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Management of special patient groups with hepatitis B virus infection: The EASL 2017 Clinical Practice Guidelines

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ABSTRACT

The morbidity and mortality of hepatitis B virus-related liver disease are linked to the persistence of the hepatitis B virus replication. Viral suppression with antiviral therapy has been shown to provide clinical benefits. Several special groups of patients with hepatitis B virus infection require special attention. In this brief report, based on European Association for the Study of the Liver 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, the current optimal management of special patient groups with hepatitis B virus infection is summarized.

Keywords: Hepatitis B virus, special patient group, pregnancy, dialysis patients

Quick Look to Guidelines

INTRODUCTION

An estimated 350 million individuals are chronically infected with hepatitis B virus (HBV) in worldwide (1,2). Each year, approximately 1 million individuals die as a result of HBV-related end-stage liver disease and its complications (3,4). The spectrum of HBV-related diseases is variable, ranging from an inactive HBV carrier state to progressive disease, which may evolve to cirrhosis and its complications, such as portal hypertension or hepatocellular carcinoma (HCC).

The aim of this brief report was to summarize the EASL 2017 Clinical Practice Guidelines (CPGs) updating the recommendations for the optimal management of special patient groups with HBV infection.

Prevention of HBV Recurrence after Liver Transplantation (LT) Post-transplant HBV recurrence may lead to graft loss and mortality as a result of HBV-induced aggressive hepatitis (5-7). Treatment with a combination of nucleos(t)ide analogs (NAs) and hepatitis B immunoglobulin (HBIG) has dramatically decreased HBV recurrence and improved the clinical outcome after LT (5-10). Entecavir (ETV) or tenofovir disoproxil fumarate (TDF) and HBIG combination therapy decrease the risk of graft infection to <5% (1,8).

Hepatitis B immunoglobulin has usually been administered for the maintenance of anti-HBs levels between 50 IU/L and 100 IU/L. However, the optimal dose and duration of HBIG use and optimal anti-HBs titer is still unclear. Previous studies reported that a short-course or HBIG-free regimens can be considered in patients with a HBV-DNA-negative status at LT (8). On the other hand, lifelong NAs and HBIG combination therapy should be administered to patients who are HBV DNA-positive at LT, those who are HBeAg positive, those with hepatitis delta virus (HDV) or HIV coinfections, and those with HCC (8-10). Renal function should be monitored in LT patients because of concomitant use of calcineurin inhibitors.

Hepatitis B virus reactivation is always potential risk in HBV-naïve patients receiving donor organs with evidence of past HBV infection. Lifelong NA prophylaxis should recommend in such recipient.

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Management of Patients with HDV Infection Chronic hepatitis B (CHB) patients should be screened for blood-borne viruses including HDV, hepatitis C virus (HCV), HAV; i.e., HDV is often predominant virus in chronic HBV and HDV coinfection. Currently, pegylated interferon alpha (PegIFNa) for ≥48 weeks is the only available agent to have antiviral activity against chronic HDV infection. Virological response rates of approximately 17%-47% (mean 25%) are observed (1), and late relapse occurs in approximately >50% of responders (1, 11). Thus, long-term HDV RNA monitoring is recommended for all treated patients. In fact, HBsAg loss may develop approximately 10% of treated patients during long-term follow-up. There is no clear data shown that long-term therapy (96 weeks) is superior compare to short-term therapy (48 weeks). NAs did not significant effect on HDV RNA levels.

NA treatment is recommended for coinfected patients with ongoing HBV DNA replication (>2.000 IU/mL) for suppressing residual HBV replication.

PegIFNa treatment is not used in decompensated coinfected patients and should be evaluated for LT.

HEPATITIS C VIRUS coinfected patients HCV coinfection accelerates disease progression and increases risk of HCC in HBV/HCV coinfected patients. Sustained virological response rates with antiviral therapy are not different between patients with chronic hepatitis C with/without chronic HBV infection (12). There is a potential risk of HBV reactivation during or after therapy with direct-acting antiviral agents (DAAs). However, the clinical significance such reactivation remains unclear. HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 after DAA for preventing HBV reactivation. HBV-experienced patients should be monitored for HBV reactivation during DAA therapy.

Human Immunodeficiency Virus coinfected patients HIV coinfection increases risk of hepatic fibrosis progression, cirrhosis, and HCC. Guidelines on the management of HIV-infected patients recommend the initiation of antiretroviral therapy (ART) in patients with HIV and HBV coinfection (13). TDF and TAF have antiviral activity against both HIV and HBV. Thus, discontinuation TDF or TAF-containing ART should be avoided in coinfected patients because of the high risk of severe hepatitis flares and decompensation due to HBV reactivation. Drug toxicity should be closely monitored during ART. TDF and TAF monotherapy can cause HIV resistance mutations.

Acute hepatitis B virus infections: These infections will recovery clinically and virologically without antiviral therapy in >95% adults. But a potentially life-threatening disease manifestation is severe or fulminant acute hepatitis B. Characteristics of severe acute hepatitis B are coagulopathy (INR>1.5), a protracted course (symptoms and signs for >4 weeks), or signs of acute liver failure. The main treatment goal in patients with acute hepatitis B is the prevention of the risk of acute or subacute liver failure. Antiviral therapy in such patients is also improving quality of life as a result of shortening the disease-related symptoms and decreasing the risk of chronicity (1, 2). Several studies indicate that the early antiviral therapy can prevent progression to acute liver failure and subsequently LT or mortality (2,14). Antiviral therapy does not increase the risk of chronicity.

Pregnancy Screening for HBV markers in the first trimester of pregnancy is strongly recommended in all women of childbearing age. Family planning should be discussed with HBV-infected women of childbearing age. Before initiating antiviral therapy for HBV infection, the pregnant woman and her spouse should be informed about the safety data of the HBV drugs. TDF should be preferred in these patients because it has an extensive safety profile and has a better resistance profile (15). There are no satisfactory data regarding the use of LAM, ADV and ETV. PegIFNa is contraindicated during pregnancy.

In a woman of childbearing age, who has no advanced liver fibrosis and is hopeful of pregnancy, it may be prudent to delay antiviral therapy until the child is born. In a woman with advanced fibrosis who decides for a planned pregnancy, TDF treatment has to be initiated and maintained. PegIFNa therapy may be attempted in some cases. If a woman become unexpectedly pregnant during antiviral therapy for HBV, treatment indications should be re-evaluated (2,15).

The combination of HBIG and HBV vaccination decreases the rate of perinatal transmission. However, this combination failure occurs in HBeAg-positive women with high HBV DNA levels (>200,000 IU/mL). TDF prophylaxis is the preferred in this setting during the last trimester of pregnancy. The duration of TDF prophylaxis is not very well known. It can be stopped at delivery or within the first 3 months after delivery (16).

The safety of antiviral therapy during lactation is unclear. Breast feeding may not be considered a contraindication in HBsAg-positive mothers, and even HBsAg can be detected in breast milk. In fact, TDF has been detected in breast milk, but its bioavailability is limited.

Patients undergoing chemotherapy/immunosuppressive therapy The risk of HBV reactivation can be high in HBsAg-positive patients and HBV-experienced patients (HBsAg-negative, anti-HBc-positive individuals) receiving chemotherapy/immunosuppressive therapy (1). The risk can be classified as high (>10%), moderate (1%-10%) or low (<1%). Moreover, all candidates for chemotherapy/immunosuppressive therapy should be screened for HBV markers before

treatment. HBV vaccination should be recommended if patients have all negative for HBV. Higher-dose and short-interval vaccination is required to achieve anti-HBs response. All HBsAg-positive patients should be referred to a specialist for diagnosis of the phase of HBV infection. All these patients should start ETV, TDF, or TAF as treatment or prophylaxis. Patients with CHB should be treated with NAs similarly to immunocompetent patients. Patients without chronic hepatitis, prophylaxis with potent NA should continue for ≥12-18 months after discontinuation of the chemotherapy/immunosuppressive therapy. Liver injury and function tests and HBV DNA levels should be tested every 3-6 months during prophylaxis and for ≥12-24 months after NA discontinuation (1,2,14,17,18).

The risk of HBV reactivation in HBV-experienced patients varies widely according to the virological status (HBV DNA positive), underlying disease (lymphoma), and the type (rituximab) and duration (long duration) of chemotherapy/immunosuppressive regimen. If these subjects are viremic, they should be treated similarly to HBsAg-positive patients. If these subjects need to be treated with rituximab or are undergoing allogeneic stem cell transplantation, antiviral prophylaxis is recommended (2,19). In these subjects with moderate or low risk of HBV reactivation, pre-emptive therapy is generally recommended. Pre-emptive therapy is based upon monitoring HBsAg and/or HBVDNA levels every 1-3 months during and after chemotherapy/immunosuppressive therapy, and starting potent NA treatment when HBV DNA is detectable or HBsAg seroreversion (1,2,14,19).

Dialysis and renal transplant patients HBV infection is more common in patients with chronic kidney disease undergoing dialysis and in those after renal transplantation (1,2). HBV infection may cause significant morbidity and mortality in such patients (1,2). Therefore, all dialysis and renal transplant patients should be screened for HBV markers. High-dose, short-term HBV vaccination should be recommended if patients have HBV seronegativity (20,21). All HBsAg-positive patients should be referred to a specialist for diagnosis of the phase of HBV infection.

All dialysis patients with CHB should receive a NA treatment. ETV is preferred for NA naïve patients. TAF could be used for NA-naïve and NA-experienced/resistant CHB patients. The doses of NAs should be adjusted based on eGFR values. TAF dose adjustment is not required if eGFR is >15 mL/min (2,22).

All HBsAg-positive renal transplant recipients should receive antiviral prophylaxis or treatment. ETV is preferred for NA-naïve patients. TAF could be used for NA-naïve and NA-experienced/resistant transplanted patients. TDF may be considered only for patients with NA resistance if TAF is not available. NA prophylaxis or treatment should be continued long-term. Long-term antiviral therapy has been shown to decrease HBV-related liver complications and improve survival. PegIFNa therapy in renal transplanted patients is contraindicated because of the risk of rejection (2,22,23).

Hepatitis B virus-experienced renal transplant recipients do not require antiviral prophylaxis or treatment. HBsAg level monitoring is recommended. If HBsAg seroreversion occurs, ETV or TAF should be started immediately.

Renal function tests should be monitored during antiviral therapy. The change of treatment type or dose is recommended when renal function deterioration ensues.

Extrahepatic manifestations Several extrahepatic manifestations, including vasculitis, purpura, mixed cryoglobulinemia, polyarteritis nodosa, arthralgias, glomerulonephritis, peripheral neuropathy, have been reported in CHB patients (1, 2). Extrahepatic manifestations may response to antiviral therapy. PegIFNa therapy can worsen some immune-mediated extrahepatic manifestations (1,2).

The main conclusions of the EASL 2017 CPGs on the management of special patients group with HBV infection are as follows;

- All HBV-positive decompensated cirrhotic patients on the transplant waiting list should be treated with NAs.
- Combination of a potent NA treatment and HBIG is recommended after LT for preventing HBV recurrence.
- PegIFNa for ≥48 weeks is the current treatment option for patients with HBV/HDV coinfection. NA treatment should be considered during HBV DNA replication.
- DAA may cause HBV reactivation in patients with HBV and HCV coinfection. HBsAg-positive patients should be considered for concomitant NA prophylaxis during and after DAA therapy.
- All HIV-positive patients with HBV coinfection should start ART irrespective of CD4 cell counts.
- Only patients with severe acute hepatitis B (<5%) should be treated with antiviral therapy and considered for LT.
- Screening for HBV markers in the first trimester of pregnancy is strongly recommended.
- Tenofovir Disoproxil Fumarate treatment is recommended in CHB pregnant women with advanced fibrosis.
- Tenofovir Disoproxil Fumarate should be started at week 24-28 weeks of gestation in all pregnant women with high HBV DNA levels and continue for approximately 12 weeks after delivery.
- HBV markers before immunosuppression should be tested in all candidates for chemotherapy/immunosuppressive therapy. All HBsAg-positive patients should receive potent NAs as treatment or prophylaxis.
- All dialysis and renal transplant patients should be screened for HBV markers.

- HBsAg-positive dialysis patients who require treatment and HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment.
- Patients with replicative HBV infection and extrahepatic manifestations should receive NA treatment.

REFERENCES

1. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-85. [CrossRef]
2. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370-98. [CrossRef]
3. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the global burden disease study 2013. Lancet 2016; 388: 1081-8. [CrossRef]
4. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007; 45: 507-39. [CrossRef]
5. Mutimer D. Review article: hepatitis B and liver transplantation. Aliment Pharmacol Ther 2006; 23: 1031-41. [CrossRef]
6. Cholongitas E, Goulis J, Akriviadis E, Papatheodoridis GV. Hepatitis B immunoglobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis B virus recurrence after liver transplantation: a systematic review. Liver Transpl 2011; 17: 1176-90. [CrossRef]
7. Roche B, Samuel D. Prevention of hepatitis B virus reinfection in liver transplant recipients. Intervirology 2014; 57: 196-201. [CrossRef]
8. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016; 64: 433-85. [CrossRef]
9. Fox AN, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. J Hepatol 2012; 56: 1189-97. [CrossRef]
10. Wang P, Tam N, Wang H, et al. Is hepatitis B immunoglobulin necessary in prophylaxis of hepatitis B recurrence after liver transplantation? A meta-analysis. PLoS One 2014; 9: e104480. [CrossRef]
11. Heidrich B, Yurdaydin C, Kabacam G, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology 2014; 60: 87-97. [CrossRef]
12. EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2017; 66: 153-94. [CrossRef]
13. European AIDS Clinical Society. Treatment Guidelines 2016; 8: 1.
14. Lampertico, P, Maini M, Papatheodoridis G. Optimal management of hepatitis B virus infection - EASL Special conference. J Hepatol 2015; 63: 1238-53. [CrossRef]
15. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology 2015; 62: 375-86. [CrossRef]
16. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016; 374: 2324-34. [CrossRef]
17. Reddy KR, Beavers KL, Hammond SP, et al. American gastroenterological association institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015; 148: 215-9. [CrossRef]
18. Idilman R, Arat M. Evaluation and management of hepatitis B virus infection in hematopoietic stem cell transplantation: before and after transplantation. Expert Rev Anti Infect Ther 2011; 9: 641-52. [CrossRef]
19. Mozessohn L, Chan KK, Feld JJ, Hicks LK. Hepatitis B reactivation in HBsAg-negative/HBcAb positive patients receiving rituximab for lymphoma: a meta-analysis. J Viral Hepat 2015: 22: 842-9. [CrossRef]
20. Fabrizi F, Martin P, Messa P. Novel perpectives on the hepatitis B virus vaccine in the chronic kidney disease population. Int J Artif Organs 2015; 38: 625-31.
21. Idilman R, Colantoni A, De Maria N, et al. Impaired antibody response rates after high dose short interval hepatitis B virus vaccination of immunosuppressed individuals. Hepatogastroenterology 2003; 50: 217-21.
22. Cholongitas E, Tziomalos K, Pipili C. Management of patients with hepatitis B in special populations. World J Gastroenterol 2015; 21: 1738-48. [CrossRef]
23. Gajurel K, Stapleton JT. Hepatitis viruses in kidney transplantation. Semin Nephrol 2016; 36: 386-96. [CrossRef]