EDITORIAL

Antiviral Therapy for Pre- and Post-Liver Transplantation Patients With Hepatitis B

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The goals of antiviral therapy for hepatitis B patients on the liver transplantation (LT) waiting list are 2-fold: 1) to achieve clinical stabilization, thereby delaying/preventing the need for LT; and 2) to attain low hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels prior to transplant, thereby reducing the risk of recurrent HBV post-LT. Lamivudine was the first nucleoside analog to be approved for use in HBV treatment, and has been shown to be safe for long-term use. The combination of hepatitis B immune globulin and lamivudine has been the most common prophylactic therapy to prevent recurrent HBV infection post-LT since the late 1990s, and lamivudine monotherapy was the mainstay of treatment of recurrent HBV in the late 1990s and early 2000.[1-3]

The initial enthusiasm of lamivudine was tempered by the realization that lamivudine does not eradicate HBV, thus most pre- and post-LT patients require lifelong treatment to maintain viral suppression. Unfortunately, long-term use of lamivudine is associated with increasing rates of drug resistance, from 15 to 30% of patients after 1 yr of treatment to 70% of patients after 4 to 5 yr.[4] Virologic breakthrough due to antiviral resistance has been reported to cause hepatitis flares and in rare instances hepatic decompensation.[4,5] In the transplant setting, where patients already have decompensated cirrhosis or are receiving immunosuppressive therapy, the risk of severe hepatitis flare and worsening liver failure is higher,[6-8] and for patients who manage to receive a timely transplant, the risk of HBV recurrence post-LT is increased.[9,10]

With the approval of 2 nucleoside/tide analogs: adefovir and entecavir, and others in development, the management of pre- and post-LT hepatitis B patients is continuously evolving. There is an urgent need for safe and effective rescue therapy for patients with lamivudine-resistant HBV, and alternative first-line antiviral therapy with a lower rate of resistance for treatment-naive patients. These therapies must have rapid and potent antiviral activity, long-term safety, and very low rates of resistance.

In this issue of the Journal, Schiff et al.[11] report the final results of a large open-label, multicenter study with 226 waitlisted and 241 post-LT patients with lamivudine-resistant HBV treated with adefovir dipivoxil 10 mg once daily for a median duration of 39 and 99 weeks, respectively. Almost all patients continued lamivudine at some time, but the exact duration of overlapping treatment is not certain.

Adefovir resulted in a mean decrease in serum HBV DNA level of 3.5 to 4.0 $\log_{10}$ copies/mL after 48 weeks of treatment, and an increasing proportion of patients had undetectable serum HBV DNA over time. The high proportion of patients with substantial viral suppression may be related to the concomitant use of lamivudine in all patients. In 1 small study of patients with compensated liver disease and lamivudine-resistant HBV, serum HBV DNA decreased at a similar rate in patients randomized to adefovir monotherapy or a combination of lamivudine and adefovir.[12] However, several recent studies have showed that combination of lamivudine and adefovir results in more marked viral suppression and lower risk of adefovir resistance than adefovir monotherapy.[13-15] Despite the use of combination therapy, 35% of waitlisted patients and 22% of post-LT patients in the current study still had detectable serum

Abbreviations: LT, liver transplantation; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen.

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HBV DNA after 96 and 144 weeks of treatment, respectively, indicating the need for more potent therapies.

Several studies reported that as many as 25 to 50% of nontransplant HBV patients have primary nonresponse to adefovir.[13,16,17] This is likely related to the suboptimal antiviral activity of the approved 10-mg dose. Rapid and consistent viral suppression is very important in LT patients who have limited hepatic reserve or are immunosuppressed. In the current study, among patients with serum HBV DNA >5 $\log_{10}$ copies/mL, 93% of waitlisted patients and 96% of post-LT patients had >3 log reduction in serum HBV DNA levels by 48 weeks but the proportion of patients with >3 log reduction in serum HBV DNA by 24 weeks was not reported. Given that 47 (10% of enrolled patients) deaths occurred within 6 months of enrollment, it would be interesting to know if these early deaths were related to more advanced liver disease or suboptimal viral response.

One of the concerns with using adefovir in LT patients is the frequent presence of impaired renal function necessitating dose reduction. Because the full dose of 10 mg daily is suboptimal in viral suppression, it would be important to know if viral rebound was observed in patients who required dose reductions and if these patients would be more likely to develop adefovir resistance.

The importance of rescue therapy was highlighted by the impressive survival (87% by week 144) in the post-LT group. The impact of rescue therapy on the survival of the waitlist group was difficult to assess since patients who underwent LT were included in the analysis. In a survey of a subset of patients in the waitlist group (102/226), 21% were reported to have been removed from the waitlist due to clinical improvement. These data are encouraging and support the notion that maintenance of viral suppression with effective antiviral therapy not only delays, but can also prevent the need for LT. However, prospective studies that continue to follow patients removed from the waitlist are needed to confirm that clinical improvements are sustained.

A key requisite of rescue therapy is a low rate of resistance. In this study, the rate of adefovir resistance was low. Two patients were detected to have adefovir-resistant mutation in the resistance surveillance program, giving a cumulative rate of genotypic resistance of 2% at weeks 96 and 144. However, 2 additional patients who had viral rebound were found to harbor adefovir-resistant mutation, so the actual rate of adefovir resistance was roughly double that reported. Recent studies have reported much higher rates of adefovir resistance in patients with lamivudine-resistant HBV.[13,18] This discrepancy may, in part, be due to the use of more sensitive assays that can detect mutants present in ≤10% of the viral population vs. direct sequencing used in this study that can detect mutants consistently only when they comprise 20% to 40% of the viral population. Also, approximately 50% of patients in the studies that reported higher rates of adefovir resistance received adefovir monotherapy. The data in the current study support the recommendation to continue lamivudine when adefovir is initiated for lamivudine-resistant HBV.

The biggest concern regarding the use of adefovir in LT patients is the potential for nephrotoxicity. In the current study, only 6% of patients in the waitlist group met the criteria for nephrotoxicity but this may be related to the short duration of follow-up (median 39 weeks). Higher rates of nephrotoxicity were reported in the other 2 groups: 47% in the on-study LT group and 21% in the post-LT group. In the vast majority of these patients, serum creatinine remained persistently elevated. While it is difficult to decipher the role of adefovir vs. other concomitant nephrotoxic medications, the finding of a high percent of patients with persistent increase in serum creatinine is concerning since these patients will require long-term, and in most instances lifelong treatment. In addition, as discussed earlier, the antiviral activity of reduced doses of adefovir has not been established.

A surprising finding in the current study is the similarly low rate of post-LT HBV recurrence in patients with or without hepatitis B immune globulin prophylaxis. The authors reported that pre-LT serum HBV DNA levels were similar in both groups. However, it is not clear when pre-LT HBV DNA level was drawn in relation to LT and the start of adefovir. The duration of post-LT follow-up was also not clear. Thus, data from this study should not be interpreted as evidence that hepatitis B immune globulin is not required to prevent HBV recurrence post-LT, particularly in patients who are known to have lamivudine resistance prior to LT.

The authors also expressed the dilemma of how best to define HBV recurrence when polymerase chain reaction assays are used to monitor serum HBV DNA post-LT. We and others have observed that low levels of HBV DNA can be detected in the serum in the absence of hepatitis B surface antigen (HBsAg).[10,19] In some patients, HBV DNA detection is transient and there is no evidence of HBV recurrence on follow-up. However, detection of HBV DNA in serum by polymerase chain reaction assays may precede the reappearance of HBsAg and can be a harbinger of HBV recurrence. We recently observed a patient with serum HBV DNA levels of 3.3 $\log_{10}$ copies/mL 47 months post-LT. Despite the absence of HBsAg and normal liver chemistries, we elected to change the antiviral regimen of this patient because serum HBV DNA persisted at the same level on repeat testing 1 month later and antiviral resistant mutations were detected. These findings indicate the need to reexamine the definition of HBV recurrence post-LT and the importance of monitoring not only HBsAg but also serum HBV DNA using a sensitive polymerase chain reaction assay in patients receiving nucleoside/tide analogs.

Despite the impressive results in the current study, there are limitations to using adefovir as a rescue therapy for lamivudine-resistant HBV, particularly in the transplant population. Thus, alternative therapies that are more potent and have better safety profiles are needed. One option is tenofovir disoproxil fumarate,

which has been approved for use in treating human immunodeficiency virus infection. In vitro studies have shown that it has activity against HBV with equimolar potency as adefovir.[20] Clinical studies have confirmed the efficacy of tenofovir in suppressing wild-type as well as lamivudine-resistant HBV and increasing data indicate that tenofovir (300 mg) is more potent than adefovir (10 mg) in suppressing HBV replication.[21-25] Tenofovir is potentially nephrotoxic but it has a better therapeutic ratio and may be superior to adefovir in patients who need dose adjustments due to renal insufficiency.

Entecavir is approved for the treatment of wild-type and lamivudine-resistant HBV. However, its activity against lamivudine-resistant HBV is lower compared to wild-type HBV.[20,26] Despite the use of a higher dose, entecavir 1 mg daily, 60% of patients with lamivudine-refractory HBV still had detectable HBV DNA after 96 weeks of treatment. In addition, viral rebound occurred in 9% and genotypic resistance was detected in 16% of patients through week 96.[27] These data indicate that entecavir is not an ideal rescue therapy for patients with lamivudine-resistant HBV.

With the availability of newer treatments with lower risk of resistance, lamivudine is no longer an appropriate first-line HBV therapy, particularly for LT patients who require long durations of therapy. Adefovir is associated with a lower rate of drug resistance but it is not an ideal first-line therapy for LT patients because its antiviral activity is weaker and it has potential for nephrotoxicity. Entecavir, the most potent of the approved nucleoside/tide analogs for HBV, with a low rate of drug resistance in nucleoside-naive patients and no reported nephrotoxicity,[28-30] is most suited as a first-line therapy. However, data in support of its use in LT patients is lacking. Combination therapy may have the greatest benefit in LT patients. Some possible combinations include: lamivudine with adefovir or tenofovir, entecavir with adefovir or tenofovir, and tenofovir with emtricitabine (Truvada). One study of combination therapy has been initiated and the results are eagerly awaited.

Significant improvements in the survival of HBV patients awaiting LT and post-LT have been made in the past 10 yr. The questions that confront transplant hepatologists are no longer "Can we stabilize HBV patients with decompensated cirrhosis or can we prevent recurrent HBV post-LT?" Rather, the questions are "What is the optimal treatment for these patients and how can we prevent antiviral resistance?" Combination therapy seems to be the most logical first-line therapy in pre-LT patients but data in support of its use are lacking. The need for hepatitis B immune globulin is diminishing but the optimal dose and duration remains to be determined. The definition of HBV recurrence post-LT need to be reexamined and the appropriate monitoring for antiviral resistance has to be defined. We have come a long way in the management of LT patients with HBV, there is still a lot of work ahead but the future is brighter than ever.

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