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Discussion

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): I congratulate the authors on their excellent presentation and on their outstanding results. This study represents what can be achieved by an accomplished surgical scientist, as discussed by Dr. Barker in his presidential address, i.e., the combination of sound surgical skills with a broad knowledge of basic science, which is in this instance, both transplant biology and infectious disease. Applications of the principles that guided this protocol, i.e., reduction in pretransplant viral load, postoperative immunoprophylaxis, and minimal long-term immunosuppression, have culminated in results heretofore not achievable.

After listening to the presentation and reading the paper, I have several questions and comments.

First of all, how were the injections of the hepatitis B immunoglobulin tolerated? This was 10 mL intramuscularly daily, which sounds awfully painful to me. We were giving this dose of antilymphocyte globulin intramuscularly in the early days of transplantation and found the patients really had a hard time. Can this be given intravenously? If so, what would be the relative titers?

Second, how would you deal with patients who are having fulminant hepatitis or rapid decompensation before the therapy with interferon could be accomplished? In particular, would lamivudine be a preferred drug in such instances, and have you had experience with this? Our experience with interferon-alpha given during the postoperative period in kidney transplants has shown that there is a relatively high loss of kidneys from rejection. In your paper, you did not mention the need for doing this, but I wonder what would be your drug of choice during the postoperative period.

Next, are there patients who would be excluded from your protocol, or would you take all patients who come?

In your paper, you mention that there were four patients with hepatocyte carcinoma and none of these patients have had evidence of recurrence over a long period of time. One of these was a relatively large tumor, as I recall, about 10 cm in size. I wonder if this protocol has any particular value in that subset of patients?

Finally, in this day of managed care, one should be concerned about the cost. I wonder if you would comment on that because you have two relatively high-cost drugs given for relatively long periods of time.

DR. RONALD W. BUSUTTIL (Los Angeles, California): Dr. Tchervenkov, I enjoyed your paper and I want to thank you again for providing me the manuscript in time to review it for this meeting.

I think it is fair to say that transplantation for chronic active hepatitis B has really come full circle. Only 5 or 6 years ago, the results of transplantation were so dismal due to disease recurrence that many programs abandoned transplantation for chronic active hepatitis B. In fact, Medicare and many insurance carriers even today do not cover transplantation for chronic active hepatitis B.

Results for hepatitis B or in patients who have chronic hepatitis B with coinfection with D virus have marginally better results than those seen with the chronic hepatitis B alone. Now with passive immunoprophylaxis using hepatitis B immunoglobulin (HBIG), the results have dramatically improved in the majority of cases.

However, to achieve this state, immunoprophylaxis with HBIG either given intramuscularly or intravenously must be given in high doses and for an indefinite period of time. Anything less results in failure. Nevertheless, there is clearly, as illustrated in this paper, a limitation to immunoprophylaxis alone because it is not effective in those patients who have a high replicative state of the DNA.

In patients who have chronic active hepatitis B who are positive for the E envelope antigen, or who have positive DNA, and are given intense immunosuppression after liver transplantation, with steroids in particular there is an activation of the glucocorticoid receptor on the hepatitis B virus, which results in intense viral replication, resulting in graft loss in close to 50% or more of cases.

Thus, this report I believe is very important because it reports outstanding results in patients who have this high-risk population of positive hepatitis B and still achieve a survival of 93%, which I would submit is probably better than the non-hepatitis B patients that this group and many other groups transplant.

At UCLA, we have used a different strategy in converting patients who are DNA positive before transplantation, and we have used the nucleoside analog lamivudine in this situation. Because of the high failure rate of using HBIG alone or lamivudine as monotherapy, we have used combination therapy of both lamivudine pretransplant to convert the patients and then long-term immunoprophylaxis HBIG post-transplant. We administer lamivudine as soon as the patient is placed on the list, and then once the patient is rendered DNA negative, the patient is ready for transplantation. The protocol for managing these patients with immunoprophylaxis is to give 10,000 units intravenously in the anhepatic phase, then give it every day for the first week postoperatively, then once a month indefinitely.

We have studied 15 patients using this protocol. Five were DNA positive. With a mean lamivudine treatment time of 28 days, all patients became DNA negative. One patient who was hepatitis B envelope antigen positive lost his envelope antigen at 105 days, and another patient lost his surface antigen at 114 days. Fourteen of 15 patients are alive, all with excellent graft function, and none of them have converted to DNA positivity.

In conclusion, I would like to ask the authors these questions. I am surprised that you had such tolerability with interferon. In our patients, when we have tried this, the patients have decompensated rather acutely, and thus we have now gone to a lamivudine strategy. Second, in your patient whom you suggested had liver decompensation due to the anti-inflammatory agent, how do you account for the fact that the DNA, the envelope antigen, and the surface antigen were all positive?

DR. AINSLIE G. R. SHEIL (Sydney, Australia): I too believe that we have just heard a landmark presentation. The worldwide hepatitic epidemic with the dangerous end-results of cirrhosis and hepatocellular cancer has given rise to patients who have not previously been treatable with anything like regular success by liver transplantation.

Although most groups are exploring the relatively new antiviral agents, the Montreal group has followed their recent protocol of reducing antigen load pretransplant, in those with replicating virus, by use of interferon—this proved universally effective with acceptable side effects—followed by lifelong therapy with hepatitis immunoglobulin, also totally successful. Not only did the protocol work, but the reduction in viral load pretransplant apparently allowed much higher levels of antibody to be achieved posttransplant by the use of comparatively low doses of hepatitis immunoglobulin. That 12 of the 13 patients should be alive and well and virus free with normal liver biopsy and function at a mean of close to 3 years post-transplantation is stunning.

Even though the number of patients with hepatitis B cirrhosis is small, it is not possible that this outcome happened by chance. Indeed, it appears that the hepatitis patients are doing even better than the nonhepatitis patients. Although I have not tested the statistics, this must be approaching significance and is an amazing outcome, especially because 4 of the 13 patients had hepatocellular cancer and in 2 of these, the tumors were quite large.

My questions:

First, the two hepatitis B patients who received transplants during the trial period but were excluded—my arithmetic shows that both these patients lost their grafts and required second grafts. I might, for completeness, ask why they were excluded and what happened to them?

Second, are you now using the protocol as a routine for hepatitis patients? Since the trial ceased in August 1996, have more recent patients had the same excellent outcomes?

Third, do the statistics suggest that the treated hepatitis B patients are in fact doing better than the nonhepatitis B patients? If this is the case, are you proposing that the patients are either more effectively immunosuppressed either because of the virus infestation or because of the antiviral treatment or else less immunologically reactive? In either case, how can you reconcile this with the absence of recurrence of the hepatocellular cancer in the four patients, especially the two with the large lesions?

Finally, I am also interested, as was the other discussant, in the question of cost. Of course, whatever the cost, it must be irrelevant compared with the cost of retransplantation or death of these patients.

DR. JEREMIAH G. TURCOTTE (Ann Arbor, Michigan): I, too, would like to congratulate Drs. Tchervenkov and Meakins and the group from McGill for this important contribution. Our program is one of those that abandoned liver transplantation in patients with hepatitis B and have now resumed such transplantations with the addition of HBIG given postoperatively.

We initially tried to use alpha-interferon but abandoned this protocol because many of our patients did not tolerate it. Our current protocol is similar to the one described by Dr. Busuttil. We have entered approximately eight patients in our new program, and there has been no recurrence to date.

A recent analysis from the United Network for Organ Sharing indicates that the so-called odds risk for a liver transplant recipient with hepatitis B dying during the first posttransplant year is approximately 50% higher than the average risk. However, most of the patients in this analysis did not receive any prophylaxis to prevent the recurrence of hepatitis B. The only diagnostic categories in this recent analysis that carry a higher risk for dying during the first year after transplantation are hepatic malignancy and hemochromatosis.

Currently, one of the many policies under consideration by UNOS is to assign a higher priority for receiving a donor liver to patients with a better chance of survival. Thus, the experience we heard today is extremely important not only to the health of the patients but to provide them access to a donor liver. Keep in mind that in the United States, more and more programs, including ours, have an average waiting time of more than 1 year before patients undergo liver tranplantation.

So the questions I have are similar to those already raised; What is the cost? For HBIG prophylaxis, the cost is many thousands of dollars. Secondly, why did you use an intramuscular preparation rather than the intravenous preparation used by most programs in the United States?

DR. GORAN B. KLINTMALM (Dallas, Texas): I have just one question. In this group of 13 patients, were there any neonatally infected patients in the group? Or were these all late, de novo, infections?

DR. JEAN TCHERVENKOV (Closing Discussion): I would like to thank all of you for the kind comments and the very pertinent questions.

To Dr. Alexander, the question of hepatitis B immunoglobulin injection, whether it was well tolerated or not. Either these patients do not want to tell me the truth or they are very stoic, but indeed it was extremely well tolerated. Except for a little bit of pain at the injection site, none of them had any problems tolerating it.

With respect to patients with fulminant hepatitis, for some reason we have not seen any in our program, so my answer to you is purely speculative. What would we do in the fulminant hepatitis patients? Indeed the results by many, especially the European groups, show that in fulminant hepatitis, hepatitis B immunoglobulin alone achieves very good results, with less than 20% recurrence in these patients. Perhaps along with Dr. Busuttil we might consider giving lamivudine in these patients because interferon takes a lot longer to work than is allowed in the framework of transplantation for fulminant hepatitis.

We have used Lamivudine in two patients, in answer to Dr. Alexander's and Dr. Busuttil's question. Our own hepatologists actually, a couple of them, had a hard time believing our results. They were in another institution and were unaware of our experience with interferon.

In two patients, we used Lamivudine instead of interferon. Both were then treated with hepatitis B immunoglobulin posttransplant and both cleared their DNA with Lamivudine quite effectively within about 8 to 10 weeks, and both were on our post-transplant protocol for hepatitis B immunoglobulin without recurrence—illustrating again, I think, what we are proposing here is not the exact medications or pharmaceuticals but really the principle of decreasing hepatitis B virus (HBV) load pretransplant and maintaining immunoprophylaxis post-transplant.

We do take all patients, and try in all patients treatment with interferon. In the four patients with hepatitis B and hepatocellular carcinoma, I do not know whether this protocol is beneficial as well in terms of preventing hepatocellular carcinoma. It can only be speculated. So my answer to that is, I do not know. It would certainly take a lot more patients to really answer that question.

The cost of hepatitis B immunoglobulin is extremely high. However, the protocol that we have designed perhaps can be further manipulated. I must say that if we calculate the amount of immunoglobulin we give in our protocol versus the one that has been described by Dr. Busuttil and the one that is probably used by most centers—and certainly Dr. Pruitt's group in Virginia uses even two to three times more immunoglobulin than what is currently used in the States—our immunoglobulin protocol actually is 30% lower in total amount compared with what is currently used.

Therefore, the cost of immunoglobulin, although very high, can perhaps be further reduced in our own patients if we convert them to a nonreplicating state pretransplant. Perhaps the amount of immunoglobulin we use can be refined in a trial that incorporates more patients. We certainly achieved levels that were higher than 1000 international units per liter, which is comparatively very high compared with 100 units that is currently achieved with the protocols used by most centers. The laboratory does not tell us exactly the levels. So this could be greater than 1000, it could be 10,000, it could be 2000. We do not know. Certainly we can manipulate the immunoglobulin protocol to perhaps achieve 500 to 1000. I do not know whether that would, however, tip the balance toward recurrence. That remains to be seen.

Dr. Busuttil's questions were very pertinent in this day and age. Over the last year or so, Lamivudine has been introduced. I do not know why in some centers interferon was not tolerated well. Perhaps we have been a little more persistent. In fact, in only one patient who required higher than three million units was interferon not tolerated well, and that patient had to be relatively urgently transplanted. Perhaps in retrospect—this was a patient who was transplanted nearly 4 years ago and Lamivudine was not available at that time—in retrospect, what we might propose is decreasing viral loads with Lamivudine on top of interferon in such patients.

Patient 4 in our series did recur transiently. However, he is now very well, and we persisted with the hepatitis B immuno-

globulin. I presume that even though his liver never got infected—hepatitis B, as you know, probably never leaves the body, and just like any of those latent viruses like cytomegalovirus, it has always a chance to recur and be reactivated under immunosuppression.

Dr. Sheil's comments were appreciated. Why did we exclude two patients? Well, one of those patients was treated on Lamivudine by one of the hepatologists at another center and therefore we could not enter in the protocol. This patient did not recur post-transplantation on HBIG. The other patient was an error on diagnosis. The HBV-DNA was reported as negative to us. In fact, the HBV-DNA was highly positive, he had a mutant form. This patient therefore was not entered in our protocol like we intended. He recurred miserably on HBIG 4 months later.

Regarding the comparisons of hepatitis B survival versus nonhepatitis B patients. We have actually looked into that further, and we will report to the American Society of Transplant Surgeons for that hepatitis B versus the nonhepatitis B patients, there was no statistical difference. However, when we looked at the subgroup of hepatitis B and hepatitis C patients, the hepatitis B patients did much better than hepatitis C patients. We have problems with our hepatitis C patients, and perhaps similar protocols could be the devised for that virus as well.

The intramuscular form was used because in Canada, hepatitis B immunoglobulin is regulated by the Canadian Red Cross and that is what is available in Canada. There is a recent report from Berlin that actually compared the intravenous form and the intramuscular form, and the intravenous form did achieve superior levels, but the intramuscular form was much better tolerated. So I suspect that we will continue using the intramuscular form.

In answer to Dr. Klintmalm's question, of the 13 patients, 5 were of Asian origin and 1 was from Syria. We suspect that each of these patients acquired hepatitis B via vertical infection in the neonatal period. Thank you.