

Liver Transplantation for Patients With Lamivudine-Resistant HBV: What is the Optimal Prophylactic Strategy?

Anna S. F. Lok

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The use of hepatitis B immune globulins (HBIG) revolutionized liver transplantation for hepatitis B. In the landmark paper by Samuel et al. in 1993, recurrence of hepatitis B virus (HBV) infection 3 years after liver transplantation was reduced from 75% in patients who received no HBIG to 36% in those who received HBIG for at least 6 months.¹ However, the benefit of HBIG was mainly seen in patients with fulminant hepatitis or coexistent hepatitis D virus infection, clinical conditions associated with low HBV replication. Among patients with HBV cirrhosis, the HBV recurrence rate was 83% in those with detectable serum HBV DNA at the time of transplantation and 58% in those with undetectable HBV DNA or hepatitis B e antigen. These results stimulated efforts to reduce HBV replication in patients with HBV cirrhosis while waiting for liver transplantation. Early studies using interferon² failed to reduce HBV recurrence because of poor tolerability and low efficacy.

The availability of lamivudine, a nucleoside analog that is safe and effective in suppressing HBV replication, in the 1990s rekindled efforts to treat patients with HBV cirrhosis. Several studies have shown that lamivudine is safe in patients with decompensated cirrhosis and effective not only in suppressing HBV replication, but also in stabilizing or in improving liver disease.³⁻⁷ However, long-term use of lamivudine was limited by the high rate of drug resistance; resistant

mutations involving the YMDD motif in HBV polymerase can be detected in 15% to 30% of patients after 1 year of treatment and in 50% after 3 years of treatment.⁷⁻⁹ Although in vitro studies showed that lamivudine-resistant mutants have decreased replication compared to wild-type HBV,¹⁰ clinical studies found that over time most patients with lamivudine resistance have increasing serum HBV DNA and alanine aminotransferase (ALT) levels, some patients develop hepatitis flares, and occasional patients experience hepatic decompensation.^{9,11,12}

In the late 1990s, the concern about fatal hepatitis flares associated with lamivudine resistance led many transplant centers to reserve lamivudine until transplantation was imminent. Around the same time, it was also recognized that while reduction in serum HBV DNA levels can be observed within 4 weeks of treatment, improvement in liver function and clinical status takes 3 to 6 months.^{3,6,7} Thus, delaying treatment until transplantation is imminent may not benefit patients who have advanced liver failure. The dilemma regarding when to initiate lamivudine treatment in the late 1990s and early 2000 was related to the unavailability of a salvage treatment that can suppress lamivudine-resistant HBV. Patients with lamivudine-resistant HBV may experience rapid worsening of liver failure leading to death or removal from the transplant waiting list. Additionally, the risk of HBV recurrence after transplantation may be increased because of high serum HBV DNA levels at the time of transplantation.

Since 2002, adefovir dipivoxil, a nucleotide analog that is effective in suppressing wild-type and lamivudine-resistant HBV, has been approved in the United States and subsequently in Europe and many other countries. However, its use as a first-line antiviral agent, particularly in patients with decompensated cirrhosis, has evolved slowly. Thus, lamivudine continues to be a first-line antiviral agent in patients with decompensated HBV cirrhosis in many transplant centers. With the move to initiate treatment earlier and the increase in waiting time on the transplant list, many transplant centers now face a rising number of patients who have lamivudine-resistant HBV prior to transplantation.

Abbreviations: HBIG, hepatitis B immune globulins; HBV, hepatitis B virus; ALT, alanine aminotransferase; PCR, polymerase chain reaction.

From the Division of Gastroenterology, University of Michigan, Ann Arbor, MI.

Address reprint requests to Anna S.F. Lok, MD, Division of Gastroenterology, University of Michigan Medical Center, 3912 Taubman Center, Ann Arbor, MI 48109-0362. Telephone: 734-615-4628; FAX: 734-936-7392; E-mail: aslok@umich.edu

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Table 1. Outcome of Patients Who Had Lamivudine-Resistant HBV Prior to Liver Transplantation

Authors	Number of patients	Post-LT prophylaxis		FU/time to HBV recurrence (mo)	Number with HBV recurrence
		HBIG (IU)	Lamivudine		
Saab et al.	1	70,000 IV, then 10,000 IV monthly	Yes	32	0
Yao et al.	1	80,000 IV, then 1,100 IM every 3 weeks	Yes	10	0
Fontana et al.	6	Indefinite, 4; 3 months, 1*; none, 1	Yes	11	1
Rosenau et al.	2	40,000 IV, then 2,000 IV as needed	Yes	0.5, 2.5	2
Seehofer et al.	3	30,000 IV, then 1,500-2,000 IV as needed	Yes	NA	3
Starkel et al.	1	10,000 IV, then 10,000 every 6 weeks	Yes	12	0

Abbreviations: HBV, hepatitis B virus; HBIG, hepatitis B immune globulins; LT, liver transplantation; FU, follow-up; IV, intravenously; IM, intramuscularly; NA, not available.
*HBV recurrence.

The outcome of patients with lamivudine-resistant HBV while on the transplant waiting list, their rate of HBV recurrence after transplantation, and the optimal prophylactic therapy after liver transplantation are unclear. Case reports (prior to availability of adefovir dipivoxil) on the rate of HBV recurrence after transplantation have provided conflicting results, possibly related to the small number of patients studied, reporting bias, and short duration of posttransplantation follow-up (Table 1).^{5,13-17}

In this issue of *Liver Transplantation*, Marzano et al. retrospectively reviewed their experience in 99 patients who received lamivudine while waiting for liver transplantation for HBV cirrhosis.¹⁸ After transplantation, all patients received lamivudine and intravenous HBIG (a mean of 50,000 IU during the first month and a mean of 6,000 IU during each subsequent month). Stored sera permitted subsequent testing for lamivudine-resistant HBV mutation. Twenty-two patients (22%) were found to have lamivudine-resistant HBV mutants at the time of transplantation, 13 were known to have virologic breakthrough defined as serum HBV DNA $>5 \log_{10}$ copies/mL (YMDD-positive group A, phenotypic resistance), and the remaining 9 had serum HBV DNA $<5 \log_{10}$ copies/mL and were not recognized to have lamivudine resistance at the time of transplantation (YMDD-positive group B, genotypic resistance).

Among the YMDD-positive group A patients, 2 underwent transplantation prior to the availability of adefovir dipivoxil, and both had HBV recurrence within the first 2 months after transplantation. These 2 patients had serum HBV DNA levels of $9 \log_{10}$ copies/mL at the time of transplantation; the high viral levels likely exceeded the neutralizing capacity of the HBIG administered. While these 2 patients received

dual prophylaxis, lamivudine is unlikely to have any effect, so these patients were, in essence, receiving HBIG monotherapy. The other 11 patients received adefovir dipivoxil for 31 to 200 days prior to transplantation and after transplantation, and all but 1 had serum HBV DNA $<5 \log_{10}$ copies/mL at the time of transplantation. None of these 11 patients who received triple prophylaxis after transplantation had HBV recurrence, including 2 patients who stopped adefovir dipivoxil 3 and 32 days after transplantation. The authors suggest that adefovir dipivoxil may not be necessary after transplantation if it successfully reduces the HBV DNA level at the time of transplantation. Although the latter 2 patients had been followed for a substantial period (43 and 64 months) after transplantation, their results may not be generalized because of the limited experience. The favorable outcome in these 2 patients is likely related to the continued administration of high-dose intravenous HBIG; maintenance of high-dose intravenous HBIG was also important in preventing HBV recurrence in previously reported cases (Table 1). It would be of interest to know whether these 2 patients required higher doses of HBIG than the other 9 patients who continued to receive adefovir dipivoxil and to determine if these 2 patients had evidence of occult HBV infection (detectable HBV DNA by polymerase chain reaction [PCR] assay in serum and/or liver).

Among the YMDD-positive group B patients, HBV recurrence occurred in 2 patients who stopped HBIG on their own but not in the other 7 patients who continued to receive dual prophylaxis, highlighting the importance of maintaining high-dose intravenous HBIG prophylaxis in patients with lamivudine-resistant HBV in the absence of adefovir dipivoxil.

Marzano et al.'s paper focused on posttransplanta-

tion HBV recurrence; whether any of the patients who had lamivudine resistance had worsening liver failure leading to removal from the transplant waiting list or death without a transplant was not addressed. With the availability of adefovir dipivoxil, and recent reports demonstrating its efficacy in patients with lamivudine-resistant HBV,¹⁹⁻²¹ it would be prudent to administer salvage therapy to patients on the transplant waiting list when breakthrough infection is recognized. The questions that now confront transplant centers are: Should lamivudine resistance be monitored using PCR assays that can detect less-overt virologic breakthrough and should resistance be confirmed by mutation testing? Should lamivudine be continued after institution of adefovir dipivoxil? And, more importantly, should lamivudine still be used as a first-line antiviral agent in patients on the transplant waiting list?

Monitoring serum HBV DNA levels with PCR assays will detect breakthrough infection earlier and permit initiation of salvage therapy prior to clinical deterioration. When possible, resistance should be confirmed as clinical trials found that 30% of lamivudine breakthrough is due to medication noncompliance. Adefovir dipivoxil monotherapy has been reported to be as effective as combination of adefovir dipivoxil and lamivudine in suppressing lamivudine-resistant HBV, but only 19 patients were enrolled in the adefovir dipivoxil arm alone, and a higher percentage of patients had hepatitis flares compared with those in the combination therapy arm.²¹ Thus, most investigators recommend a minimum of 3 months' overlap. Whether lamivudine should be continued indefinitely remains unclear. In patients with lamivudine-resistant HBV, wild-type HBV is still present and may be suppressed by lamivudine. In vitro and clinical case studies showed that lamivudine is effective in suppressing adefovir-resistant HBV, suggesting that continuation of lamivudine may reduce the risk of adefovir resistance.^{22,23} The lower rate of adefovir resistance (4%-6% after 3 years of therapy)^{24,25} argues for using adefovir dipivoxil as a first-line antiviral agent in patients waiting for a liver transplant. Indeed, some transplant centers have adopted this approach. Other transplant centers such as Marzano's continue to use lamivudine as a first-line antiviral agent because the virus suppression is more rapid, the cost is lower, and there is no concern for nephrotoxicity.

Marzano et al. confirmed that patients with lamivudine-resistant HBV before transplantation can have successful outcomes after transplantation, but the rate of HBV recurrence was higher than in patients with no lamivudine resistance: 4 (18%) of 22 vs. 4 (5%) of 77.

Their study showed that in patients with a high serum HBV DNA level, suppression of HBV replication with salvage therapy prior to transplantation is important. Although the authors suggested that adefovir dipivoxil may not be necessary for patients with low serum HBV DNA levels, their results may not apply to transplant centers that use lower doses of HBIG. In vitro studies suggest that in patients with lamivudine-resistant HBV mutations, corresponding changes in overlapping S gene may reduce binding to HBIG.²⁶ Additionally, patients with lamivudine-resistant HBV may have low serum HBV DNA levels initially that increase over time. Thus, unless serum HBV DNA levels are monitored very frequently, HBV DNA levels may have unknowingly increased at the time of transplantation and inadequate posttransplantation prophylaxis would be administered. Addition of adefovir dipivoxil before transplantation, as soon as breakthrough infection is diagnosed (using PCR monitoring and more recent definition of $>1 \log_{10}$ copies/mL increase in HBV DNA) can reduce ALT and improve liver function. It may also enable HBV recurrence to be prevented without resorting to long-term high-dose HBIG, although data supporting this approach are lacking.

Few areas in clinical medicine have progressed as much in the past 15 years as liver transplantation for hepatitis B. However, new questions have emerged along with the progress. What should be the first-line antiviral agent(s) in hepatitis B patients waiting for a liver transplant? Should antiviral resistance be monitored? How much HBIG is needed in the era of nucleos(t)ide analogs? Can addition of adefovir dipivoxil in patients with lamivudine-resistant HBV reduce HBV recurrence to similarly low rates as in patients with wild-type HBV? Increasing data indicate that lamivudine monotherapy is not optimal for hepatitis B patients waiting for a liver transplant. Some investigators use this combination as an induction therapy to achieve rapid viral suppression and adefovir as maintenance therapy. Whether combination therapy with lamivudine and adefovir dipivoxil or monotherapy with newer antiviral agents that are more potent and have low risk of drug resistance, such as entecavir or tenofovir, will be better first-line antiviral agents remains to be determined. Regardless of the choice of initial antiviral therapy, close monitoring of viral response with sensitive HBV DNA assays is necessary to detect breakthrough infection as early as possible so salvage therapy can be instituted. Currently, most transplant centers use combination prophylaxis (lamivudine or adefovir dipivoxil plus HBIG), many programs are evaluating lower doses or shorter duration of HBIG when used in

combination with an antiviral agent, but the minimum dose and duration of HBIG needed for optimal results have not been established. Marzano et al. showed that addition of adefovir dipivoxil can reduce HBV recurrence in patients with lamivudine-resistant HBV. Further studies are needed to determine if lower doses of HBIG will suffice with the addition of adefovir dipivoxil and if lamivudine should be maintained.

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