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Improved Clinical Outcomes With Liver Transplantation for Hepatitis B-Induced Chronic Liver Failure Using Passive Immunization

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Objective

The goals were to summarize the results of liver transplantation for chronic hepatitis B disease (HBV) at the University of Virginia, correlate pretransplant viral markers with posttransplant hepatitis B immunoglobulin (HBIg) requirements, and identify the relation between viral protein in the liver and clinical reinfection.

Summary Background Data

Liver transplantation is an accepted treatment for end-stage liver disease from chronic HBV infection, although lifelong antiviral treatment (with HBIg or antiviral agents) is still necessary. Patients with evidence of active viral replication (detectable serum HBV-DNA or e antigen) at the time of transplant have a higher rate of allograft infection. Whether clinically stable patients receiving HBIg immunoprophylaxis have detectable viral products in their grafts remains unknown.

Methods

Forty-four transplants performed for HBV disease at the University of Virginia since March 1990 were reviewed. Most patients underwent aggressive passive immunoprophylaxis with HBIg to maintain serum HBV surface antibody (HBsAb) levels ≥500 IU/l for the first 6 months after the transplant, and ≥150 IU/l thereafter. Patients had viral markers quantified, underwent pharmacokinetic analysis of HBsAb levels to adjust dosing, and were biopsied routinely every 3 to 6 months and when indicated.

Results

Forty-four transplants were performed in 39 patients. Actual 1-year and 3-year graft survival was 95% and 81%, respectively, and 1-year and 3-year patient survival was 98% and 96%, respectively. After the adoption of indefinite HBIg prophylaxis, nine grafts became infected (all in recipients positive for HBV e antigen). Three occurred within 8 weeks of transplantation and were associated with a short HBsAb half-life and a wild-type virus. Six occurred >8 months after the transplant, and most of these were associated with viral mutation. Quantification of pretransplant markers was an overall poor predictor of HBIg requirements after the transplant. Immunohistochemistry demonstrated transient low-level expression of core protein in the liver in 23% of patients without serum or clinical evidence of recurrent hepatitis.

Conclusions

An excellent outcome is possible after liver transplantation for chronic HBV disease using HBIg dosed by pharmacokinetic parameters. Currently, quantification of pretransplant serum markers of the HBV antigen load does not predict the intensity of posttransplant treatment required for good clinical outcomes. Because HBV is not eradicated from the patient, some form of indefinite antiviral therapy continues to be warranted.

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The early results of liver transplantation for hepatitis B virus (HBV)-induced chronic liver failure were problematic, with rapid HBV allograft infection leading to a 50% mortality rate in the first 3 years after the transplant.[1–4] Recently, passive immunotherapy using hepatitis B immune globulin (HBIg) has reduced morbidity and mortality rates to an acceptable level.[5–10] Several areas of concern remain,

however, including a higher allograft infection rate in patients who have active viral replication at the time of transplantation (detectable HBV-DNA or HBV e antigen [HBeAg])[8]; the real or theoretical risks of long-term HBIg use, including mercury toxicity,[11] hepatitis C virus transmission, and allergic reactions[12]; expense; and the induction of HBV mutants.[13–19] The most common mutation reported to date has been at the "a" locus (amino acid 145) of the gene for the hepatitis B surface protein, which has been described both in immunization failures[20,21] and liver transplant recipients treated with HBIg.[13–17] In addition, it remains unclear whether passive antibody therapy prevents allograft infection or merely controls the activity of infected allografts.

The goals of the current study were to define the achievable outcome of transplantation for chronic HBV using pharmacokinetically based HBIg dosing, to attempt to predict HBIg needs based on quantification of preoperative HBV antigens, and to correlate histologic activity and evidence of graft infection with actual clinical hepatitis recurrence.

METHODS

Patients

All patients transplanted for HBV-induced chronic liver failure between March 1990 and March 1997 were studied. Initial immunosuppression with cyclosporine A, azathioprine, and prednisone was used in all cases. Passive immunosup/pression with intravenous polyclonal HBIg (North American Biologicals, Boca Raton, FL) was administered under informed consent and protocol approved by the University of Virginia Human Investigation Committee, as previously described.[10] Dosing of HBIg changed with accumulated experience. All patients received 10,000 IU during the anhepatic phase of transplantation. Patients 1 to 10 received an additional 10,000 IU daily for the next 6 days, then were redosed when actual or pharmacokinetically projected serum anti-HBs titers dropped to <500 IU/l. Four of the first 5 patients had immunoprophylaxis stopped after 6 months. Patients 11 to 27 received 10,000 IU of HBIg on postoperative days 1 and 2, then as needed to maintain anti-HBs levels >500 IU/l. If troughs were <500 IU/l 48 hours after transplant, the HBIg dose was changed to 5000 IU every 6 hours for 3 to 4 days, and pharmacokinetics were reassessed. For transplants 28 to 44, patients who were HBeAg+ before the transplant received an additional 10,000 IU of HBIg immediately after the transplant and 5000 IU every 6 hours for 2 days; HBeAg− patients were dosed on the same schedule as patients 11 to 27. After hospital discharge, all patients were redosed with HBIg to maintain serum anti-HBs levels >500 IU/l for the first 6 months, >250 IU/l for months 6 to 12, and >100 to 150 IU/l after 1 year. Patients were biopsied every 3 to 6 months and as indicated by altered liver function. Definitive allograft infection was diagnosed by the presence of detectable serum HBV-DNA or HBV surface antigen (HBsAg), and HBIg therapy was stopped. Most of these patients were subsequently treated with lamivudine.

For outcome comparisons, patients undergoing 255 transplants for diagnoses other than HBV disease during the same time period and with follow-up of ≥1 year were studied.

HBV Marker Assays

Qualitative HBsAg and HBeAg were measured using the commercial enzyme immunoassays AUSAB and HB-E(rDNA) (Abbott Laboratories, Diagnostics Division, Abbott Park, IL). Quantitative serum anti-HBs was assayed using the commercially available AUSZYME MONOCLONAL in conjunction with AUSAB (Abbott). Quantitative HBsAg was performed using AUSRIA II-I125/AUSAB (Abbott) on serial dilutions of serum. Quantitative HBeAg was assayed with AxSYM HBE 2.0 Quantitative, an automated microparticle enzyme immunoassay (Abbott). Serum HBV-DNA was quantified by Southern blot (Specialty Labs, Santa Monica, CA).

Histology

Biopsies were fixed in 10% formalin, processed, embedded in paraffin, and stained with hematoxylin and eosin in a standard fashion. Immunohistochemical studies were performed on the paraffin sections by an automated immunostainer (Ventana ES, Ventana Medical Systems, Tucson, AZ) using a standard avidin–biotin complex method with diaminobenzidine as the chromagen. All biopsies were stained with an anti-HBcAg monoclonal antibody (dilution 1:800; Dako, Carpenteria, CA) and a polyclonal anti-HBsAg preparation (dilution 1:40; Biogenex, San Ramon, CA). Primary antibodies were eliminated from duplicate slides as negative controls; appropriate positive controls known to contain the antigen in question were processed simultaneously.

All biopsies were examined by a senior transplant pathologist (MJG) without knowledge of the patient's clinical status. "Hepatitis" was defined as the combined presence of portal or periportal or intralobular chronic or mixed inflammation with evidence of hepatocyte necrosis. The presence of portal or sinusoidal inflammation alone, without evidence of hepatocyte dropout, was considered insufficient for the histologic diagnosis of hepatitis.

Statistics

Continuous variables are expressed as mean ± SEM and were compared using Student's t test assuming equal or unequal variances (depending on the results of an F-test). Nonparametric variables were compared by chi square analysis or Fisher's exact test. The relations between serum

Table 1. COMPARISON BETWEEN PATIENTS TRANSPLANTED FOR CHRONIC HBV DISEASE AND NON-HBV DISEASE

Patient Group	Crude Survival (%)	Actual 3-yr Graft Survival (%)	Actual 3-yr Patient Survival (%)	% Treated for Rejection	% Treated with OKT3	Complications (±SEM)/Patient*
Hepatitis B	87	81	96	67	3	0.8 ± 0.1
Non-hepatitis B	67†	63‡	70§	63	15‖	1.4 ± 0.1†

* Excluding rejection and death.
† $p = 0.01$.
‡ $p = 0.06$.
§ $p = 0.003$.
‖ $p = 0.04$.

markers were compared by regression analysis, all with the aid of computer software.

RESULTS

Patient Outcome

Forty-four transplants in 39 patients were performed during the study period. All patients were HBsAg+ at initial transplant. Seventeen patients (39%) had quantifiable HBV-DNA in the serum; 26 patients (59%) were HBeAg+. The Mean age was 49.2 years (range, 30 to 68 years). Thirty-four of the 39 patients (87%) were alive as of this writing after a mean follow-up of 42 ± 3 months (range, 7 to 90 months). Of the five retransplants, three occurred after allograft infection after HBIg therapy was stopped 6 months after the transplant, one was for allograft infection despite HBIg therapy, and the last was for late hepatic artery thrombosis and hepatitis C infection, without evidence of active HBV infection. All 4 patients who received HBIg for only 6 months had clinical allograft infection; it occurred a mean of 3.5 ± 1.1 months after stopping therapy. The one patient who did not require retransplantation was alive 6 years off therapy.

Of the 40 grafts placed under "indefinite" HBIg immunoprophylaxis, 9 (in 8 patients) had clinical reinfection. Three allograft infections occurred early (2, 6, and 8 weeks after the transplant); they were associated with a persistently short HBsAb half-life and a wild-type virus (2 patients assayed). One patient survives on lamivudine, one patient died from congestive heart failure, and one patient was retransplanted, became reinfected, and subsequently died >3 years later from a cerebrovascular accident. Six late allograft infections occurred 8 to 36 months after the transplant (mean, 19 ± 4.4 months); of the four viral strains sequenced, three demonstrated viral mutation at the "a" determinant of the surface protein gene, as previously described.[17] Five of these patients survive on lamivudine with stable graft function; the sixth was the previously noted patient who died of a stroke. The other three deaths in the series were from myocardial infarction, hepatitis C-induced liver failure, and multisystem organ failure after a multidrug-resistant mycobacterial infection.

Patients undergoing transplantation for chronic HBV disease had outcomes as good as or better than those transplanted contemporaneously for other diagnoses (Table 1). One-year actual graft and patient survival rates were also better in the HBV group ($p < 0.05$). There were no significant differences between the groups for operative variables, including transfusion requirements (HBV, 7.4 ± 0.7 units/transplant; non-HBV, 10.7 ± 0.9 units/transplant), or the incidence of treatment for cytomegaloviral disease (HBV, 14%; non-HBV, 21%). Complications were defined as a deviation from the routine postoperative care requiring rehospitalization or an invasive procedure and included reoperations, infections (including treatment for cytomegalovirus), hepatic artery thrombosis, need for retransplantation, biliary tract complications, renal failure, posttransplant lymphoproliferative disease, and skin cancer; complications excluded death and rejection, which were analyzed separately. There has been one case of posttransplant lymphoproliferative disease in the HBV group to date, and other complications have also occurred at frequencies similar to the non-HBV patients. A male predominance in the HBV group (95% *vs.* 60% in the non-HBV group, $p = 0.0001$) was noted.

Prediction of HBIg Requirements

Attempts were made to correlate pretransplant HBV markers with the risk of allograft infection or HBIg requirements to achieve the targeted levels of HBsAb (Table 2). Pretransplant HBeAg+ status was associated with allograft infection: after the initiation of aggressive HBIg immunoprophylaxis, 9 of 26 HBeAg+ transplants had clinical reinfection *versus* 0 of 14 HBeAg− patients. The presence of pretransplant HBV-DNA was not associated with reinfection. The presence of HBeAg before the transplant also predicted a shorter HBsAb half-life at day 3 after the transplant, as did the presence of serum HBV-DNA. Beyond these relations, the actual quantified levels of pretransplant HBsAg, HBeAg, and HBV-DNA were poor predictors of

Table 2. PRETRANSPLANT MARKERS OF VIRAL ACTIVITY, OUTCOME, AND ANTI-HBS HALF-LIFE

Outcome Measure	HBsAg+	HBeAg+	HBeAg(−)	HBV-DNA+	HBV-DNA(−)
Graft infection	9/40 = 23%	9/26 = 35%*	0/14 = 0%	5/17 = 29%	4/23 = 17%
Anti-HBs half-life (hr)	19.9 ± 3.1	10.5 ± 3.0*	29.7 ± 6.9	14.7 ± 3.5†	26.2 ± 5.2
R^2, antigen level *vs.* anti-HBs half-life	0.14	0.17		0.05	

* $p \leq 0.02$ *vs.* HBeAg(−).
† $p = 0.04$ *vs.* HBV-DNA(−).

HBsAb half-life (and HBIg use). There was no correlation between pretransplant levels of HBsAg, HBeAg, and HBV-DNA.

Pathology

Three hundred ninety-seven biopsies were performed in 39 patients (3.1 biopsies/year of patient follow-up). Results are shown in Table 3. All nine patients with clinical allograft infection had positive liver immunohistochemistry for core protein. The finding of core protein in the liver and detection of HBsAg in the serum (clinical recurrence) always occurred within 1 month of each other. The 3 patients who had graft infection within 6 months of the transplant had core and surface protein detectable in all biopsies after transplantation. Four patients with late graft infection had persistently negative immunohistochemistry up to the time of recurrence. Two had core protein on biopsy 6 and 9 months after the transplant, followed by a series of immunohistochemically negative biopsies, followed by graft infection and the reappearance of detectable core and surface protein in the liver. Surface protein was detected in five of the nine cases of graft infection. Three of the nine patients had evidence of hepatitis on hematoxylin and eosin stain when core protein was first recognized, four of the nine subsequently developed hepatitis, and two of the nine still have no evidence of hepatitis (at 6 and 18 months of follow-up).

Seven patients without clinical recurrence developed immunohistochemically detectable core protein in the liver that became undetectable on subsequent biopsies (Fig. 1). This finding is at a low level (typically ≤1% of hepatocytes) but is reproducible on repeated staining; is not associated with simultaneous clinical disease, elevations in liver function tests, or pathologic evidence of hepatitis on hematoxylin and eosin staining; and first occurs a mean of 7 ± 1.4 months (range, 3 to 15 months) after the transplant. One patient was core-positive on one biopsy, negative on a second, positive on a third, and subsequently negative on all follow-up biopsies. Two of these seven patients had similar low-level expression of surface protein in the liver that has also cleared on subsequent biopsies.

Six of nine patients with graft infection had genotyping of the "a" locus of the S gene, as previously described.[17] Both patients tested with early graft infection (1 and 2 months after the transplant) had wild-type virus; 3 of the 4 patients tested with late reinfection (8 to 18 months after the transplant) had the "a" locus mutation as described for escape from HBV immunization.[20,21] None of the patients with grafts infected with the mutant virus had immunohistochemically detectable surface protein on biopsy.

DISCUSSION

Liver transplantation for chronic HBV disease has become an accepted practice, largely because of the use of passive HBIg immunoprophylaxis. This study was intended to define the outcomes obtainable by a program dedicated to the care of these patients, to develop a method to predict the intensity of posttransplant HBIg therapy, and to begin to

Table 3. HISTOPATHOLOGY

Clinical Status	Total Transplants	Core(+) by IH	Surface(+) by IH	Hepatitis by H&E
No graft infection	31	7 (all now negative)	2 (both now negative)	3‡
Graft infection	9	9*	5†	7

IH = immunohistochemistry; H&E = hematoxylin and eosin.
* Two had been transiently positive 16 and 30 months prior to clinical recurrence and are again positive.
† All three grafts with documented "a" locus mutant viruses are surface protein negative.
‡ All with documented hepatitis C infection.

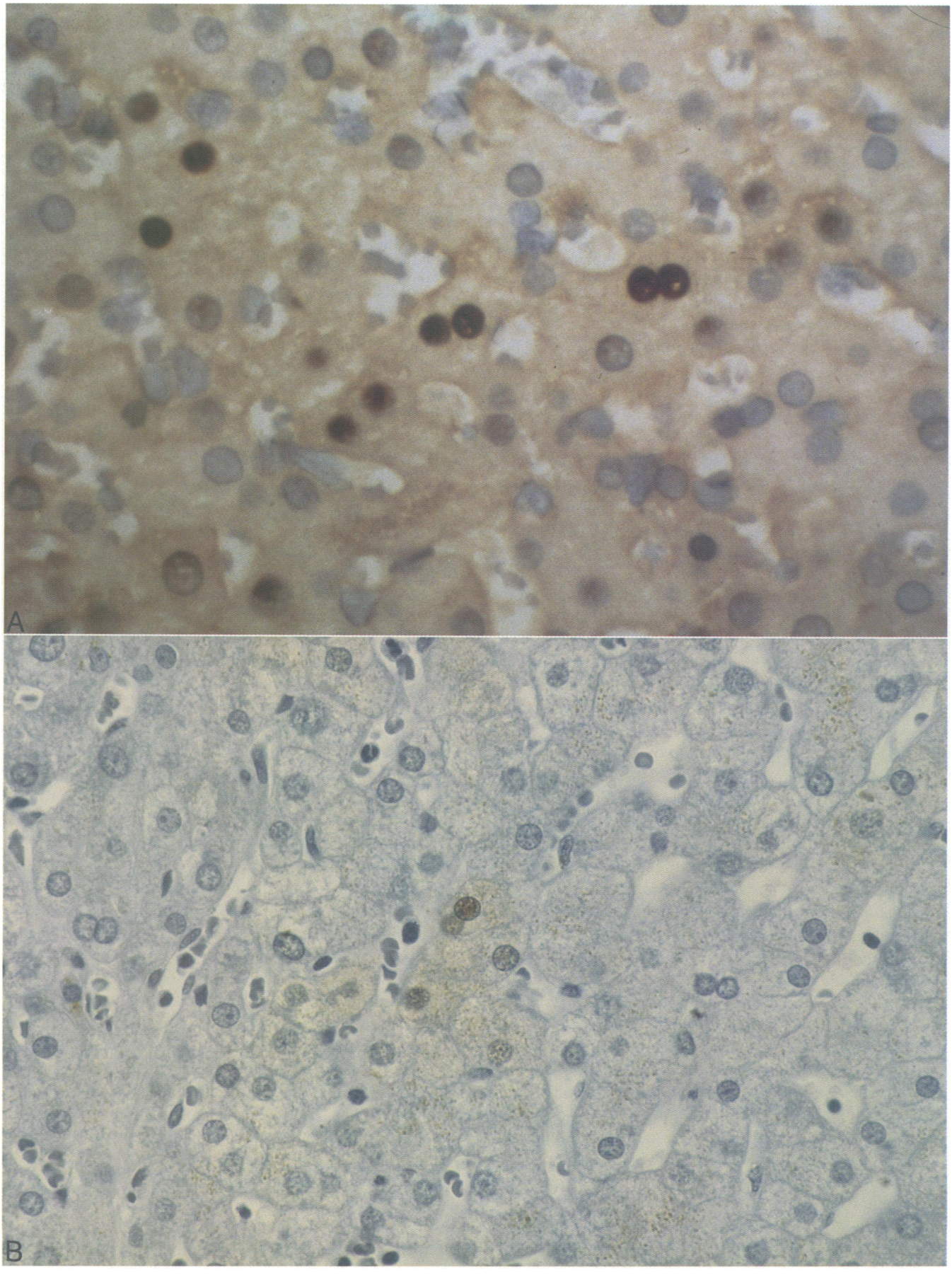

Figure 1. Immunohistochemical staining for HBV core protein in (A) a patient with clinical recurrence (100×) and (B) a patient without clinical reinfection but transiently detectable protein (40×). Note the differences in frequency of stained nuclei between the two specimens.

address the mechanism of HBIg-mediated prevention of allograft infection.

The outcomes in terms of graft and patient survival were surprisingly good, particularly when compared with the concurrent group of patients transplanted at the same institution for other diagnoses. Two explanations for these differences are immediately apparent. First, patients in the HBV group may have been relatively healthier than those transplanted for other diagnoses, although several were ICU-bound before transplant. Second, and probably more importantly, was a possible Hawthorne effect, where inclusion in the study group itself improved outcome. Patients transplanted for HBV were followed by a dedicated nurse coordinator, were seen more often (*e.g.*, during HBIg infusions), and underwent more frequent biopsies because of the study protocol. Third, many patients originated from outside our normal referral base and may have, therefore, gone through some ill-defined screening process. Finally, the availability of lamivudine to treat patients with graft infection has undoubtedly prolonged graft and patient survival. Although six patients with recurrence have maintained stable function on lamivudine, as described by other groups,[22,23] the long-term consequences of its use are unknown, and the induction of resistant strains, particularly at the YMDD locus,[18,19] may limit the usefulness of this therapy.

The greatest disadvantages to our current treatment protocol remain patient inconvenience and the significant but necessary investment in institutional time and resources to achieve these results. Although most patients now can receive HBIg locally, the product has uneven availability and produces enough symptoms acutely that many patients still chose to travel several hours every 6 to 8 weeks to receive their doses at our institution. In addition, concerns regarding chronic sequelae unique to this intensive application of the current formulation of HBIg are real (*e.g.*, viral transmission and mercury toxicity), although these side effects appear to be uncommon and mild.[12]

We had hoped that pretransplant quantification of serum viral antigens would accurately predict the HBIg dosing schedule and thus eliminate or reduce the need for HBsAb monitoring. Although qualitatively HBeAg+ patients were more likely to suffer allograft infection and the presence of either serum HBeAg or HBV-DNA predicted a shorter HBsAb half-life, the overall correlation was poor between pretransplant HBsAg, HBeAg, and HBV-DNA levels and anti-HBsAg half-life (and HBIg dosing). Thus, we continue to monitor pharmacokinetic data intensively to determine immunoglobulin dosing based on projected antibody levels. It is possible, however, that in the future low-risk patients, particularly those who are HBeAg− before the transplant, may be found to require lower levels of HBsAb throughout their course and thus need less frequent HBIg dosing to prevent graft infection.

The antiviral mechanism of clinical HBIg immunoprophylaxis is poorly defined. It is likely that significant extrahepatic reservoirs of virus exist, because allograft infection has been noted after the cessation of long-term HBIg therapy. Whether the immunoglobulin prevents infection of a transplanted liver or controls a low-level reinfection is unknown; the immunohistochemical data presented favors the latter. The identification of hepatocytes staining for core protein at such a low frequency ($\leq 1\%$) may be an artifact, although control specimens were consistently negative and restaining of the same specimen gave similar results. Furthermore, staining for core protein even in explanted livers can be relatively rare.[24] We find it more plausible that the passive immunity afforded by HBIg prevents some local or systemic activity of the virus that is important in the progression of a low-grade infection to fibrosis, cirrhosis, and liver failure.

The mechanisms that lead to allograft infection are still being determined. Our data and those of others seem to indicate, however, that early infection is associated with wild-type virus and probably indicates an initial inadequate binding of viral antigens in patients with active replication (HBeAg and HBV-DNA+) and large antigenic loads. However, viral mutation appears to be associated with delayed infections, implying an escape from HBIg passive immunity based on alterations in the relevant surface protein epitope or epitopes. This would explain why patients with grafts infected with mutant virus had core protein but not surface protein detected on immunohistochemical staining of biopsy specimens. The single patient in our series with a late graft infection known to be caused by wild-type virus had trough HBsAb levels lower than dictated by protocol because of an acute shortage of HBIg; this may have been caused by a mechanism similar to that proposed for early reinfections. These data suggest that long-term maintenance of these patients may require a new approach that minimizes the likelihood of surface protein mutation, perhaps using antiviral agents in combination with HBIg or on an alternating schedule. Unfortunately, viral mutation to lamivudine in the setting of liver transplantation is already well described.[18,19]

The ultimate goal of our program is to identify and test new approaches (or combinations of therapies) designed to decrease the complexity, cost, and sequelae of transplantation for HBV-induced liver failure while maintaining the excellent results described for passive HBIg therapy. As currently practiced, our protocol is too complicated to use in centers that transplant HBV patients infrequently and lack the interest, resources, and expertise to treat these challenging patients. Currently, there are several avenues that may allow some simplification in the management of HBV-infected patients. Lamivudine and other antiviral agents will continue to be useful, although their exact role is being defined. They are probably inadequate by themselves to prevent allograft infection indefinitely, and will most likely be used in conjunction with immunoglobulin; whether the two should be used simultaneously, sequentially, or on an alternating basis remains to be determined. An improved

formulation of HBIg without a mercury-based preservative is under investigation. Ultimately, definition of the host response defect that allows the progression of hepatitis and damage to the liver is critical so that correction of this deficit, either before or after the onset of end-stage liver disease (and transplantation), can be used to control viral replication free of any immunotherapy.

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Discussion

DR. RALPH R. BOLLINGER (Durham, North Carolina): Thank you, Dr. Laws, Dr. Copeland, Distinguished Members, and Guests of the Southern Surgical Association.

To understand better the impressive data just presented by Dr. Pruett, Dr. Sawyer, and colleagues, we must put this report into historical perspective. In March 1990, liver transplantation for hepatitis B was frankly a disaster. Recurrent hepatitis B disease, not just infection of the liver, was the rule after transplantation; and multiple, often unsuccessful retransplants, were routine. Compare that reality to the superb results obtained by the University of Virginia group: 81% actual graft survival at 3 years and 96% actual patient survival at 3 years.

With this success though has come some unanticipated problems. Hepatitis B immunoglobulin, HBIG, cannot be stopped. The proper dose is unknown. It is an expensive, inconvenient, labor intensive therapy with a therapeutic agent that is sometimes in short supply, an agent that sometimes can induce viral resistance.

It works, but I would have to say it's a partial therapy. It's encouraging, but it's incomplete as an answer to hepatitis B-induced liver failure. And it raises several questions, Dr. Pruett. What is HBIG doing? Perhaps, it is working not only on the virus but also on the host as well.

Although your hepatitis B and nonhepatitis B patients had similar rejection rates — 67% and 63%, respectively — there was a large difference between them in terms of the use of OKT-3. We know that soluble immunoglobulin is immunosuppressive in allo and xeno transplantation, especially for complement-dependent mechanisms. Did your HBIG-treated hepatitis patients have less steroid resistant rejection, or did you limit the use of OKT-3 in them to avoid excessive immunosuppression?

Second, the outcomes of your hepatitis B group were so much better than those of your other liver transplant patients that I doubt many fulminant hepatic failure patients were included. What were the UNOS status codes, that is, the level of medical urgency for your patients? And were they comparable for the two groups?

Third, where are the extrahepatic reservoirs of hepatitis B that infect the new livers after sometimes very long periods following transplantation?

Finally, in 1997 with the availability of HBIG and lamivudine therapy, should hepatitis B patients be retransplanted? I am talking about patients who lost their own liver and then lost a transplant from hepatitis B. Now this is a pointed question because you may be selecting drug-resistant strains of hepatitis B in such patients.