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Review Article

Managing hepatitis B: Before and after liver transplantation

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BACKGROUND

Worldwide, an estimated 400 million people have chronic hepatitis B (CHB) infection. Up to 40% of persons with CHB may eventually develop complications of hepatitis B virus (HBV) infection, including liver cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC). For many of these patients, liver transplantation remains the only curative option. Prior to the availability of effective prophylactic agents against HBV recurrence, liver transplantation for CHB-related complications was associated with high recurrence rate and poor survival, and was considered a relative contraindication. The introduction of lamivudine and hepatitis B immune globulin (HBIG) was a major milestone in the prevention of HBV recurrence. This combination was effective in preventing graft loss due to HBV recurrence, and remains the cornerstone of HBV prophylaxis to this day in many transplant centres. This review discusses the current strategies in managing HBV infection before and after liver transplantation.

MANAGEMENT OF HEPATITIS B BEFORE LIVER TRANSPLANTATION

In CHB patients who require liver transplantation, antiviral therapy prior to the pre-transplant setting is an essential part of management. The aim of pre-transplant antiviral therapy is to prevent further progression of liver disease, with the hope that transplantation can either be delayed or the liver improves sufficiently to prevent the need for a transplant. By reducing the viral load, the rate of HBV recurrence after transplantation may potentially also be lessened. Currently, there are 2 classes of antiviral agents available for the treatment of CHB: immunomodulatory agents including conventional and pegylated interferon, and the oral nucleotide/nucleoside analogues including lamivudine, adefovir, entecavir, telbivudine, and tenofovir. There is, currently, no established role for interferon-based therapy in the pre or post-liver transplant setting in the management of HBV infection. Oral therapies form the cornerstone for HBV management before and after liver transplantation.

The management of CHB patients in the pre-transplant settings differ from the non-transplant settings, in that, virtually all patients have significant underlying liver disease. The most common indications for liver transplantation for CHB include severe acute flares of CHB with decompensation, cirrhosis with decompensation, and the development of HCC. For patients with severe acute flares, this occurs usually because of three main reasons, and the management will be dependent on the cause. If the patient is already on antiviral therapy, a flare may occur due to the development of drug resistance mutations of the HBV or from drug non-compliance. In the former, an add-on strategy rather than switching therapy is preferred, using a drug without cross-resistance to the initial agent.[1] For example, in those patients receiving lamivudine or telbivudine who develop drug resistant mutation, the addition of adefovir or tenofovir is recommended.

If it is due to non-compliance, restarting the stopped agent will often suffice. Although, if the drug has a low barrier to resistance, non-compliance may increase the chance of subsequent resistance developing after recommencing treatment. In this setting, recommencing treatment with a combination of two drugs from different classes may be beneficial. For treatment-naïve patients undergoing severe acute flares, the recommendation would be to commence treatment using a drug with high barrier to resistance, such as entecavir or tenofovir. For severe acute flares with decompensation, it is likely that the immediate short-term mortality is not affected by the type of oral antiviral agents used.[2] The major determinant factor is likely to be the underlying liver reserve and the presence of established fibrosis and more importantly, cirrhosis. Age is also likely to be important, as it signifies a longer history of CHB infection, and increases the likelihood of underlying significant fibrosis or cirrhosis. Despite the choice of antiviral agent not affecting the short term outcome significantly, these patients are likely to remain on life-long antiviral therapy; therefore it is still important to use a drug with high genetic barrier to resistance. Furthermore, if resistance does occur with a less potent drug,

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further decompensation may be fatal if the patient already has established cirrhosis.

For CHB patients with cirrhosis and chronic decompensation or HCC, patients should also be on antiviral therapy, irrespective of the viral load. The reason for this is because these patients are also unlikely to tolerate any flares of their HBV infection. There is also the possibility that with long-term viral suppression, the liver function may improve with time to sufficient levels which may obviate the need for liver transplantation. Indeed, trials have shown improvements and reversal of advanced fibrosis and cirrhosis with long-term antiviral therapy.[3,4] For patients already on antiviral therapy, it is important to monitor their viral load closely, especially for those patients treated with older agents associated with high resistance rates. For those with persistent viraemia or evidence of virological rebound, adding on a second drug would be recommended. For those with undetectable viral load and treated with an older agent with low barrier to resistance, a case can be made for these patients to be switched over to a newer drug so that the risk of flares from drug resistance can be minimized.

Patients with decompensated liver cirrhosis may have significant renal impairment which may or may not be related to their liver condition. It is important to adjust the dosages or dosing intervals of antiviral drugs according to their renal function so that adverse effects are minimized.

MANAGING HEPATITIS B AFTER LIVER TRANSPLANTATION

Prior to effective antiviral prophylaxis becoming available, liver transplantation for HBV-related disease was associated with severe recurrence of hepatitis B infection with subsequent graft loss and poor survival. The availability of HBIG and lamivudine was a major milestone in hepatitis B prophylaxis after liver transplantation. HBIG was the first agent shown to be effective in reducing HBV recurrence, using a high dose intravenously to maintain anti-HBs titres >100 IU/L.[5] By combining with lamivudine, a synergistic effect was achieved, reducing the recurrence rate of infection to 0–10% when given over a long term. This combination strategy has been adopted almost universally, becoming the standard of care in most centres worldwide. However, HBIG requires regular parental injections to maintain the antibody titres at a protective level, and therefore, can be cumbersome. In addition, it is expensive and may not be readily available. Modified regimens including the usage of a lower dose of HBIG given intramuscularly was also shown to be efficacious.[6] Previous meta-analyses have confirmed that the combination of HBIG with oral antiviral therapy is superior to single agent therapy.[7,8] However, most of the studies included in these meta-analyses have used lamivudine rather than the newer antiviral agents. The use of lamivudine monotherapy without HBIG has been associated with high rates of resistance and subsequent virological rebound and breakthrough flares.[9,10] Prior to the availability of effective rescue therapy, this approach would have led to uncontrolled hepatitis B recurrence and potential graft loss.

Adefovir dipivoxil, a nucleotide analogue, was the second agent approved for the treatment of CHB, and is an effective rescue agent against lamivudine-resistant strains of HBV. The introduction of a second oral agent from a different class to lamivudine, and without cross resistance, set the stage for possible HBIG-free strategy. The combination of lamivudine and adefovir without HBIG has been shown to be effective in preventing HBV recurrence after transplantation.[11] More recently, the development of newer oral nucleoside and nucleotide analogues with high barriers to resistance have become available for hepatitis B treatment, expanding the therapeutic options for prophylaxis after transplantation. These newer drugs have superseded lamivudine as first line therapy for CHB, and are likely to become the mainstay of therapy for post-transplant HBV management in the future. A recent study has demonstrated the effectiveness and safety of entecavir as monotherapy without HBIG in preventing HBV recurrence.[12]

The choice of antiviral agents to use as prophylaxis is dependent on the resistance profile of HBV and previous treatment approaches prior to transplantation. In treatment of naïve patients and those either on entecavir or tenofovir, continuation of these agents after transplantation as monotherapy i may be sufficient. For patients on lamivudine, telbivudine, or adefovir alone at the time of transplantation, a combination of lamivudine and adefovir/tenofovir as prophylaxis after transplantation is a reasonable approach. In the absence of documented rt204 mutation, an argument can be made for using entecavir or tenofovir as monotherapy.

With the currently 5 approved oral agents available for HBV treatment, it is likely that over time, there will be a shift towards using a HBIG-free regimen. There may still be a role for HBIG use as limited-duration therapy, especially for those patients with high viral load at the time of transplantation. Other immunoprophylaxis including active vaccination strategies have yielded mixed results, but have been overall unconvincing.[13,14] It is not surprising given that most patients would have been exposed to HBV antigens for most of their lives without mounting an adequate immune response. The effect of immunosuppression after transplantation may also diminish the immune response to vaccination strategies. In patients treated with oral antiviral agents alone without HBIG,