Hepatitis B infection and liver transplantation

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On a global scale, chronic infection with the hepatitis B virus (HBV) is a significant problem, affecting an estimated 300 to 400 million people worldwide. HBV prevalence in Canada is low but increasing. In areas with large numbers of immigrants from endemic areas, HBV may be a significant cause of end-stage liver disease. Cirrhosis and hepatocellular cancer (HCC) are the end results of chronic HBV infection. While therapy with interferon (IFN) may be of benefit to some patients, those with marginal hepatic reserve may decompensate with IFN therapy and are at risk of bacterial infections (1,2). Although some decompensated patients may respond to IFN at substantially reduced doses, those with significant decompensation (ie, Child’s class C) appear less likely to benefit (3). But it is precisely those with decompensated HBV infection who urgently require treatment. With most other liver diseases, patients in similar circumstances would routinely be offered liver transplantation. Until recently, however, HBV-related liver disease was considered a contraindication for transplantation in both Canada and the United States. HBV is now considered a relative contraindication for transplantation in Canada. Outside of patients in investigational studies, few Canadians with HBV infection undergo transplantation.

Hépatite B et transplantation hépatique

RéSUMé : Les patients souffrant d’hépatite B chronique ont souvent présenté un taux élevé de réinfection de l’allogreffe provenant des importants réservoirs d’HBV, leur évolution à long terme étant moins favorable que celle des receveurs de transplantation indemnes d’infection à HBV. L’infection chronique au HBV a donc été considérée comme une contre-indication à la transplantation. La prophylaxie contre les récurrences de l’HBV sous forme d’immunisation passive au moyen de fortes doses d’hyperimmunoglobulines antihépatite B et de l’antiviral lamivudine a récemment été associée à une réduction du risque de réinfection. Grâce à une prophylaxie appropriée, la transplantation hépatique peut donc être une solution envisageable chez les patients infectés au HBV. On passe ici en revue l’expérience acquise à ce jour et l’état actuel des connaissances sur l’HBV et la transplantation en mettant l’accent sur les questions entourant la prophylaxie.

Key Words: Hepatitis B, Immunoglobulin, Lamivudine, Liver transplantation, Prophylaxis
HISTORICAL CLINICAL OUTCOME AFTER TRANSPLANTATION

Even with removal of the native liver, there are numerous extrahepatic reservoirs (4) in which HBV can be found (lymphoid tissue, bone marrow, kidney, pancreas, etc.). Moreover, HBV DNA can be found in circulating mononuclear leukocytes post-transplant, even in the absence of HBV DNA in the allograft (5). The persistence of HBV in combination with post-transplant immunosuppression therefore creates an environment in which the transplanted liver is at high risk of reinfection.

Until recently, significant allograft reinfection, with poor allograft and patient long-term survival, has been documented. American data from the United Network for Organ Sharing liver transplant registry (6) reveal that from 1987 to 1992, the 60-month survival for adults who received transplants for HBV was only 48%, compared with 77% for both primary biliary cirrhosis and autoimmune hepatitis adult patients. In perhaps the largest study to date, Samuel and colleagues (7) reviewed the European experience, which included 334 patients (summarized in Table 1). They reported that patients with cirrhosis with active replication pretransplantation, as indicated by positivity for serum HBV DNA, had a three-year actuarial risk of allograft reinfection of 83%. Those with cirrhosis who were HBV DNA hepatitis B early antigen (HBeAg) seronegative had a three-year actuarial risk of 58%. Certain subgroups — those who received transplants for acute fulminant HBV and delta agent coinfection — experienced markedly lower risks of reinfection: 17% and 32%, respectively. Importantly, the European study determined that the overall three-year actuarial survival of those who developed allograft reinfection was only 54%, versus 83% in those without allograft reinfection. Patients with allograft reinfection who received transplants for cirrhosis had an actuarial survival rate of only 44%. Interestingly, approximately 80% of the patients in the study received some form of immunoprophylaxis.

From these data it is clear that patients who received transplants for hepatitis B have a significant risk of allograft reinfection and decreased survival compared with similar patients who are HBV-free. Patient outcome is related to viral load because those who are actively viremic (serum HBV DNA positive) are more likely to be reinfected than those not actively replicating (serum HBV DNA negative). Subgroups with delta agent coinfection and those who received transplants for acute fulminant hepatitis B are less likely to suffer allograft reinfection. In the latter case, it is likely that the immunological defences that resulted in fulminant hepatitis, combined with the short period of viral infection, result in a decreased viral burden, especially in extrahepatic tissues. In the former case, it is well accepted that the delta virus modulates HBV activity (8). Patients who received transplants for HBV-related HCC have even worse outcomes for survival, even when compared with patients who received transplants for non-HBV associated HCC (9,10).

The very poor outcome in this group is only partly a direct result of malignancy. These patients have a greater risk of allograft reinfection compared with those who received transplants for HBV-related cirrhosis, a one-year actuarial recurrence rate of 85.4% versus 65% (10). This increased risk of allograft recurrence in patients with HCC appears to include those whose HBV DNA was not actively replicating pretransplantation. The increased risk of reinfection associated with HCC may be a sequelae of peritransplant chemotherapy, but the possibility of micrometastases with increased extrahepatic viral burden is plausible (10).

CLINICAL-PATHOLOGICAL ASPECTS OF ALLOGRAFT REINFECTION

Allograft reinfection with HBV tends to be an aggressive disease, and the natural history follows that of chronic HBV infection in the nontransplant setting, but over a contracted time period (11). Acute hepatitis with a serum transaminase flare heralds allograft reinfection, and is followed by chronic hepatitis. End-stage cirrhosis can occur early, even a few years after transplantation, and there have been published reports of cirrhosis developing less than a year after transplantation (11,12). A particularly dreaded form of allograft reinfection known as fibrosing cholestatic hepatitis (FCH) is characterized clinically by progressive jaundice and liver failure. The histologic evolution of FCH is that of aggressively progressing fibrosis with scant inflammation, diffuse hepatocyte ballooning and numerous ground glass cells (13,14). Aside from sporadic case reports of remission with nucleoside therapy (15,16), FCH is generally regarded as a fatal condition, with death typically occurring a few months after the initial diagnosis. FCH is generally accepted to result from direct cytopathogenicity of the virus due to enhanced viral transcription in the setting of immunosuppression (17,18). FCH is not unique to liver transplantation. It has been reported to result from severe reactivation of latent HBV infection in renal (19) and bone marrow (20) transplant recipients and as a consequence of AIDS (21). There is no widely accepted efficacious medical treatment for FCH although the author’s centre has experienced success with lamivudine (unpublished observation). In general, without

| Subgroup                  | % allograft reinfection | % survival |  |
|---------------------------|-------------------------|------------|
| Cirrhosis (HBV DNA+)      | 83±6.6                  | NA         |  |
| Cirrhosis (HBV DNA-)      | 58±7.7                  | NA         |  |
| All HBV cirrhosis         | 67±4.4                  | 44         |  |
| Delta coinfection         | 32±5 (cirrhosis)        | 40±16 (fulminant) | NA |
| Fulminant HBV             | 17±7                    | NA         |  |
| Allograft reinfection     | –                       | 54         |  |
| No allograft reinfection  | –                       | 83         |  |
| Overall                   | 50±3                    | 63±3       |  |

Data from reference 7. HBV Hepatitis B virus; NA Not available
aggressive viral prophylaxis, retransplantation for allograft reinfection is futile because long term survival is poor, with the second allograft inevitably developing reinfection (22).

IMMUNOPROPHYLAXIS WITH HEPATITIS B HYPERIMMUNOGLOBULIN

Clearly the poor outcome of patients who received transplants for HBV is secondary to allograft reinfection. The aim of passive immunization of allograft recipients with hyperimmunoglobulin against hepatitis B surface antigen (HBsAg) is to protect the transplanted liver in a manner similar to that of immunity conferred by vaccination. Over the past decade immunoprophylaxis has been attempted in various dosing regimens and for varying durations (Table 2).

In the late 1980s and early 1990s small series from centres in Hannover (23) and Berlin (24) appeared to demonstrate that the long term administration of hepatitis B immunoglobulin was efficacious in preventing allograft reinfection. In a large study from Paris with 110 patients, Samuel et al (25) demonstrated that cirrhotic patients whose HBV DNA was not actively replicating pretransplantation (n=24) had a significantly lower two-year actuarial risk of recurrence of 29%, versus 96% in those whose HBV DNA was actively replicating (n=16). Overall, the hepatitis B cirrhotic group, as a whole, had an actuarial two-year risk of 59% while those who received transplants with coinfecting delta agent (and cirrhosis) had a much lower risk: only 13% (n=49). Those who received transplants for fulminant hepatitis B (n=17) had no apparent risk (0%) of reinfection. The monthly target anti-HBsAg titre in this study was 100 IU/L. A group from Berlin (26), also aiming for 100 IU/L, subsequently reported similar findings: 69% two-year allograft recurrence in those with viremia pretransplantation (n=16), compared with 28% in those without detectable serum HBV DNA pretransplantation (n=29). From these studies it appears that when aiming for a target titre of 100 IU/L, beneficial immunoprophylaxis is largely limited to those whose HBV DNA was not actively replicating at transplantation. The collective European experience has convincingly demonstrated that although short term prophylaxis (less than six months) is of little benefit (7), long term administration appears to reduce the risk of allograft recurrence.

In the past few years several American centres have reported their experience using much higher doses of intravenous hepatitis B hyperimmunoglobulin (HBIG) than the Europeans. Terrault et al (27) at the University of California, San Francisco (UCSF) administered 10,000 U (45 mL) intravenously during the anhepatic phase of surgery, followed by 10,000 U intravenously for the next six days and then monthly. Their recently published report (27) indicates

<table>
<thead>
<tr>
<th>Centre location</th>
<th>n</th>
<th>Serum target titre (IU/L)</th>
<th>Overall % reinfection</th>
<th>Dose</th>
<th>Comment*</th>
</tr>
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<tbody>
<tr>
<td>Paris (25)</td>
<td>110</td>
<td>100</td>
<td>29 (two-year actuarial)</td>
<td>Typical dose: 10,000 U IV anhepatic phase, 10,000 U daily next 6 postoperative days followed by 10,000 U whenever serum titre &gt;100 IU/L</td>
<td>HBV DNA+: 29% reinfection; HBV DNA–: 96% reinfection</td>
</tr>
<tr>
<td>Berlin (26)</td>
<td>45</td>
<td>100</td>
<td>42 (two-year)</td>
<td>10,000 U anhepatic phase, 1000-2000 U first postoperative week then doses as needed to maintain serum titre &gt;100 IU/L</td>
<td>HBV DNA+: 69% reinfection; HBV DNA–: 28%</td>
</tr>
<tr>
<td>San Francisco (27)</td>
<td>24</td>
<td>&gt;500</td>
<td>19 (two-year)</td>
<td>10,000 U anhepatic phase, 10,000 U daily next 6 postoperative days then 10,000 U monthly</td>
<td></td>
</tr>
<tr>
<td>Virginia (28)</td>
<td>27</td>
<td>&gt;500: day 0-7; &gt;250: day 8-90; &gt;100: after day 90</td>
<td>7 (mean follow-up 20 months, range 2-55)</td>
<td>Typical dose: 10,000 U anhepatic phase, 10,000 U daily next 6 postoperative days, 10,000 U weekly for initial 4 weeks then 10,000 U every 2 weeks subsequent 8 weeks followed by 10,000 U monthly</td>
<td>63% of patients HBeAg seropositive</td>
</tr>
<tr>
<td>Stanford (30)</td>
<td>17</td>
<td>100</td>
<td>0 (mean follow-up 11 months)</td>
<td>10,000 U anhepatic phase, 10,000 U daily next 6 postoperative days then 10,000 U monthly</td>
<td>53% of patients HBeAg seropositive</td>
</tr>
<tr>
<td>Jerusalem (31)</td>
<td>11</td>
<td>400</td>
<td>9 (1/11 patients) mean follow-up 21.5 months, range 8-42)</td>
<td>10,000 U anhepatic phase, 10,000 U daily next 6 postoperative days then 10,000 U monthly</td>
<td>82% of patients HBV DNA negative</td>
</tr>
<tr>
<td>Nice (32)</td>
<td>112</td>
<td>500</td>
<td>7.59 (five-year actuarial)</td>
<td>10,000 U anhepatic phase, 10,000 U daily next 6 postoperative days, 10,000 U 14.21 and 30 days post-transplant then monthly</td>
<td>All patients HBV DNA, HBeAg negative</td>
</tr>
<tr>
<td>Seoul (33)</td>
<td>13</td>
<td>100</td>
<td>8 (1/13 patients) (5 patients died &lt;60 days, 8 survivors 104-1095 days)</td>
<td>40,000 U anhepatic phase, 40,000 U daily next 6 postoperative days then 40,000 U monthly except for HBeAg-negative patients who received 10,000 U</td>
<td>HBeAg–: 15% (2/13)</td>
</tr>
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*Hepatitis B virus (HBV) DNA/hepatitis B early antigen (HBeAg) status refers to pretransplantation status. IV Intravenous
a two-year recurrence rate of 19% (n=24) in a predominantly nonreplicating or delta coinfe cted group, compared with 76% in a cohort not receiving HBIG (n=28). Trough anti-HBs titres were not prospectively used to adjust HBIG dosing but when analyzed retrospectively from stored samples, averaged 1275 IU/L. Those who experienced reinfec tion had trough titres less than 490 IU/L. Although allograft reinfection was defined as HBsAg seropositivity, 67% of pa tients followed for longer than one year were positive for se rum HBV DNA by polymerase chain reaction (PCR) even though liver biopsy immunoperoxidase stains were negative for both HBV core and surface antigen. McGory et al (28) at the University of Virginia used a similar basic dosing sched ule as investigators at UCSF but gave extra doses of HBIG to maintain anti-HBs trough levels within a target range: more than 500 IU/L days 0 to 7; more than 250 IU/L days 8 to 90; and more than 100 IU/L thereafter. The majority of patients received HBIG weekly for four weeks, followed by HBIG every other week for eight weeks, before continuing with a monthly regimen. Ninety-three per cent of these patients (n=27) remained seronegative for HBsAg and HBV DNA (by hybridization assay) at follow-up ranging from two to 55 months. Seventy-six per cent of patients were free from allograft recurrence at 12 months or longer post-transplantation. It is noteworthy that 63% of the patients were HBeAg seropositive pretransplantation. Although the HBeAg group required more frequent doses of HBIG to maintain target levels, the vast majority were not reinfected. The same investigators also reported successful retransplantation for allograft reinfection with their protocol (29). So and colleagues (30) at Stanford University recently presented their experience employing the same HBIG protocol as that used by UCSF (27), with similarly excellent results.

Elsewhere around the world, results of high dose HBIG prophylaxis protocols have been similar to or better than the American experience. Ilan et al (31) from Israel, aiming for trough levels of 400 IU/L, reported only one recurrence in 11 patients. Only two patients in this cohort were serum HBV DNA positive pretransplantation. At the recent XVI International Congress meeting held in Barcelona, a group from Nice reported an incredible five-year actuarial reinfection rate of only 7.59% in 112 patients, none of whom was replicating pretransplantation (32). A somewhat unusual characteristic of this patient cohort was that 72% (77 of 107) of the cirrhotic patients were delta agent seropositive. Lastly, looking at viremic patients, Lee and co-workers (33) from Seoul, Korea reported administering heroic doses of HBIG – 40,000 IU intravenously – for the first seven days, followed by monthly dosing of 40,000 IU to cirrhotics whose HBV DNA was actively replicating pretransplantation (11 of 13 patients were serum HBV DNA positive). They report only one patient with allograft recurrence, and none of their eight patients surviving greater than 60 days has been reinfected. The target titre of HBIG with this aggressive regimen was only 100 IU/L, which confirms that patients whose HBV DNA is replicating pretransplantation can be successfully prophylaxed but will require substantially more HBIG than patients whose HBV DNA is nonreplicating/replicating at low level.

There are a number of concerns regarding the use of high dose HBIG for immunoprophylaxis. Despite its intravenous administration, the HBIG preparation available in Canada and used at American centres is licensed only for intramuscular use. A group from McGill University (34) has reported adequate titres of HBIG intramuscularly; however, large volume intramuscular injections may be problematic in the immediate postoperative period when transient thrombocytopenia and residual coagulopathy increase the risk of intramuscular hemorrhage. Patients may later complain of pain associated with the monthly intramuscular injections.

HBIG also contains antibody products, and intravenous infusion could result in immune-complex mediated symptoms. Although anaphylaxis has not been reported, myalgia and back pain may occur, which necessitates a slow infusion, occasionally with a narcotic premedication.

Furthermore, there is potential mercury toxicity from large frequent doses of HBIG regardless of the route of administration because HBIG preparations contain thimerosal as a preservative. American researchers routinely monitor serum mercury levels, and although mercury toxicity does not appear to be a problem, there has been one report of suspected neurological mercury toxicity after transplantation (35). Fortunately, this case was reversible after chelation therapy.

Another potential problem with HBIG use is the continued effectiveness of the product – in the nontransplantation setting, infection with HBV envelope-escape mutants have been reported after vaccination with monoclonal vaccines (36-38). Although the development of mutant strains has not yet been considered to be a significant problem in transplantation, HBV surface antigen mutations have also been reported after HBIG administration with allograft reinfection (37,39-41).

The major concern regarding high dose HBIG is cost and availability. Terrault et al (27) from UCSF published their cost per patient: US$53,000 for the first year and US$35,000 for each year thereafter. The cost of HBIG from American suppliers has since increased. The continual availability of HBIG is also a concern because shortages from manufacturers have occurred. That these patients have a residual low level viremia, detectable by PCR if not hybridization assays, without other evidence of allograft reinfection (27), suggests that HBIG, if used as a single agent, may have to be continued indefinitely. A lack of availability of HBIG in the quantities necessary for adequate long term immunoprophylaxis would therefore leave patients at risk of allograft reinfection.

**PRIMARY PROPHYLAXIS WITH ANTIVIRAL AGENTS**

During its replicative life cycle, HBV undergoes a stage of RNA-dependent transcription (reverse transcription) (42) similar to that of the retroviruses (eg, HIV). The antiretroviral agent lamivudine (2'-deoxy-3'-thiacytadine) has recently been demonstrated to be both well tolerated and effective at
suppressing HBV replication in patients with chronic hepatitis (43,44). Given the effectiveness of lamivudine in suppressing HBV replication and its widespread availability in oral formulation, it is tempting to consider HBIG-free prophylaxis employing this agent. Results of a recently published study (45) reported only one case of allograft reinfection in 10 patients surviving the immediate post-transplant period. This suggests that lamivudine monotherapy is the ideal agent for post-transplant prophylaxis, in terms of both effectiveness and economy. This optimism, however, must be tempered by recent reports of the emergence of lamivudine-resistant strains of HBV both in the transplant setting (46-49) and in nontransplanted patients (50). Bain and collaborators (46) at the University of Alberta recently reported that 50% of their long term surviving patients (n=4) developed allograft reinfection with escape mutants more than a year after transplantation (46). The selection of lamivudine-resistant strains with subsequent allograft reinfection appears to be a widespread phenomenon; it has also been independently reported at the University of Miami (47) and in the United Kingdom (48). Lamivudine resistance may develop after prophylactic therapy or during treatment of allograft reinfection. In a recent interim analysis, 20% of patients (n=10) treated for either post-transplant allograft reinfection or de novo infection developed resistant strains (49). In each analyzed case, the site of the mutation was identical to that of lamivudine-resistant HIV strains (51). The mutation has been identified as a point mutation within the YMDD (amino acid sequence ‘tyrosine-methionine-aspartate-aspartate’) motif of the RNA-dependent viral replicase. In each reported instance, the mutation is a point mutation substituting methionine for valine or isoleucine (ie, YVDD, YIDD) (47-50,52). The exact incidence and significance of these YMDD mutations have yet to be defined but should emerge soon. Although allograft loss and worsened patient survival as a result of reinfection with lamivudine-resistant strains have not been reported, it should be noted that the studies to date have involved small numbers of patients with relatively short follow-up.

TREATMENT OF ESTABLISHED ALLOGRAFT REINFECTION

As mentioned previously, allograft reinfection has historically been associated with poor long term patient survival. Before lamivudine was widely available, there was no accepted treatment for this condition, although success was reported with parenteral ganciclovir (15,53), oral ganciclovir (16) and oral famciclovir (54,55). Although encouraging, these reports either involved small numbers of patients or were isolated case reports. The success of these conventional antiviral agents in allograft reinfection is, by no means, unequivocal because countering case reports of treatment failures with ganciclovir (12,56) have also been published, as well as only mixed success with famciclovir (55). Of interest, famciclovir has not been noted to be of any benefit in treating allograft reinfection with lamivudine-resistant strains (46,48). Ganciclovir and famciclovir have not been reported in any prophylaxis transplant study. Lamivudine reportedly is of benefit in the treatment of established allograft reinfection (49,57), although if this antiretroviral agent becomes widely adopted in prophylaxis protocols, the problem of treating allograft recurrence with lamivudine-resistant strains will have to be addressed.

CONCLUSIONS AND FUTURE TRENDS

Clearly transplant hepatology has evolved such that it is now possible for patients with HBV infection to receive transplants. Subgroups of infected patients, eg, those with acute fulminating infection and delta agent coinfection, have an inherently lower risk of allograft reinfection, which is minimized even further with prophylaxis. Immunoprophylaxis with high dose HBIG appears to decrease the risk of reinfection to acceptable levels in patients chronically infected but whose HBV DNA was not actively replicating. If enough HBIG is given, even those with chronic, replicating infection may have an acceptable risk of reinfection. The main obstacles to high dose HBIG prophylaxis are those of continued availability of the product, practicability of administration and health care economics given the cost and long term duration of treatment.

Monotherapy prophylaxis with lamivudine is promising, but the long term outcome has not been determined. The many recent reports of reinfection with lamivudine-resistant strains, however, is disconcerting. Future prophylactic strategies may mirror the treatment of HIV disease with the administration of multiple antiviral agents. A reasonable current approach is to combine lamivudine administration with HBIG. Such an approach, reported favourably by Markowitz et al (58) at the University of California, Los Angeles, would allow the HBV DNA of more patients to become nonreplicating before receiving a transplant and remain so afterwards. Another strategy is to attempt conversion to a nonreplicating state pretransplantation with low dose IFN, as has been attempted at McGill University (34) with HBIG alone or in combination with lamivudine after transplantation.

There is a tremendous pool of potential transplant candidates with HBV in Canada, and the health care costs of any hepatitis B transplantation program will be high. Liver transplantation, however, greatly improves the functional quality of life of recipients (59), and the majority return to work (59,60). Overall costs of giving these patients transplants may therefore be offset because previously debilitated patients are able to return to a level of health such that they can once again contribute to society.

REFERENCES


39. Ghany MG, Ayola B, Villamil FG, et al. HBV reinfection in liver transplant (LT) patients (PTs) who remained HBsAg negative post-LT. Hepatology 1996;24:1165A.


52. Tisdale M, Kemp SD, Parry NR, Larder BA. Rapid in vitro selection of human immunodeficiency virus type I resistant to 3' thiaimidine inhibitors due to a mutation in the YMDD region of reverse transcriptase. Proc Natl Acad Sci USA 1993;90:5653-6.