Hong Kong Journal of Nephrology (2015) 17, 8–13

Available online at www.sciencedirect.com

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journal homepage: www.hkjn-online.com

REVIEW ARTICLE

Antiviral treatment for chronic hepatitis B infection in renal transplant recipients

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Available online 4 March 2015

KEYWORDS
adefovir;
entecavir;
hepatitis B virus;
lamivudine;
renal transplantation

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.

乙型肝炎病毒 (HBV) 慢性感染所導致的肝臟併發症，並不利於腎臟移植接受者 (RTR) 的預後，因此口服核苷/核苷酸類似物 (NA) 療法佔有重要的角色。對於 HBsAg 陽性的腎臟移植接受者，lamivudine (LAM) 一方面可有效抑制 HBV DNA 的水平及促進肝臟生化的正常化，同時更能顯著改善病人的短期和長期存活率；然而與之相關的抗藥性仍然居高不下。事實上，RTR 間抗藥性 HBV

List of abbreviations: ADV = adefovir; ALT = alanine transaminase; DNA = deoxynucleic 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.

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http://dx.doi.org/10.1016/j.hkjn.2015.01.001

感染的預防與處置已成為一個重大的臨床課題。在初治的 HBsAg 陽性 RTR 之間，entecavir (ETV) 的功效已獲得證實，兼具低抗藥性與良好耐受性。在 LAM 抗藥病人間，ETV 可明顯改善肝酵素上升，雖然病毒學反應稍低於初治病人之間。誠然，對於已出現 LAM 抗藥性 HBV 感染的 RTR，adefovir (ADV) 或 tenofovir (TDF) 均為可行用藥，然而基於腎臟毒性問題，在植入腎臟呈中至重度功能障礙的患者間，其使用必須加倍謹慎，並在有需要時作出適當的劑量調整及腎功能監測。隨著有效抗病毒療法的實施，HBsAg 陽性 RTR 的長期存活已取得明顯改善，並接近 HBsAg 陰性患者的存活水平。在目前已有多種第一線與救援用藥可供 HBsAg 陽性 RTR 應用之下，NA 的選擇因素應包括抗病毒效力、抗藥狀況、對植入腎臟的影響、藥物價格、供應是否充足等。

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 hepatitic 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 remain 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), telbivudine (TBV), adefovir (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%]; HBeAg 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]