REVIEW

Liver Transplant and Chronic Hepatitis B Virus Infection

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Abstract

Hepatitis B immune globulin use for preventing hepatitis B virus recurrence after liver transplant has changed our behavior radically, and it now seems that hepatitis B immune globulin has a vital role in preventing recurrence. New nucleotide or nucleoside analogues have promising results in treating chronic hepatitis and in posttransplant hepatitis B virus-infected patients. Hepatitis B immune globulin and other antivirals act on different pathways, so it is logical to combine these drugs to achieve maximum response in suppressing hepatitis B virus (HBV)-replication.

Until late in 1980s, hepatitis B virus (HBV) related liver disease constituted a relative and sometimes absolute contraindication for liver transplant (LT); as posttransplant HBV recurrence was almost universal; particularly if no immunoprophylaxis was given. The high rate of HBV reinfection after liver transplant is probably due to enhanced viral replication resulting from immunosuppression and direct stimulatory effects of steroid therapy on the glucocorticoid-responsive enhancer region of the HBV genome.[1, 2] Extrahepatic reservoirs of HBV (eg, peripheral blood mononuclear cells, spleen, and other organs) also may have contributed to graft reinfection. The risk of acquiring HBV infection after liver transplant in hepatitis B surface antigen (HBsAg)-negative recipients is low, but rates as high as 10% have been reported.[3] Dickson and associates reported that HBsAg-positive hepatitis developed in 18 of 23 recipients of LTs (78%) from anti-hepatitis B core (HBc)-positive donors, compared with only 3 of 651 recipients of livers from anti-HBc negative donors (0.5%).[4] Although the significance of this problem remains unclear, reactivation of HBV replication also has been reported in recipients who are HBsAg-negative, anti-HBc positive pretransplant, and those who have received liver grafts from donors who are HBsAg- and anti-HBc-negative.

Patients with HBV-related cirrhosis who are candidates for transplant can be conceptually divided into those with high risk versus low risk of reinfection. High-risk patients include those patients with cirrhosis who are hepatitis B envelope (HBe)Ag-positive or HBeAg-negative but with high serum HBV DNA levels, and patients with antiviral drug-resistance before transplant. Low-risk patients include those patients with fulminant HBV, coinfection with hepatitis delta virus, and cirrhotic patients who are HBeAg-negative with low serum HBV DNA levels.[5]

All studies have shown that graft and patient survival are affected by the presence of reinfection. Preventing HBV reinfection is of pivotal importance in HBV-related LT, and this includes use of antiviral therapy and hepatitis B immune globulin (HBIG) during peritransplant. To achieve this target HBIG, its use was one of the cornerstones of therapy.

Hepatitis B immunoglobulin use

In 1987, the Hannover group reported that immune prophylaxis with HBIG to maintain serum anti-HBs levels > 100 IU/L for a minimum of 6 months after LT prevents HBV reinfection in LT recipients.[6] These results were confirmed by a large, multicenter European study published in 1993 demonstrating a prominent reduction of HBV recurrence.[7] Since 1993, use of high doses of intravenous, long-term hepatitis B immune globulin has become routine after LT owing to HBV-related liver diseases. It is now generally

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accepted that the first dose of HBIG (usually 10 000 IU; range, 2000 to 20 000 IU) should be administered during the anhepatic phase during LT, followed by daily administration of 400 to 10 000 units (changes on protocol) during the first 5 to 10 postoperative days, irrespective of actual anti-HBs levels, and in some protocols, guided by HBsAg levels.[8]

Long-term administration of HBIG has changed the prognosis of almost all LT patients with HBV. In cases with HBV replication (HBV-DNA serum positivity), at the time of LT, this prophylactic measure is much less effective, reinfection being frequent and severe. The main goal in patients with HBV-related liver diseases is to suppress HBV replication throughout the pretransplant and posttransplant period. Introduction of the nucleos(t)ide oral analogues in the treatment of HBV infections has been an important step to achieve this goal. These drugs are now used pre-LT and post-LT, and in combination with HBIG, and have achieved a high efficacy (more than 90%) in preventing graft reinfection, distinctly improving post-LT survival of these patients.

At the conventional dosage of 10 000 IU per month, the cost of HBIG is USD $100,000 in the first year after LT, and USD $50,000 per year thereafter.[9] To reduce these costs, strategies include reducing the amount of HBIG administered, ceasing HBIG some time after LT while continuing lamivudine (LAM) and/or other oral nucleos(t)ites, or actively vaccinating patients while attempting to withdraw HBIG. When used as single agents, HBIG and LAM reduce recurrence rates by approximately 50%. However, when used in combination, they seem to have a synergistic effect, reducing recurrence rates to less than 5% at 5 years.[10] Practically all transplant centers still administer HBIG during the early posttransplant period, but the dosage and duration of HBIG varies markedly across transplant centers. Hepatitis B immune globulin dosage regimen is tailored according to the predicted risk of reinfection, cost, and availability. Combination low-dose intramuscular HBIG and LAM prophylaxis has been used extensively in Australasia, where an intravenous HBIG preparation is not available. This protocol requires 800 IU intramuscular HBIG be administered at LT, and daily, for 1 week immediately after LT. Thereafter, 800 IU HBIG is given monthly. Lamivudine is being put on the wait list for LT and continued indefinitely.[11] Long-term results using this protocol have been published.[12] In 147 patients, the largest study of combination prophylaxis to date, the actuarial rate of recurrence was 4% at 5 years—equivalent to results achieved with high dosage intravenous HBIG regimens. Karasu and associates reported the results of their single-center study, using a combination of lamivudine and low-dose HBIG on 80 patients. Of those patients, pretransplant HBV DNA was positive in 10, and all became negative under lamivudine therapy before transplant. In the other 8 treatment naive replicative patients, lamivudine was begun at transplant. The rate of recurrence was 5% using the lower limit of HBIG as 50 IU/L in the maintenance period, with a mean follow-up of 20.8 ± 17.7 months. Hepatitis B immune globulin was administered intravenous in dosages of 4000 IU during the anhepatic phase. Later, 400 or 800 IU was given intramuscularly daily for 5 to 10 days and 2 to 4 weeks thereafter, according to serum anti-HBs titre.[13] They also claimed that although the number of adult patients who underwent LT because of HBV infection exceeded 300 patients, and duration of follow-up was much longer in their transplant center; the recurrence rate was still around 6% with the same prophylaxis protocol.

Oral nucleoside/nucleotide analogs

Although combination prophylaxis gives the chance to decrease the dosage of HBIG, cost remains important. There are 2 methods regarding discontinuation of HBIG. The first is simply discontinuation of HBIG and perpetuating monoprophylaxis with nucleoside/nucleotide analogues. The second is a trial of active immunoprophylaxis or vaccination to induce formation of anti-HBs.

The largest trial of HBIG withdrawal involved 29 patients, 14 of whom received indefinite LAM (with only 1 month of initial HBIG) with the remainder continuing use of a combination of HBIG/LAM. In this Spanish, multicenter, controlled trial, published in 2003, using lamivudine and HBIG for 18 months, after LT, both drugs were compared in the first month followed by lamivudine alone until month 18—there were no differences in the reappearance of HBsAg (0% in both groups) or in the detection of HBV DNA by sensitive techniques (< 1000 copies/mL): 80% negative in the HBIG plus lamivudine, 93% negative in the lamivudine alone. All patients received lamivudine before LT. Those who were HBV DNA-positive until this marker became negative, while those without HBV replication received lamivudine approximately 15 to 30 days before LT had never been

assessed. Furthermore, following these patients during the next 5 years, the authors showed that the efficacy of the therapy persisted, with no significant differences detected after this time in the index of reinfection.[14, 15]

In the only prospective study of long-term HBIG-free combination adeno-associated virus and LAM prophylaxis, both drugs were commenced while the patients were on the wait list for transplant in 26 HBsAg-positive patients, of whom 19 progressed to transplant.[16] Those with documented LAM-R were excluded. All patients received intramuscular HBIG the day of transplant and for 1 week after LT. After a median of 1 year after LT, there were no recurrences and no antiviral drug-related significant adverse events.

The emergence of lamivudine resistance with prolonged use, either as monotherapy or in combination with HBIG, has forced us to use other drugs. Adefovir can be substituted, or even added to, lamivudine, when lamivudine resistance is detected. In cases of advanced cirrhosis, while on the LT wait list, both drugs may be given together as soon as HBV replication is detected to obtain the most-rapid clearance of HBV DNA and reduce the risk of emerging resistant mutants, thereby making LT possible without reinfection of the graft. It is clear that in patients with LAM-R, addition of adeno-associated virus to LAM, rather than substitution of adeno-associated virus for LAM, is superior in preventing adeno-associated virus resistance.[17]

However, in treatment-naive patients, this drug has diminished use as primary anti-HBV therapy, as it is less potent than other drugs, and there is nearly a 20% rate of primary nonresponse.[18]

Adeno-associated virus also may induce a reversible rise in serum creatinine. The major ongoing role for adeno-associated virus is in the management of LAM-R HBV. A large, prospective study of adeno-associated virus in 467 LAM-R wait listed or post-LT patients confirmed the safety and virologic efficacy of adeno-associated virus in the peri-LT setting.[19] In this study, 61 patients underwent an LT, whereas 23 of those receiving adeno-associated virus therapy did not receive HBIG. The rate of HBV recurrence after a median of 36 weeks after the LT was not influenced by the use of HBIG (12% with HBIG vs 13% without). However, the relatively short follow-up and a lack of data on some patients limit the conclusions. Adeno-associated virus also has been used to replace HBIG in patients receiving long-term combination HBIG/LAM prophylaxis. In a larger, prospective, randomized study of 34 patients who were at least 12 months post-LT, 18 continued HBIG/LAM, and 16 switched to adeno-associated virus/LAM.[20] No patient in either group developed a breakthrough at a median of 21 months after the switch, and there were significant cost-savings compared with continued HBIG-containing prophylaxis.

A new generation of nucleos(t)ide analogues (eg, entecavir, tenofovir, and telbivudine) recently has been introduced in HBV infection therapy. Studies comparing these new therapies with lamivudine in chronic hepatitis B with or without compensated cirrhosis show better therapeutic profile and a lower probability of emergence of resistance. However, the experience of its use in advanced cirrhosis and in pre-LT or post-LT is limited, and trials in this situation are ongoing.

Based on data in the pretransplant setting, it is expected that adefovir monoprophylaxis will be associated with emergence of adefovir-resistant mutants. Entecavir, which is a more-potent agent with lower resistance rates in nucleoside-naive cases[21] and without risk of nephrotoxicity, would be more attractive for monoprophylaxis in posttransplant patients. However, entecavir must be avoided in patients with previous lamivudine resistance, who should be preferably treated with adefovir or tenofovir. At 5 years, resistance to entecavir occurs in only 1.2% of naive patients, but this increases to 51% in patients with pre-existing LAM-R.[22] Tenofovir is more potent than adefovir, having a better resistance profile,[23] but it also may give rise to renal dysfunction, particularly in patients receiving nephrotoxic immunosuppressive agents, such as calcineurin inhibitors. Finally, telbivudine monotherapy has moderate resistance,[24] and therefore is not a good option for transplanted patients. Thus, entecavir is the most-promising monoprophylaxis option in the post-LT HBV setting. Tenofovir should be the first-line therapy in cases with previous lamivudine resistance. Well-designed studies are warranted to determine whether prophylactic monotherapy with a potent anti-HBV agent, such as entecavir or tenofovir, might be effective in HBV transplant patients.

Hepatitis B virus vaccine and newer treatments

Another topic for preventing HBV recurrence after LT is HBV vaccine use. Although results of the first study

of active immunization with higher and multiple doses of hepatitis B vaccines is encouraging, subsequent studies found that response rates were poor (8% to 80%), and anti-HBs titers achieved in the responders were low.[25] We will wait to see the results of new, ongoing studies using new vaccines and adjuvants.

An alternative to HBIG for preventing recurrence after LT, hyperimmune anti-HBs (hepatitis B antibody) plasma, which has been prepared from HBV-vaccinated donors with high titre anti-HBs by plasma apheresis, has been used and found to be as effective as HBIG and is 10-fold less expensive.[26] New molecules for immune prophylaxis will probably appear in the market. As an example, 2 human monoclonal antibodies directed against HBsAg epitopes—libivirumab and exbivirumab—were used in combination, and were found to be effective in preventing posttransplant hepatitis B recurrence in a 52-week trial.[27]

In conclusion, HBIG use for preventing HBV recurrence after LT has changed our behavior radically and until now, it seems that HBIG has a vital role. Nevertheless, new nucleotide or nucleoside analogues are being developed for treating HBV. Some have promising results in treating chronic hepatitis and in posttransplant HBV-infected patients. Hepatitis B immune globulin and other antivirals act in different pathways, so it is logical to think that various combinations of these drugs will result in more-effective and cost-saving outcomes. Further studies are needed to bear out these results.

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