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CLINICAL PRACTICE GUIDELINES

Prophylaxis and treatment in liver transplantation. VII Consensus Document of the Spanish Society of Liver Transplantation☆

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KEYWORDS
Donor-derived infection;
Core positive grafts;
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Vaccination

Abstract Whilst prophylaxis of hepatitis B is universally accepted after liver transplantation (LT), national recommendations for the prophylaxis and treatment of hepatitis B virus (HBV) infection after LT are lacking in Spain. The aim of the VII consensus meeting organised by the Spanish Society of Liver Transplantation (SETH) was to set recommendations on the prophylaxis and treatment of hepatitis B after LT.

The scientific evidence and strength of recommendations was evaluated by using the ''Grading of Recommendations Assessment, Development and Evaluation'' (GRADE) system. This document describes the recommendations and their level of evidence for: the definition and risk factors for hepatitis B recurrence after LT, monitoring and prophylaxis of hepatitis B recurrence at different periods after LT, treatment of hepatitis B before and after LT, and the prophylaxis of HBV infection by the recipients of LT with hepatitis B core antigen positive donors.

PALABRAS CLAVE
Infección adquirida;
Donante anticore;
Inmunoglobulina específica;
Análogos nucleósidos;
Vacuna

Profilaxis y tratamiento de la infección por virus de la hepatitis B en el trasplante hepático. VII Documento deconsenso de la Sociedad Española de Trasplante Hepático

Resumen A pesar del consenso universal sobre la necesidad de administrar profilaxis para evitar la recurrencia de la hepatitis B después del trasplante hepático (TH), no existen hasta el momento unas recomendaciones nacionales sobre las pautas concretas para la profilaxis y el tratamiento de la infección por el virus de la hepatitis B (VHB) en el TH. El objetivo de la

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VII reunión de consenso organizada por la Sociedad Española de Trasplante Hepático (SETH) fue unificar criterios y protocolos clínicos entre todas unidades de TH en España, sobre cómo prevenir y tratar la reinfección por el VHB después del TH.

La evidencia y las recomendaciones de este documento se han llevado a cado acuerdo al sistema Grading of Recommendations Assessment Development and Evaluation (GRADE).

En el presente documento se describen las recomendaciones y su grado de evidencia para: la definición de la recurrencia del VHB post-TH y sus factores de riesgo, la monitorización y la profilaxis de la recurrencia del VHB tras el TH en sus diversas etapas, el tratamiento de la hepatitis B antes y después del TH, y la profilaxis de la infección por VHB los receptores de TH con donantes anti-HBc positivo.

Introduction

Hepatitis B virus (HBV) infection is a significant cause of morbidity and mortality on a global level. End-stage liver disease or hepatocellular carcinoma (HCC) due to HBV currently account for between 5 and 10% of liver transplantation (LT) cases in the west and are the most common indication for LT in Asia.[1] Prophylaxis of post-transplantation recurrence of the infection is always necessary. Until the appearance of hepatitis B immunoglobulin (HBIg), end-stage liver disease due to HBV was considered a contraindication for LT, as recurrence of the infection was common, leading to graft loss in a high number of patients and a mortality rate of over 50% a few years after transplantation.[2] Since the introduction of effective means of preventing and treating reinfection, outcomes in LT with this indication have improved and the overall survival of patients who receive transplants due to cirrhosis secondary to HBV infection exceeds 85% at one year and 75% at five years post-transplant.[3]

In spite of the universal consensus on the need to administer prophylaxis to post-LT hepatitis B recurrence,[4–6] there is no agreed strategy with regard to the regimen to follow and it could be said that there are almost as many regimens as LT units. The objective of the consensus meeting organised by the Spanish Society of Liver Transplantation (SETH) was to unify criteria and clinical protocols about how to prevent and treat post-LT HBV reinfection across the 24 LT units in Spain.

The evidence and the recommendations of this document were compiled based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which offers 5 evidence grades (I: randomised controlled studies; II-1: non-randomised controlled studies; II-2: cohort or case-control studies; II-3 case series, uncontrolled experiments; III: expert opinions, descriptive epidemiological studies) and 2 recommendation grades: 1: strong, and 2: weak.

Risk factors for post-LT HBV recurrence

The risk of recurrence is not the same in all patients and will vary depending on various factors.[7–9] It is essential to assess the risk of recurrence in each patient in order to design the most suitable prophylaxis strategy.

- *High risk:* the main risk factor for recurrence is the presence of detectable viral load at the time of the LT, especially with a high viral load >2,000–20,000 IU/ml.[5,7] A history of viral multidrug resistance and poor patient adherence to treatment are also risk factors for recurrence.[8] Hepatitis delta virus (HDV) coinfection does not increase HBV recurrence, but recurrence itself is still a risk given the lack of an effective medication for HDV in the post-transplant period.[9] HIV coinfection is also considered a risk factor for recurrence. Although HCC recurrence has been associated with greater hepatitis B recurrence, pre-transplant HCC does not appear to be a determining risk factor for HBV recurrence.
- *Low risk:* if HBV-DNA is indetectable at the time of LT.[5] However, with the new antiviral drugs, the cut-off points to be considered low risk are not well defined and they could perhaps be less strict.[10] In fact, some studies that have used oral antivirals without HBIg as prophylaxis have not observed recurrence with pre-LT HBV-DNA levels below 1,000–2,000 IU/ml.[11–13]

Definition of post-LT HBV recurrence

With the new treatments for hepatitis B, which are increasingly potent and have an ever greater genetic barrier to viral resistance, the definition of recurrence has taken on different nuances and clinical significance.[14]

- *Serological recurrence (reverse seroconversion):* appearance of HBsAg in blood. This can occasionally be transient and not accompanied by the reappearance of HBV-DNA.
- *Virological recurrence:* appearance of HBV-DNA in serum. Often accompanied by serological recurrence, under treatment with new nucleotide analogues (NA), it may not be accompanied by clinical recurrence.
- *Clinical recurrence:* serological/virological recurrence and increased ALT with histological damage.

Steps in the prophylaxis of post-LT HBV recurrence

The prevention of post-LT recurrence of HBV infection must begin in the pre-transplant period, with the administration of NAs, with the aim of the patient preferably receiving the LT with an indetectable HBV viral load. This has been demonstrated to prevent HBV recurrence and graft loss. The next step will be to prevent reinfection following liver transplantation, by administering HBIg and NAs.

Pre-LT hepatitis treatment

Prophylaxis of HBV infection in LT is indicated in the pre-LT period with the aim of achieving undetectable HBV-DNA by the time of the LT. Patients with cirrhosis due to HBV (compensated or decompensated) or HCC and detectable viral load on the waiting list must receive oral antivirals that offer high potency and a high genetic barrier (entecavir [ETV], tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]), which are indicated whenever HBV-DNA is detectable.[4,5,15]

The choice of NA will take into account previous resistances to antivirals, and the dose must be adjusted based on kidney function.[4,5,16]

In patients with risk factors for kidney or bone disease, ETV and TAF are the drugs of choice.[4] In patients with previous resistance to lamivudine (LAM), TDF or TAF should be used.[4,5] TAF, which has a better kidney and bone safety profile than TDF,[17,18] would be indicated in patients with resistance to LAM and kidney or bone disease,[4,5] although it is not currently marketed in Spain.

For LT to be indicated, liver function must be assessed at baseline and in the first three to six months after starting antiviral treatment, not merely virological response.[16,19,20] If LT is indicated, it is not necessary to wait until the viral load is undetectable.[21]

Patients on the LT list should be followed up every three months (HBsAg, HBV-DNA), closely monitoring their liver and kidney function.[15,16,21]

Approximately 30% of patients with decompensated cirrhosis who receive antiviral treatment are able to get off the LT list due to improvement of their liver function.[22]

Recommendations for pre-LT hepatitis B treatment

All patients with compensated or decompensated cirrhosis due to HBV or with HCC and detectable HBV-DNA must receive antiviral treatment with oral antivirals that offer high potency and a high genetic barrier (ETV or TDF/TAF) (evidence grade I, recommendation grade 1).

In choosing an antiviral treatment, previous antiviral resistances and the presence of kidney or bone disease as risk factors should will need to be taken into account, and the drug dose should always been adjusted based on kidney function. In patients with resistance to LAM, TDF (or TAF in case of kidney or bone disease) should be used. If kidney or bone disease are present as risk factors, ETV or TAF (the drug of choice in case of resistance to LAM) should be used (evidence grade I, recommendation grade 1).

If LT is indicated, it is not necessary to wait until HBV-DNA is undetectable (evidence grade II, recommendation grade 1).

Post-LT hepatitis B prophylaxis

All patients should receive indefinite prophylaxis.[23] The combination of HBIg and a NA is the standard recommended prophylaxis as it avoids post-LT recurrence of HBV infection in more than 95% of patients. It is common to continue the antiviral used prior to LT, which would be an NA offering high efficacy and a high genetic barrier to resistances (ETV/TDF). It is well established that the combination of ETV or TDF with HBIg is more effective than combinations with less potent NAs or those offering a lower genetic barrier to resistance such as LAM.[24,25]

HBIg regimen

The disadvantages of HBIg, such as its high price, parenteral administration or side effects, have led to a constant search for strategies to optimise its administration regimen.[26] The use of low doses,[11,27] subcutaneous administration[28] and its withdrawal in the population at low risk of recurrence[29–32] have demonstrated high efficacy in post-LT hepatitis B prophylaxis. Moreover, no anhepatic phase regimen in either the first week or maintenance period has been found to be superior to another in studies that have combined HBIg with new NAs (ETV/TDF).[33] Taking this into account, and looking at the various protocols of the Spanish LT 24 programmes, the recommended doses in the various phases are:

- Anhepatic phase: 1,000–5,000 IU/IV.
- First week: 1,000–2,000 IU/IV or IM/day.
- First month: 1,000–2,000 IU/week or on-demand dose to maintain anti-HB titres >200 IU.
- Maintenance: 1,000 IU/month or on-demand dose to maintain anti-HB titres >100 IU.

From the first week post-LT, subcutaneous HBIg at a dose of 500 IU 1 ml can be used if weight is <75 kg or 1,000 IU 2 ml if weight is ≥75 kg.

HBIg suspension

In patients at *low risk of HBV recurrence*, the role of HBIg is not well established and, with the appearance of the new NAs, appears less relevant.[34] Studies that have evaluated short HBIg regimens with ETV/TDF have demonstrated effective prophylaxis in all patients, with transient serological or virological recurrence in few patients and clinical recurrence in none.[35–39] The time of HBIg in these studies ranges from 5 days[38] to more than a year post-transplant.[35–37] Moreover, in patients with no history of resistance to LAM, ETV can be a good option given its less nephrotoxic profile.[40] Patients with resistance to LAM and at risk of kidney or bone disease will be candidates for TAF in future, once it enters the market. It is also necessary to emphasize the importance of adherence to treatment in the success of monotherapy.[30]

Although it has traditionally been thought that HDV infection is a risk factor for recurrence as there is no effective treatment for its post-LT reactivation, a recent study suggests that NA monotherapy may be safe in transplant recipients with HBV and HDV coinfection, provided that com-

bined treatment with HBIg is used for an extended period of at least 12–24 months post-transplant.[41]

Prophylaxis without HBIg

In selected patients at low risk of recurrence, ETV or TDF monotherapy without HBIg has been found to be safe and effective in post-LT hepatitis B prophylaxis.[12,13,42] Patients receiving this regimen present HBsAg persistence or serological recurrence in 8–15% of cases, but this is not accompanied by virological recurrence and transaminase levels remain within normal limits.

Suspending prophylaxis

Neither HBIg nor NAs are capable of eliminating the viral infection. In the context of LT, extrahepatic viral replication in the mononuclear cells of peripheral blood appears to play a relevant role in graft reinfection. What is more, NAs inhibit viral replication but do not act on cccDNA, which remains integrated in the hepatocyte nucleus and appears to be the principle agent responsible for recurrence of the infection in patients with no infection in serological/virological markers.[43] In fact, several studies in transplanted patients have detected the presence of HBV cccDNA in a high proportion of patients years post-LT.[44,45] It is because of this that post-LT prophylaxis of HBV recurrence is considered to be life-long.

Lenci et al. demonstrated in their study that suspending prophylaxis after at least three years of combined treatment may be safe in patients at low risk of recurrence, in whom two sequential liver biopsies show no HBV cccDNA or whole DNA in liver tissues.[46] Nevertheless, these techniques are not well standardised and this strategy can only be considered in a research context.

Vaccine

The studies that have assessed the efficacy of post-LT vaccination have been very heterogeneous in terms of the characteristics of the patients included, donor type (cadaveric or living), vaccine type, use of adjuvants, vaccination protocol, response definition and simultaneous use of HBIg or LAM.

The response rates in transplanted patients with chronic infection have ranged from 0 to 75%.[47–63] In general, the response is poor and for the set of studies as a whole is less than 30%.[64]

In patients who received transplants due to acute liver failure due to HBV, with the exception of a single study (no response in five patients),[52] the response rates were much better, between 75 and 100%.[47,51,53,55,61,63] It is likely that, unlike the patients with chronic HBV infection, these patients did not develop immune tolerance, and this may explain the better response to vaccination.[64]

One complication of the use of repeated vaccine doses to maintain sufficient levels of anti-HBs is the development of escape mutations,[65] with the consequent loss of efficacy and development of HBV infection recurrence if used alone as a prophylaxis strategy.

For these reasons, post-LT vaccination is not accepted as a strategy for post-LT prophylaxis of HBV recurrence in patients with chronic infection in order to suspend antiviral prophylaxis and could only be considered in the context of clinical trials.[64,66] Its use could be considered in patients who have received transplants due to liver failure.

Monitoring post-LT HBV recurrence

Transplanted patients must receive life-long monitoring for disease caused by HBV.[4–6]

- Combination with HBIg: anti-HB titres should be determined every one to two months and HBsAg and HBV-DNA three months for the first two years, then every six months.
- Without HBIg: patients on NA monotherapy should be monitored every three months for the first year, every six months for the second year and every six to twelve months from the third year, with HBsAg and HBV-DNA.

Kidney function should be monitored at each visit.

Recommendations for post-LT prophylaxis

All patients should receive indefinite prophylaxis. The combination of immunoglobulin (HBIg) and a potent NA (ETV/TDF/TAF) is the standard prophylaxis recommended to avoid recurrence of the HBV infection after transplantation (evidence grade II-1, recommendation grade 1).

With high-efficacy NAs (ETV/TDF/TAF), it is possible to use low doses of HBIg (evidence grade II-1, recommendation grade 1).

In patients at low risk of recurrence (HBV-DNA indetectable at the time of LT), it is an option not to use HBIg or to suspend it between the first week and three months post-LT, continuing NA maintenance monotherapy (evidence grade II-2, recommendation grade 1).

Post-LT vaccination is not accepted as a strategy to suspend antiviral prophylaxis (evidence grade II-2, recommendation grade 1).

In those who have received liver transplants due to acute liver failure due to HBV, vaccination is more effective than in chronic infection and its use could be contemplated (evidence grade II-3, recommendation grade 2).

Treatment and follow-up of post-LT hepatitis B recurrence

Treatment of HBV recurrence and the choice of antiviral drug must follow the same principles as pre-LT, using ETV, TDF or TAF,[4,5,16,67] although the series published with both ETV[68–70] and TDF[70–73] have been short. HBIg should be interrupted if used.[66]

The choice of antiviral must take into account the regimen used previously. In patients with resistance to LAM, TDF should be used. In patients with kidney dysfunction or bone disease, ETV is preferable, unless there is resistance to LAM. In these cases, TAF would be indicated. The combination of ETV and TDF may be required in case of multidrug resistance.[21]

Outcomes of HBV recurrence treatment are good in terms of attaining HBV-DNA negativity.[16,66,67] There is little information about the rate of HBsAg loss, which appears to be low.[74]

Virological follow-up (HBsAg, HBV-DNA) should be performed every three months (first year), then every six months, indefinitely.[75,76]

Recommendations for treatment of post-LT hepatitis B recurrence

Treatment of HBV recurrence and the choice of antiviral drug must follow the same regimens as pre-LT, with HBIg administration not being indicated (evidence grade I, recommendation grade 1).

In choosing an antiviral treatment, previous antiviral resistances and the presence of kidney or bone disease as risk factors should will need to be taken into account, and the drug dose should always been adjusted based on kidney function. In patients with resistance to LAM, TDF (or TAF in case of kidney or bone disease) should be used. If kidney or bone disease are present as risk factors, ETV or TAF (the drug of choice in case of resistance to LAM) should be used. The combination of ETV and TDF may be required in case of multidrug resistance (evidence grade I, recommendation grade 1).

HBV infection prophylaxis in recipients from anti-HBc positive donors

The prevalence of anti-HBc positivity in donors in Spain is around 12%, rising to 27% in those over 60.[77]

The risk of developing *de novo* hepatitis B (DNHB) post-LT varies depending on the recipient's serological status, being high (48–77%) in naïve (anti-HBc negative/anti-HBs negative) patients and very low (0–5.5%) in anti-HBc positive/anti-HBs positive patients. In anti -HBc positive/anti-HBs negative and anti-HBs positive/anti-HBc negative recipients (patients vaccinated pre-LT) the prevalence is intermediate, at 13–19.5% and 9.7–20%, respectively.[78–82] The presence or absence of anti-HBs in an anti-HBC positive donor does not appear to affect the risk of DNHB.[77,83] Although it is somewhat surprising that patients with anti-HBs positivity alone as the result of pre-LT vaccination have a similar risk of developing DNHB to recipients with only anti-HBc positivity, the explanation could lie in the fact that the studies do not analyse the anti-HBs titres obtained or their evolution post-LT, while it is known that cirrhotic patients who respond to vaccination often obtain relatively low anti-HBs titres which fall gradually following the LT due to immunosuppression. Sintusek et al. demonstrates losses of protective anti-HBs titres (>10 mIU/ml) of 46%, 57% and 82% at one, two and three years, respectively.[84]

DNHB can appear at any time post-LT,[78–80] so prophylaxis must be indefinite.[76]

Recipients from anti-HBc positive donors who are *naïve* or either anti-HBc or anti-HBs positive in isolation are considered candidates to receive prophylaxis, which those who are both anti-HBc and anti-HBs positive do not require it.[79] HBsAg negative/anti-HBc positive recipients who receive an anti-HBC negative graft likewise do not require it.

Prophylaxis with HBIg, LAM or combined prophylaxis (HBIg + LAM) had demonstrated a significant reduction in the risk of DNHB in recipients from anti-HBc positive donors. Thus, in a meta-analysis of 21 studies that included 788 patients, the use of prophylaxis reduced the rate of DNHB compared to no prophylaxis in *naïve* recipients (from 47.8 to 12%), recipients with anti-HBc positivity only (from 15.4 to 3.4%) and vaccinated recipients (anti-HBs + only) (from 9.7 to 0%). The best results were therefore obtained in patients vaccinated pre-LT who received prophylaxis post-LT (0% DNHB), which highlights the value of pre-LT vaccination, independently of the indication for post-LT antiviral prophylaxis. In the same study, prophylaxis with LAM demonstrated lower rates of DNHB than HBIg, especially in the group of recipients at highest risk (naïve) (3.4 vs 27%).[79] Furthermore, in another systematic review of 13 studies that included 183 patients, prophylaxis with LAM showed similar results in terms of DNHB development to combined prophylaxis with LAM + HBIg (2.7 vs 3.6%).[85]

The little information available on the use of ETV or TDF as prophylaxis for recipients from anti-HBc positive donors has shown them to have 100% efficacy in preventing DNHB.[86,87] These drugs have been little used to date due to their high cost in relation to LAM.

LAM monoprophylaxis has been seen as the regimen of choice in prophylaxis for recipients from anti-HBc positive donors due to its cost-effectiveness,[4,76,77] although it is associated with a 3% rate of DNHB development, generally due to the emergence of HBV mutations associated with resistance.[75] With the notable reduction in the price of ETV and TDF now in Spain, these drugs should be recommended as the first option for prophylaxis.[5,66]

Regardless of whether antiviral prophylaxis is indicated, all recipients from anti-HBc positive donors must receive follow-up (HBsAg, HBV-DNA) every three months (first year), then every six months indefinitely.[75,76]

DNHB treatment in those receiving prophylaxis with PAM should be with TDF or TAF (in case of kidney or bone disease). In those not receiving LAM, the choice of antiviral drug should follow the criteria indicated for the treatment of HBV infection.[4,5]

Role of post-LT vaccination in HBV infection prophylaxis in recipients from anti-HBc positive donors

There is scant information on the efficacy of post-LT vaccination outside the context of living donors in Asian and paediatric patients. In general, these patients appear to be better candidates for vaccination than those receiving transplants due to cirrhosis caused by HBV, with response rates between 55 and 90%.[63,65,88,89] Obtaining high anti-HBs titres through pre-LT vaccination >1,000 mIU/ml and maintaining anti-HBs >100 mIU/ml post-LT has allowed the use of LAM as prophylaxis to be avoided.[90] In another study in paediatric patients, titres >200 mIU/ml pre-LT were associated with an absence of DNHB without the need for antiviral prophylaxis.[91]

It is possible that the use of pre-LT vaccination, obtaining high anti-HBs titres and maintaining post-LT anti-HBs titres >100 mIU/ml through the administration of repeated doses of vaccine could avoid the need for antiviral prophylaxis, although this has not been investigated in adult recipients from cadaveric donors and therefore cannot currently be recommended as a prophylaxis strategy in place of antivirals.

Recommendations for HBV infection prophylaxis in recipients from anti-HBc positive donors

The risk of post-LT DNHB in recipients from anti-HBc positive donors varies depending on the recipient's serological status, being high in *naïve* (anti-HBc negative/anti-HBs negative) recipients, intermediate in recipients who are either anti-HBc or anti-HBs positive in isolation and low in those who are anti-HBC positive/anti-HBs positive. *Naïve* recipients and those who are either anti-HBc or anti-HBs positive in isolation (regardless of anti-HBs titre) should receive antiviral prophylaxis, and this must be indefinite (evidence grade II-1, recommendation grade 1).

LAM has been seen as the drug of choice in prophylaxis for recipients of livers from anti-HBc positive donors due to its cost-effectiveness (evidence grade II-1, recommendation grade 1).

With the current reduction in the cost of ETV and TDF these drugs should be used as the first option in place of LAM because of their high genetic barrier (evidence grade II-2, recommendation grade 1).

Regardless of whether antiviral prophylaxis is indicated, all recipients from anti-HBc positive donors must receive follow-up (HBsAg, HBV-DNA) every three months (first year), then every six months indefinitely (evidence grade II-1, recommendation grade 1).

Post-LT vaccination in recipients from anti-HBc positive donors appears to show good outcomes, although there is not yet sufficient evidence to recommend this prophylaxis strategy in place of antivirals (evidence grade III, recommendation grade 2).

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Conflicts of interest

Travel/conferences: JC: Astellas, Novartis, Chiesi; GC: Novartis, Astellas; MCB: Biotest. LG and JIH: Gilead; SP: Abbvie, Gilead, Bayer; MP: Gilead, BMS. TS: Astellas, Novartis, Gilead, Abbvie. Consulting: SP: Bayer. No other conflicts of interest are declared.

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Appendix A. Authors participating in the working group representing their respective liver transplantation programmes

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