0, 1, 2 and 12 months. The patients with positive HBsAg should be evaluated for viral load (HBV DNA by Real time PCR)⁴⁷.

In vaccinated population, anti-HBs titles should be evaluated.

4) THE DIFFERENCE BETWEEN HBV THERAPY, PROPHYLAXIS AND MONITORING

The term therapy is reserved for treatment of patients with liver damage (chronic hepatitis B).

The term prophylaxis is used to characterize the use of antiviral agents in order to prevent viral reactivation. Prophylaxis can be performed on all individuals at risk (universal) or initiated only if evidence of reactivation, consisting in increased level of HBV DNA and / or seroreversion of HBsAg (i.e. HBsAg negative individuals that become positive) and hepatitis flare (targeted). Inactive HBsAg carriers treated with low risk immunosuppressive therapies should maintain a strategy of periodic monitoring HBV reactivation.

Monitoring is done by testing HBV DNA and aminotransferases periodically, with some authors suggesting a three to six months interval^{7,46}. It was demonstrated that the increase of HBV DNA occurs early in the natural history of reactivation, preceding the aminotransferases flare^{48,49}. If monitoring is the strategy, prophylaxis or therapy for HBV should be initiated as soon as there is increase in viral load.

5) WHICH RHEUMATIC PATIENTS SHOULD START THERAPY AND / OR PROPHYLAXIS OF HBV REACTIVATION?

Reactivation of HBV depends fundamentally on two issues: phase of infection (active, inactive or occult B infection) and

Table 3. Treatment strategies according to HBV stage

HBsAg POSITIVE	
Chronic hepatitis B	Antiviral therapy (entecavir or tenofovir)
Inactive HBsAg carrier state	<ul style="list-style-type: none"> • High risk therapy[†] Prophylaxis (entecavir, tenofovir, lamivudine*)
(HBV DNA below 2.000 IU/ml)	<ul style="list-style-type: none"> • Low risk therapy[‡] Monitoring
+HBsAg negative, Anti-HBc positive, (± anti-HBs)	<ul style="list-style-type: none"> • High risk therapy[†] • Monitoring

[†] glucocorticoids > 7.5 mg / day for long periods, anti-TNF, rituximab, cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, mepolizumab and azathioprine

[‡] glucocorticoids <7.5 mg / day, sulphasalazine, hydroxychloroquine and other compounds

*in very selected cases, with low or undetectable HBV DNA and immunosuppressive therapy expected for short period (less than 12 months)

Table 4. Strategies for hepatitis B treatment, prophylaxis and monitoring

Antiviral therapy	Entecavir	0,5 once daily (1 mg in cases resistant to Lamivudine)
	Tenofovir	300 mg once daily
Prophylaxis	Same as for therapy	Adverse effects (very rare): headache, nausea, fatigue,
	Lamivudine	100 mg once daily
Monitoring	HBV DNA, ALT and HBsAg periodically (6/6 months)	Adverse effects (< 1%): renal tubular dysfunction proximal, osteoporosis, diarrhea, nausea, vomiting, skin rash

type of immunosuppression.

- *Chronic hepatitis B infection (HBsAg positive, HBV DNA ≥ 2000 IU/ml, increased or normal ALT, necroinflammation and fibrosis on liver biopsy).*

This group of patients should start antiviral therapy for hepatitis B, whether performing or not immunosuppressive therapy^{7,14,15}. Immunosuppressive therapy in patients with chronic hepatitis B under antiviral therapy is safe⁵⁰.

- *Inactive HBsAg carriers (HBsAg positive, HBV DNA < 2000 IU / ml, normal ALT)*

In these patients, there is a risk of HBV reactivation, which is related with the type of immunosuppression used. The use of steroids in medium or high dose (> 7.5 mg / day for long periods), anti-TNF drugs, rituximab, cyclophosphamide, methotrexate, leflunomide, calcineurin antagonists, mycophenolate mofetil and azathioprine is associated with high risk of reactivation (14 to 70%) and thus these patients should perform universal prophylaxis, regardless of viral load²⁵. Patients receiving glucocorticoids < 7.5 mg / day, sulphasalazine, hydroxychloroquine and gold compounds are considered at low risk for HBV reactivation⁴⁶. In these patients we recommend monitoring of HBV DNA, ALT, AST and HBsAg every 6 months, starting prophylaxis / therapy in the case of HBV reactivation (HBV DNA ≥ 2000 IU / ml and / or seroreversion of HBsAg).

- *Occult hepatitis B virus infection*

The management of occult B hepatitis virus infection is still a controversial issue. There are not enough data in the literature on this subgroup of patients. In two recent papers, no evidence of HBV reactivation was found in rheumatic patients treated with anti-TNF therapy and resolved hepatitis B (anti-HBc positive)^{27,30}. Prophylaxis in this setting is not recommended. It is suggested monitoring for HBV reactivation (mainly those submitted to highly immunosuppressive treatments).

This concepts and decision algorithm is schematized in table 3.

6) WHEN TO START AND TO STOP PROPHYLAXIS?

Prophylaxis should be started 2 to 4 weeks before the beginning of immunosuppressive therapy. As already mentioned, the risk of HBV reactivation is greater after the withdrawal of immunosuppression (immune restoration period). Therefore, prophylaxis should be maintained for at least 6 to 12 months after the suspension of immunosuppressants^{14,15}.

7) WHICH DRUGS TO USE?

Drugs with anti-HBV activity are based primarily on two groups: nucleoside / nucleotide analogues (NA) and pegylated interferons.

Pegylated interferons (alpha-2b or Peginteron® and alpha-2a or Pégasys®) have not only antiviral but also immunomodulator effects and may lead to acute hepatitis flares. They should not be used in this context.

The nucleoside / nucleotide drugs (NA) are orally administered (one pill a day), well tolerated and safe. There are several NA approved for the therapy of chronic hepatitis B: lamivudine and adefovir, which are first generation drugs having high levels of resistance⁵¹, and entecavir and tenofovir, with high potency and low resistance profile⁵². Lamivudine is an inexpensive drug, but due to its low genetic barrier, with rates of resistance as high as 20% after one year and up to 75% at five years, it is no longer recommended as first line treatment of HBV. However, most studies of prophylaxis of HBV reactivation in patients undergoing immunosuppression are with lamivudine⁴³⁻⁴⁵. This drug can be a valid option in selected cases, like prophylaxis in HBsAg negative / anti-HBc positive during short term immunosuppression, such as the case of hematologic or oncologic disorders. Nevertheless, in patients with higher viral loads (HBV DNA above 10^7 IU/ml) and in those in whom the duration of immunosuppressive therapy is expected to be held for more than a year, drugs with high potency and high genetic barrier (entecavir and tenofovir) should be considered as first line¹⁵ (table 4). They have excellent resistance profiles, with a rate of resistance of 1,2% at 65 years and 0% at 3 years respectively^{53,54}. Entecavir and tenofovir have been successfully used as prophylactic agents to avoid HBV reactivation in patients under immunosuppressive therapy^{55,56} or to treat hepatitis flares, in cases where prophylaxis was not done^{57,58}.

CONCLUSIONS AND RECOMMENDATIONS:

1. Hepatitis B reactivation during immunosuppressive treatment can occur in any stage of HBV chronic infection; it can be severe and sometimes fatal due to liver failure. The withdrawal of the immunosuppression is also a risk phase.
2. All patients who are candidates for immunosuppressive therapy should be screened for the status of HBV infection.
3. The screening should include ALT, HBsAg, anti-HBs and anti-HBc.
 - a) In patients with HBsAg positivity, viral load (HBV-DNA) should be performed.
 - b) In patients having HBsAg negative / anti-HBc positivity (\pm anti-HBs) occult hepatitis B infection is a possibility.
 - c) Patients negative for all HBV markers should be vaccinated as soon as possible.
4. The management (whether prophylaxis or monitoring) of patients undergoing immunosuppressive with evidence of present or past HBV infection therapy is determined by the stage of HBV infection and the intensity of the immunosuppressive regimen.
5. HBsAg positive patients should be evaluated by a specialist in liver diseases to decide whether to start therapy (active carriers) or prophylaxis (inactive HBsAg carriers under high risk immunosuppressive therapies). Monitoring for HBV reactivation is indicated in inactive carriers under low risk immunosuppressive therapies and occult hepatitis B infection.
6. In HBsAg negative / anti-HBc positivity (\pm anti-HBs) pa-

tients, monitoring is indicated in cases of high risk immunosuppressive therapy.

7. Prophylaxis of HBV reactivation should be initiated 2 to 4 weeks before the beginning of immunosuppressive therapy and maintained 6 to 12 months after its suspension.

8. The drugs recommended for prophylaxis are nucleos(t)ide analogs like entecavir or tenofovir. Lamivudine can be used in selected cases (occult B hepatitis virus infection).

9. Monitoring HBV reactivation should be performed periodically (each 3 to 6 months) with the determination of aminotransferases and HBV DNA levels.

This article has been co-published in *Acta Reumatol Port* 2011;36:110-118

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