Introduction

Three professional organizations dedicated to the science and art of liver transplantation -- the International Liver Transplantation Society (ILTS) (http://www.ilts.org/), the European Liver Transplant Association (ELTA), and the Liver Intensive Care Group of Europe (LICAGE) (http://www.md.ucl.ac.be/licage/home.swf) -- convened in Berlin, Germany, for an unprecedented international meeting and program focused on scientific advances in clinical management of liver transplant (LT) recipients. In addition to state-of-the art symposia on topics such as surgical techniques, anesthesia and critical care, artificial liver support technologies, and postoperative complications, nearly 400 oral and more than 275 poster abstracts were presented. The entire program can be seen at http://www.ilts-berlin.de/. This report focuses on one aspect of the meeting -- outcomes of liver transplantation in patients with hepatitis B virus (HBV) infection.

HBV Infection

HBV is a DNA virus that belongs to a class of viruses called hepadnaviruses. In immunocompetent individuals, HBV is not highly virulent (likely to produce severe disease), but it is highly infectious (easily transmissible). Carriers are the major source of disease transmission, and the major vector is blood and other bodily fluids from infected individuals. Chronic HBV infection affects more than 350 million people worldwide and approximately 1.25 million people in the United States. There are about 300,000 new cases of HBV infection each year in the United States that lead to 15,000-30,000 new cases of chronic HBV infection.[1] In the United States, approximately 4000 LTs are performed each year, and hepatitis B is the sixth most common indication for orthotopic LT among adult patients. However, less than 5% of adult LTs were performed in the United States for chronic HBV infection during the 1990s.[2] Worldwide, HBV disease is among the leading causes of fulminant hepatic failure, cirrhosis, and hepatocellular carcinoma. It is hoped that the widespread use of vaccinations and antiviral therapy ultimately may lead to eradication of this life-threatening virus.

HBV Infection: Here and There

HBV infection is a very different disease in North America and Western Europe than in the Subsahara and the Far East. In North America and Western Europe, the incidence is relatively low, infection occurs mostly in early adulthood, the mode of transmission is primarily intravenous (IV) drug abuse and sexual intercourse, and the associated risk of hepatocellular carcinoma (HCC) is low. By contrast, in the Subsahara and Far East, the incidence is much higher, infection occurs in infants and toddlers, the main mode of transmission is perinatal, chronicity is more likely, and the associated risk of HCC is high.

The initial infection with HBV results in acute hepatitis marked by increased serum transaminase levels and often by clinical jaundice. Acute HBV infection may be complicated by submassive or massive liver necrosis, and in rare cases leads to fulminant hepatic failure. The mortality rate of fulminant hepatic failure exceeds 80% to 90% in the absence of emergent liver transplantation (LT).

The risk of developing chronic HBV surface antigen (HBsAg) carrier status after acute HBV infection varies from 5% to 95%, and is inversely related to the duration of infection; 25% to 33% develop cirrhosis or HCC.[3] In an early series, the 5-year survival rate for adult HBsAg carriers with cirrhosis was 55%.[4] de Jongh and colleagues[5] reported a 5-year survival probability of 71% in patients with histologically proven HBsAg-positive cirrhosis.[5] Variables independently related to survival were age, bilirubin, and ascites. Survival of patients with compensated vs decompensated cirrhosis at 5 years was 84% and 14%, respectively.

LT for HBV Infection

LT in patients infected with HBV was particularly problematic in the pioneering years of the field. Because the virus is not eradicated by LT, infection of the liver graft is almost certain in the absence of targeted pharmacologic management, especially in the immunosuppressed recipient. Without prophylaxis, recurrence of HBV infection after LT is 80% to 100%, is associated with a rapid rate of disease chronicity, and frequently causes death within the first posttransplant year.[6] Patients who are HBV DNA positive (HBV DNA+) or HBV "e" antigen positive (HBeAg+) before transplantation are at the greatest risk of recurrence. Of the 7 HBV genotypes (A - G), genotype A is the most common in the United States and Western countries. In an analysis of 33 patients transplanted for HBV disease and treated postoperatively with hepatitis B vaccine (recombinant) or HBIg (*Energix-B*), HBV replication was most common pretransplantation in patients with genotype A. However, the lowest risk of HBV recurrence also occurred in this group.[7]

During the 1970s and 1980s, no prophylactic regimen was available to prevent HBV recurrence and graft infection after LT and results were dismal. Consequently, HBV infection was considered a contraindication to LT in many US programs as late as the early 1990s. As HBV recurrence prophylaxis protocols have evolved, results of LT have improved significantly for this indication. In the late 1990s, HBV DNA-negative (HBV DNA-) status became an accepted indication for LT. Debate continues however, about transplanting HBV replicant patients (HBV DNA+ and/or HBeAg+) who are at higher risk of recurrence, despite postoperative HBV prophylaxis.

This report includes a review of the literature as well as summaries of presentations during the session on Hepatitis B from the Joint Meeting of ILTS, ELTA, and LICAGE, held July 11-13, 2001 in Berlin, Germany, on outcomes in LT for HBV infection. Passive immunization with HBIg, lamivudine monotherapy, and combination therapy with HBIg plus lamivudine are discussed in terms of their efficacy in preventing recurrence of HBV infection after LT.

Passive Immunization With HBIg

HBIg is a polyclonal antibody to HBsAg. The mechanism of action of HBIg is not directed against the virus within the infected tissues, but rather at the HBsAg coating of circulating virions, thereby preventing entry of the virus into hepatocytes. A landmark multicenter European study by Samuel and associates[8] confirmed that the rate of recurrent HBV infection could be reduced and that survival could be improved when HBIg was used after LT. Patients given long-term HBIg (ie, > 6 months) had significantly better outcomes compared with individuals given short-term HBIg treatment or no immunoprophylaxis. Immunoprophylaxis was more likely to be successful in patients who lacked evidence for viral replication (HBV DNA-, hepatitis B e antigen negative [HbeAg-]) prior to LT.

Since then, the regimen of HBIg administration has become standardized: 10,000 IU during the anhepatic phase of LT surgery, then 10,000 IU daily during the first postoperative week, then according to the hepatitis B surface antigen antibody (HBsAb) blood levels (target value ≥ 100 IU/L) thereafter. To be effective, passive immunoprophylactic therapy is indefinite because HBV recurrence is high when HBIg therapy is interrupted or withdrawn.[9] Nevertheless, long-term passive immunization with HBIg to HBsAg is an effective way to prevent or to delay HBV recurrence after LT, especially in HBV DNA- patients.[10] Pruett and McGory[11] reported the findings from a meta-analysis of major US studies of the use of HBIg in LT. Their conclusions are summarized as follows:

- Recurrence of HBV in HBV DNA+ patients after LT can be prevented with continuous high-dose HBIg.
- The dose of HBIg required to prevent posttransplant HBV recurrence is difficult to predict.
- Failure of HBIg therapy manifests in 2 ways: (1) early infection of the liver graft with wild-type HBV, and (2) later graft infection with a mutant virus.
- Combination therapy with HBIg and lamivudine (*Epivir*) appears to be a promising strategy for preventing HBV recurrence.

In a meta-analysis of European HBIg trials, Kruger

[12]

concluded that HBIg is efficacious in decreasing the rate of recurrence and severity of HBV infection. In these trials,

HBIg was most effective when administered in high doses over a long period of time and outcomes were not as good when DNA replication was active at the time of transplantation.

Although long-term prophylaxis with HBIg has significantly improved access to and outcomes of LT for patients with HBV disease, survival is cut short in 20% to 36% as a result of recurrence.[13] HBIg therapy also has its pitfalls: the need for intramuscular (IM) or IV injections, high cost, significant side effects (myalgia, back pain, flulike syndrome), and the necessity of lifelong regular follow-up for testing of blood titers. Moreover, some questions are not yet answered, such as: What is the best way of administration (IV or IM)?, What is the ideal titer level?, and What is the best regimen with respect to timing of administration of HBIg?

The use of monoclonal antibodies would offer several potential advantages. However, these preparations are not used because of the difficulty in obtaining human monoclonal antibodies and the narrow degree of specificity in which escaped HBsAg mutants frequently occur in treated patients.

Anti-HBV Nucleoside Analogues

Lamivudine, a nucleoside analogue, is a dideoxynucleoside reverse transcriptase inhibitor. Lamivudine is a potent inhibitor of HBV replication and the first effective, and well-tolerated, oral treatment for chronic HBV infection.[3] At a dosage of 100-150 mg/day orally, lamivudine has been shown to be efficacious in the prevention of HBV recurrence after LT. Although lamivudine is well tolerated, treatment must be indefinite and virologic breakthrough by YMDD variant HBV (tyrosine-methionine-aspartate-aspartate amino acid motif of HBV polymerase), aka lamivudine-resistant strains of HBV or YMDD mutants, has been described. The incidence of lamivudine resistance increases with duration of therapy and high levels of HBV replication.

The effects of extended lamivudine therapy in Asian patients with chronic HBV infection were evaluated by the Asia Hepatitis Lamivudine Study Group. Preliminary results of 358 Chinese patients at 1 year showed marked histologic improvement in patients treated with 100 mg daily.[14] Necroinflammatory activity improved by at least 2 points on the Knodell score and progression of fibrosis was halted in 56%. At 1 year, 334 of these patients were randomized to treatment with lamivudine or placebo for 12 months.[15] As expected, the rate of sustained suppression of HBV-DNA replication was significantly greater in patients treated with lamivudine. YMDD mutants emerged in 38% of these patients, but they continued to clear HBsAg and their HBV DNA and alanine aminotransferase levels were maintained at lower than baseline.

Several multicenter trials were conducted to determine the prophylactic efficacy of lamivudine as preemptive therapy, therapy initiated before LT and continued thereafter.

The US Lamivudine Compassionate Use Study reported the longest duration of lamivudine treatment in a large group of LT recipients.[16] Thirty-three patients were treated for a median of 85 weeks. Median serum HBV DNA levels at entry became undetectable within 16 weeks of starting therapy. At 6 and 12 months, 72% and 50% of patients, respectively, were HBV DNA-. A virologic breakthrough rate of 45% (13 patients) was reported after a median of 61 weeks of treatment. YMDD mutants were identified as the cause in 54% (only 7 patients tested).

The inhibitory effects of lamivudine against HBV infection recurrence were evaluated in a multicenter trial of lamivudine monotherapy in LT recipients and patients with decompensated chronic HBV cirrhosis waiting for LT.[17] Thirty-seven LT recipients completed 52 weeks of therapy. The recurrence rate was 40% in patients followed for > 12 weeks and HBsAg was detected in 32%, 31%, and 41% at 1, 2, and 3 years, respectively, after transplantation. Data from patients with decompensated cirrhosis who received more than 1 week of therapy were also analyzed; marked biochemical and virologic improvement was common.

A potential benefit of lamivudine monotherapy is the avoidance of the high cost of long-term immunoprophylaxis. Replacement of HBIg (administered for at least 6 months without recurrence) in 24 LT recipients (all HBsAg positive/HBV DNA negative before transplantation) by long-term lamivudine treatment was investigated by Naoumov

and colleagues.[18] Patients were randomized to receive either lamivudine (n = 12) or HBIg (n = 12) for 52 weeks. Twenty-one patients completed the study with no evidence of HBV recurrence (11 on HBIg, 10 on lamivudine). Replacement of HBIg with lamivudine appeared to be effective for prevention of HBV recurrence in low-risk LT recipients.

Lamivudine is the first effective, well-tolerated oral agent for treatment of chronic HBV infection. Clinical improvement and stabilization occur in some patients with end-stage liver disease (ESLD), thereby increasing pretransplant survival and, in some rare cases, eliminating the need for LT. Lamivudine may also be effective in preventing recurrence of HBV infection after LT, thereby improving graft and patient survival.[19-21] However, the emergence of YMDD mutations may limit its usefulness in monotherapy.

A newer nucleoside analogue, adefovir dipivoxil, has demonstrated potent activity against HBV, including wild-type and lamivudine-resistant virus, but has not been evaluated in transplant recipients.[22,23]

Combination Therapy

The combination of HBIg and lamivudine appears to be more effective than monotherapy with either agent in HBV DNA- and HBV DNA+ patients. This regimen may also prevent the development of YMDD mutants, a problem with lamivudine monotherapy. The recurrence rate after LT has been reported to be higher in patients who were HBeAg+ at the time of LT.[24,25] Machicao and colleagues[26] retrospectively compared the 12-month outcome of 28 patients (12 HBeAg+, 16 HBeAg-) transplanted for HBV receiving combination therapy according to pre-LT HBeAg status. In contrast to previous studies, they found that pre-LT HBeAg status did not affect HBV recurrence, patient or graft survival, or liver histology. The reinfection rate in HBV DNA+ patients was very low (0% at 1 year).

Buti and colleagues[27] presented preliminary results of a study in which 46 patients are to receive lamivudine for at least 15 days pretransplantation and combination therapy for 4 weeks. Then, patients were randomized to either combination therapy or lamivudine monotherapy until 18 months after transplantation. Twelve patients have completed the study and 18 patients have completed 12 months of follow-up. Based on these preliminary results, the investigators concluded that a short course of combination therapy followed by lamivudine monotherapy is as efficacious as continuous, long-term combination therapy in preventing HBV recurrence after LT.

Rosenau and colleagues[28] followed 31 LT recipients given combination therapy with lamivudine and HBIg. Administration of lamivudine was begun a median of 200 days posttransplantation in 27 patients and at the time of LT in 4 patients. HBIg was begun intraoperatively and continued throughout the study. At the time of LT, 25 patients were HBV DNA-. Of the 6 HBV DNA+ patients, 2 had YMDD mutants.[29] These were the only patients that had HBV recurrence. They concluded that HBV reinfection could be prevented with combination therapy in patients with controlled viral replication.

Posttransplant HBV Vaccination

Vaccination with the recombinant anti-HBV vaccine is successful in immunocompetent individuals (the seroconversion rate is 90%), but in immunosuppressed patients (before LT in cirrhotic patients and after in LT recipients), the seroconversion rate is low. In spite of considerable evidence to the contrary, it has been suggested that posttransplant vaccination against HBV may be a cost-effective alternative to long-term HBIg therapy.[30] However, these results have not been replicated.[31] Tisone and colleagues[35] conducted a pilot study of a double-reinforced course of HBV vaccination in 16 patients transplanted for HBsAg+ cirrhosis from 2-7 years earlier. At 4 months after discontinuation of HBIg therapy, 3 double IM doses of recombinant vaccine (40 micrograms [mcg] at 0, 1, and 2 months) were given. Lamivudine therapy was continuous throughout the study. Nonresponders received 6 intradermal doses (10 mcg) 15 days apart. At 3 months, only 1 patient had a good response. The investigators concluded that a double-reinforced course of HBV vaccination is ineffective as protection against HBV reinfection. Further evaluation of the efficacy of posttransplant vaccination is indicated.

The Use of HbcAb+ Donors

Five percent of donors in the United States and 12% in Spain have serum immunoglobulin G to the HBV core antigen -- in other words, are hepatitis B core antibody positive (anti-HBc+) donors. Anti-Hbc is a marker for past infection with HBV. The risk of infection from anti-HBc+ donors is 33% to 78% in the United States.[32] However, cadaveric HBcAb+/HBsAg- liver donors are now accepted in most centers for HBV cirrhotic patients as excellent results have been achieved with postoperative combination therapy.[33-35]

Summary

Due to advances in antiviral therapy, patients with ESLD from HBV infection are now considered excellent candidates for LT with cadaveric or living-related grafts. Patient and graft survival rates are high and the rate of HBV recurrence is low. The current standard of care for prophylaxis against HBV reinfection after LT is indefinite HBIg therapy. However, this protocol is very costly and requires lifelong management of antibody to HBsAg blood titer and regular IV or IM HBIg administration. Other protocols, such as lamivudine monotherapy or the combination of lamivudine plus short-term HBIg, are under investigation. The main complication of long-term lamivudine therapy is the development of resistant YMDD mutants. Combination therapy with long-term HBIg plus lamivudine lowers the risk of recurrence and may prevent the development of YMDD mutants.

For many years, HBV DNA+ patients were not considered candidates for LT. However, the results of indefinite combination therapy are so good that these patients should not be excluded from this life-saving procedure. Most of these patients are now receiving pretransplant lamivudine in an attempt to render them HBV DNA- and decrease the risk of posttransplant recurrence. However, this practice might favor the appearance of YMDD mutants before LT, thereby increasing the risk of posttransplant recurrence. Although great strides have been made in this area, there is still some distance to go before HBV infection can be eradicated or cured.

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