REVIEW ARTICLE

Antiviral treatment for chronic hepatitis B infection in renal transplant recipients

Desmond Y.H. Yap, Tak Mao Chan*

Division of Nephrology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong

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Summary Chronic infection with hepatitis B virus (HBV) leads to adverse clinical outcomes in renal transplant recipients (RTRs) because of increased hepatic complications. The use of oral nucleos(t)ide analogs (NAs) has brought the management of HBV infection in RTRs to a new paradigm. Lamivudine (LAM) can effectively suppress HBV DNA levels, normalize liver biochemistry, and significantly improve short- and long-term patient survival in HBsAg-positive RTRs. However, it has the burden of high drug resistance. The prevention and management of drug-resistant HBV infection in RTRs has emerged as an important clinical issue. In treatment-naïve hepatitis B surface antigen (HBsAg)-positive RTRs, ETV has demonstrated high efficacy, low resistance rates, and favorable tolerability. Entecavir can also significantly improve transaminasemia in LAM-resistant patients, although the virological response is relatively modest in comparison to the virological response in treatment-naïve patients. Adefovir (ADV) and tenofovir (TDF) are viable options for LAM-resistant HBV infection in RTR; however, their use in patients with moderate to severe allograft dysfunction entails a balance between the potential risk and benefit, the appropriate dose adjustment, and allograft function monitoring for nephrotoxicity. The long-term patient survival of HBsAg-positive RTRs has significantly improved with the progress in these effective antiviral treatments, and is approaching the survival rate of their HBsAg-negative counterparts. Many efficacious options of first-line and rescue therapies are available, but the choice of NA in HBsAg-positive RTR should take into consideration antiviral potency, drug resistance pattern, renal allograft function, and the cost and availability of drugs in different localities.

List of abbreviations: ADV = adefovir; ALT = alanine transaminase; DNA = deoxyribonucleic acid; ETV = entecavir; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; LAM = lamivudine; NA = nucleos(t)ide analog; RTR = renal transplant recipient; TDF = tenofovir.

* Corresponding author. Division of Nephrology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong.
E-mail address: dtmchan@hku.hk (T.M. Chan).

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Introduction

Chronic infection with hepatitis B virus (HBV) is associated with adverse clinical outcomes in renal transplant recipients (RTRs). These undesirable outcomes stem from early complications such as fulminant hepatic flares or fibrosing cholestatic hepatitis, and from late complications such as cirrhosis, decompensated liver failure, or hepatocellular carcinoma.1–8 Universal HBV immunization programs, prudent infection control measures and transfusion practices in dialysis units, increased use of erythropoietin stimulating agents, meticulous matching of donor-recipient HBV status, and the use of HBV hyperimmunoglobulins during the perioperative period have substantially contributed to reducing HBV transmission in dialysis patients and RTRs. However, in endemic areas such as the Asia–Pacific region where the prevalence of chronic HBV infection can be up to 10–15% in the dialysis population in some cities,9,10 a considerable number of hepatitis B surface antigen (HBsAg)-positive patients will undergo kidney transplantation; hence, managing HBV infection in RTRs remains an imperative clinical challenge.

In the general population, oral nucleos(t)ide analogs (NAs) and interferon-based therapies are treatment options with proven efficacy for chronic HBV infection. However, the administration of interferon in RTRs was associated with low treatment efficacy and a high incidence of precipitating allograft dysfunction, and thus should be avoided.11,12 In this context, oral NAs have become the mainstay of treatment for HBsAg-positive RTRs. The aim of therapy is to forestall short- and long-term hepatic complications. The two common approaches to initiate antiviral therapies in HBV-infected RTRs are based on commencing immunosuppressive treatments (i.e., the "prophylactic" approach) or if there is evidence of imminent HBV reactivation (i.e., the "pre-emptive" approach). Previous studies have highlighted that administering antiviral therapy as a prophylactic treatment or as a pre-emptive treatment in RTRs results in much superior outcomes, compared to salvage treatment (i.e., treatment commenced after evidence of hepatic dysfunction).9,13 One recent retrospective study compared "prophylactic" and "pre-emptive" initiation of lamivudine (LAM) in HBsAg-positive RTRs, and found no statistical difference between these two approaches in preventing liver function derangement or virological breakthrough.14 However, close monitoring of the HBV DNA level with rapid "turn-around" time is a prerequisite to an effective and safe "pre-emptive" strategy.

The optimal treatment duration of NAs in RTRs remains undefined because of the paucity of data in this area. Most HBV-infected RTRs require lifelong NA administration, although preliminary experience suggests that the cessation of treatment may be feasible in carefully selected low-risk patients after stable viral suppression and sufficient duration of treatment, provided that there is close surveillance to detect a disease flare after stopping treatment.1,15 The currently available choices of NAs for the treatment of HBV infection locally include LAM, entecavir (ETV), tenofovir (TDF), adevarovir (ADV) and tenofovir (TDF) (Table 1). The following discussion reviews the data on these agents for the treatment of chronic HBV infection in RTRs.

Lamivudine

Lamivudine is a nucleoside analog of cytidine and a reverse transcriptase inhibitor of HBV and human immunodeficiency virus (HIV). Because LAM was the first oral NA available for the treatment of chronic HBV infection, it has the most extensive efficacy and safety data in HBsAg-positive RTRs. Data from our group and other investigators have demonstrated that using LAM in HBsAg-positive RTRs effectively suppresses HBV DNA and significantly improves liver transaminasemia.1,16,17 One meta-analysis that pooled data from 14 prospective clinical trials reports that, after approximately 14 months of LAM treatment, the rate of HBV DNA undetectability was 91% [95% confidence interval (CI), 86–96%]; HBsAg clearance, 27% (95% CI, 16–39%); alanine transaminase (ALT) normalization, 81% (95% CI, 70–92%); and LAM-resistance, 18% (95% CI, 10–37%).18 The long-term benefit of LAM treatment was also exemplified by significantly improved patient survival in HBsAg-positive RTRs with 10- and 20-year patient survival rates of 90% and 83%, respectively (the patient survival was 83% and 34%, respectively, in HBsAg-positive RTRs who have not received antiviral therapy).1,7,19 The data thus shows that the patient survival rate in the medium term nearly approaches that of HBsAg-negative RTRs.19,20 However, hepatic complications remain the cause of death in 40% of HBsAg-positive RTRs, even in the era of effective antiviral therapies.19

Prolonged LAM administration is associated with the progressive development of drug resistance, and the cumulative resistance rate for LAM is > 60% after 5.7 years of treatment.18,19,21,22 The emergence of LAM-resistance is usually coupled with liver function derangement, which can be transient or persistent and has variable severity; however, recent data from our group suggests that the development of LAM-resistance does not significantly affect the liver stiffness score, incidence of cirrhosis or hepatocellular carcinoma, or patient survival during 10–14 years of follow-up.19
Adefovir

For historical reasons, a considerable number of HBsAg-positive RTRs have received protracted LAM treatment and consequently developed drug resistance. This poses a substantial challenge in managing these patients—many effective rescue therapies are potentially nephrotoxic and limited efficacy and safety data are available in this area. Prior to the availability of an alternative NA, it was a prevailing practice to maintain patients on LAM, despite the appearance of drug resistance; however, the introduction of ADV offered the first alternative to circumvent this clinical problem. Adefovir is a nucleotide reverse transcriptase inhibitor that exhibits antiviral activity against wild-type and LAM-resistant HBV; the primary clinical application of ADV is for the latter microorganism. The short-term efficacy of ADV as mono- or add-on therapy has been demonstrated in RTRs. In this context, ADV monotherapy in 11 RTRs with dosage adjustment (according to allograft function) significantly reduced HBV DNA levels with acceptable tolerability and no virological breakthrough at 1 year. Other groups that have examined ADV as an add-on therapy to LAM have reported HBV DNA undetectability rates of 35.7%, 42.8%, and 88.0% after 12 months, 24 months, and 36 months of treatment, respectively, in LAM-resistant RTRs. Furthermore, sustained normalization of ALT and virological suppression was achieved in 92.8% of patients after 1 year of follow up. However, these virological responses could be variable and relatively modest, compared to the responses of treatment-naive patients. Substituting with ADV could inhibit HBV viral replication better and improve liver transaminase levels, compared continuing LAM in HBsAg-positive RTR (75% of patients vs. 14.3% of patients had persistent normalization of ALT in one study); such a clinical response has been sustained for at least 2 years.

Nephrotoxicity is an important concern for ADV treatment, which occurs in 30–50% of RTRs, despite dosage modification, and may require drug discontinuation. The exact mechanism of nephrotoxicity by ADV is not well understood, although alterations in renal tubular transporter, apoptosis of renal tubular epithelial cells, and mitochondrial toxicity have all been implicated. Our experience suggests that ADV can be safely administered without significant allograft function deterioration on follow up in patients with a serum creatinine level below 150 μmol/L or creatinine clearances above 40 mL/min. However, ADV at the currently approved dose is not very potent, compared to other agents. It remains unclear whether its efficacy may be further compromised after dosage reduction in patients with allograft dysfunction.

Entecavir, tenofovir, and telbivudine

ETV is a deoxyguanosine analog that potently inhibits reverse transcription during HBV replication. In treatment-naive RTRs who expect to receive prolonged antiviral therapy, ETV offers a new promise because of its efficacy in treatment-naive and LAM-resistant patients, its very low resistance rate, and the absence of nephrotoxicity. Recent data from our group suggests that the use of ETV in treatment-naive RTRs significantly decrease HBV DNA levels, and the cumulative rate of HBV DNA undetectability

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<th>Nucleos(t)ide analogs</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Lamivudine</td>
<td>- Most extensive data on efficacy and safety in treatment-naïve HBsAg-positive RTRs</td>
<td>- High rates of resistance after prolonged administration (&gt;60% after 5 years of treatment)</td>
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<td>- Available data on long-term patient outcomes</td>
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<td>- Relatively inexpensive</td>
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<td>Adefovir</td>
<td>- Main indication is for rescue therapy for LAM-resistant HBV in RTRs, although it has some efficacy in treatment-naïve patients</td>
<td>- Nephrotoxic</td>
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<td>- Variable and relatively modest efficacy, especially after dosage reduction in RTRs with allograft dysfunction</td>
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<td>- More costly</td>
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<td>- Lower efficacy and emergence of ETV resistance when used in LAM-resistant subjects</td>
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<tr>
<td>Entecavir</td>
<td>- Effective for treatment-naïve RTRs and LAM-resistant HBsAg-positive RTRs</td>
<td>- Expensive</td>
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<td>- Very low resistance rates in treatment-naïve patients</td>
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<td>- Non-nephrotoxic</td>
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<td>Tenofovir</td>
<td>- Potent therapy for treatment-naïve RTRs and LAM-resistant HBsAg-positive RTRs</td>
<td>- Potentially nephrotoxic, especially in patients with organ transplant or pre-existing renal impairment</td>
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<td>- Very low resistance rates</td>
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<td>- May be useful in multidrug-resistant patients</td>
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<td>- Potential for ETV resistance when used in LAM-resistant patients</td>
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<td>Telbivudine</td>
<td>- Effective in treatment-naïve HBsAg-positive RTRs</td>
<td>- Relatively little clinical efficacy data in HBsAg-positive RTRs</td>
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<td>- Relatively low resistance rates, compared to LAM</td>
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<td>- Non-nephrotoxic</td>
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<td>- Lower cost, compared to other new NAs</td>
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ADV = adefovir; ETV = entecavir; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; LAM = lamivudine; NA = nucleos(t)ide analog; RTR = renal transplant recipient; TBV = telbivudine; TDF = tenofovir.
was 60%, 100%, and 100% at 12 months, 24 months, and 36 months, respectively (the time-to-HBV DNA undetectability and time-to-ALT normalization were 15.7 ± 4.6 months and 12.6 ± 3.7 months, respectively). More importantly, no resistance to ETV emerged in treatment-naive HBsAg-positive RTRs, after a follow up of 34.7 ± 22.9 months. Another recent study also corroborated our observations and revealed that ETV treatment achieved HBV undetectability rates of 74%, 96%, and 100% after 6 months, 12 months, and 24 months, respectively, in treatment-naive RTRs.35

In this study, ETV treatment was well tolerated and appeared to have superior viral suppression, compared to LAM-treated historical controls. ETV is an option for managing LAM-resistant HBsAg-positive RTRs. Experience regarding the use of ETV in RTRs who developed LAM- or ADV-resistance has been examined in one study with 10 solid organ transplant recipients (8 patients were RTRs). In this series, ETV appreciably declined HBV DNA, and the HBV undetectability rates were 50% in HBeAg-positive and HBeAg-negative patients after 16.5 months of therapy. Our recent data also showed that ETV treatment could effectively suppress HBV viral replication and normalize liver biochemistry in LAM-resistant RTRs, although the cumulative rates of HBV undetectability were only 27%, 45%, and 45% after 6 months, 12 months, and 24 months of treatment, respectively.35 The allograft function also remained stable after approximately 3 years of follow up. Similar to the general population, the efficacy of ETV in LAM-resistant HBsAg-positive RTRs could be variable and relatively less effective, compared to its efficacy in treatment-naïve subjects.19,30,35 A higher dose of ETV (1 mg daily) is used to treat LAM-resistant HBV infection in the general population. However, the dosage reduction required in RTRs who have allograft dysfunction may potentially compromise the antiviral efficacy. Furthermore, we also reported that genotypic resistance to ETV emerged in two (of 10) LAM-resistant RTRs with a surge in ALT and HBV DNA levels after 20.0 ± 3.5 months, which suggests that vigilant monitoring is important when ETV is used in LAM-resistant RTRs.35

TDF is a nucleotide analog that exhibits robust activity against the viral reverse transcriptase of HIV and HBV. It was initially licensed for the treatment of HIV infection; it was subsequently approved for use in chronic HBV infection because of its high potency and very low resistance rates for treatment-naïve patients and LAM-resistant patients.13,35 Data regarding the use of TDF in HBsAg-positive RTRs is scarce. Daudé et al35 showed promising short-term efficacy on HBV viral suppression and favorable renal profile at 1 year in seven solid organ transplant recipients (3 patients were RTRs) who only had partial response to other NAs such as LAM, ADV, or ETV.39 One recent small series also supported the efficacy and tolerability of TDF as recue therapy in four LAM-resistant HBsAg-positive RTRs.14 Furthermore, TDF is reportedly useful for treating HBsAg-positive RTRs with multidrug resistance.40 However, potential nephrotoxicity is an important concern when using TDF in RTRs.41 TDF overall seems less nephrotoxic than ADV, but the mechanism of nephrotoxicity by TDF remains poorly understood. Renal tubular epithelial cell apoptosis, changes in renal tubular transporters, and mitochondrial toxicity are possible mechanisms of TDF-related nephrotoxicity.31 A history of organ transplantation and pre-existing renal insufficiency were proposed as independent risk factors for developing nephrotoxicity in TDF-treated patients.42 TDF represents a highly effective antiviral option, especially for LAM-resistant patients; therefore, it will be worthwhile to initiate formal studies in HBsAg-positive RTRs to investigate its long-term efficacy, impact on allograft function, optimal dosage adjustment, and patient subgroups who could well tolerate this treatment.

To date, there is no data regarding the use of TBV in RTRs. The relatively low resistance rate, absence of nephrotoxicity, and the relatively lower cost in comparison to other NAs nevertheless makes TBV an attractive therapeutic option for treatment-naïve RTRs.43,44 Recent data in the general population also suggest that TBV may have renoprotective effects for patients at risk of renal impairment.45 Whether such benefits can be extrapolated to RTRs remain to be tested.

**Concluding remarks**

The use of oral NAs has transformed the landscape of managing HBsAg-positive RTRs, and is associated with significantly improved short- and long-term clinical
outcomes. The prevention and management of drug-resistant HBV infection in RTRs remains an important clinical challenge, especially because some effective therapeutic options also have potential nephrotoxicity. The choice of NAs for HBsAg-positive RTRs should take into consideration antiviral potency, drug resistance pattern, renal allograft function, and the cost and availability of drugs in different localities (Fig. 1). The use of antiviral therapy constitutes an integral part of managing HBsAg-positive RTRs, but regular surveillance for long-term hepatic complications such as cirrhosis and liver cancer is also very important for optimizing patient outcomes. In this context, current data suggest that monitoring with ultrasonography and alpha-fetoprotein level assays can facilitate early detection of hepatocellular carcinoma, which will render patients more amenable to tumor resection and thus enhance patient survival. 46–48

Conflicts of interest
The authors have no conflicts of interest to declare.

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