

Dr. Jay S. Epstein
Director, Food and Drug Administration
Center for Biologics, Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Attn: Don Jehn, Executive Secretary, BPAC

July 11, 2006

Re: Letter to the FDA regarding Hepatitis B Globulin for liver transplantation recipients.

Patients with end-stage Hepatitis B induced liver disease have been difficult to manage prior to the last 15 years. The clinical results after transplantation without the use of antiviral therapy and hepatitis B immune globulin showed very rapid re-infection of the transplanted liver with a high rate of failure/death within the first 2 years after transplantation. This observation precluded Medicare from approving the indication of Hepatitis B induced liver failure as appropriate for liver transplantation.

However, following the pioneering European experience using anti-HBs immune globulin, protocols were developed in the US, which allowed for liver transplantation without a significant rate of allograft infection. In fact the aggressive use of Hepatitis B immune globulin as a solitary agent essentially reversed the dismal outcomes. Individuals with chronic HBV went from having some of the worst outcomes to those with the very best outcomes. Indeed, with the subsequent development of reverse transcriptase inhibitors (from the HIV therapy initiative), outcomes after liver transplantation remain excellent, but the therapeutic window appears to be much wider. Not surprisingly the use of multiple antiviral agents also reduces the risk of mutation.

However, the lynchpin of antiviral therapy after liver transplantation continues to be hepatitis B immune globulin as recently restated in the Asian-Pacific consensus statement on the management of chronic Hepatitis B (Liver International 2005; 25; 472-489 pg 480). Hepatitis B immune globulin remains as a key therapy in Europe as described by Samuel (Liver Transplantation 2004; 10 supplement 2: S74-85). In the US, the American Association for the Study of Liver Diseases (AASLD) 2005 practice guidelines for individuals as potential liver transplant recipients acknowledges the spectacular improvement in outcomes for patients with HBV induced liver disease (Hepatology 2005; 41(6):1-26) and the essential role of anti-HBs therapy in achieving those outcomes.

The experience noted from both Asia and Europe are consistent with that seen in the US. Transplant results are excellent when combinations of Hepatitis B immune globulin and oral antiviral therapy are used simultaneously. It is well demonstrated in the literature that use of antivirals alone, give suboptimal results with recurrence rates of around 45%. With combination therapy of anti-HB and antivirals, it is possible to reduce recurrence rates to close to 0%. It is also well documented in the literature that the risk of recurrence goes up significantly upon premature termination of anti-HBs, and there are numerous examples of that happening. Unfortunately, the lack of guidelines for proper use of anti-HBs clearly contributes to those failures.

Interestingly, the results after liver transplantation in the United States have been comparable of those around the world, despite differences in HBV genotypes and differences in immunoglobulin products. The preparation techniques and sources of antibodies differ by country and manufacturer. However, the reasonably uniform clinical outcomes attest to the efficacy of the anti-HBs administration as a therapeutic agent. Our institution (University of Virginia) has consistently used the product from NABI pharmaceuticals as the source of anti-HBs activity, when it has been available. In those times of limited availability, we used products from Bayer with apparent equivalent outcomes. We have been very pleased with the clinical outcomes after liver transplantation through all the reiterations of the product. Initially the product was one which was only designed for intramuscular use, which was cautiously given intravenously. The product has changed, but the excellent clinical outcomes after liver transplantation for HBV have remained the same.

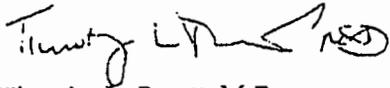
It is a hardship to the patients in the United States, and incomprehensible to the liver transplant community that the FDA has not recognized the utility of anti-HBs for the indication of liver transplantation for HBV induced liver disease. Citizens of this country have capricious insurance coverage, Medicare coverage and access to care predicated upon the lack of official designation of efficacy. In fact even though Medicare approves HBV as an indication for liver transplantation, some recipients risk liver infection from HBV because Medicare may not pay for a drug that is given off-label for a non-FDA approved indication. Fortunately, this sequela has been relatively infrequent, but is one that has been noted. People from around the world have looked to the United States as leaders in the evolution of these forms of therapy and are justifiably mystified as to reasons why our regulatory agencies do not recognize the efficacy of anti-HBs therapy for liver transplantation. Certainly the lack of the guidance of efficacy labeling has resulted in quite variable treatments, some of which may have led to recurrent disease within the allograft, increased cost to the healthcare system or even death due to recurrent liver disease. Considerable confusion and inadequate therapy would be avoided with the development of an appropriate label for guidance in therapy. I enclose 2 of our articles and representative articles from Asia and review articles written by Asian and European authors, stating the

efficacy of hepatitis B immune globulin in the treatment of patients with HBV induced liver disease.

I wholeheartedly support the approval of Nabi-HB for the liver transplant indication. There is absolutely no doubt in anybody's mind that anti-HBs play an essential role in optimizing outcome in hepatitis B positive liver transplant recipients.

If there is any further information I can add or provide to the committee, I would be happy to do so. I apologize for being unable to appear to discuss these issues in person but clinical duties preclude that.

Sincerely,

A handwritten signature in black ink, appearing to read "Timothy L. Pruett" with a stylized flourish at the end.

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