

**Blood Products Advisory Committee**  
**March 18, 2004**  
**Gaithersburg, MD**

**Issue Summary for Topic I:** Clinical Trials for Licensing Hepatitis B Immune Globulin Intravenous (HBIGIV) to Prevent HBV Liver Disease Following Liver Transplantation in HBV+ Recipients

**ISSUE:** HBIGIV currently is used to treat hepatitis B virus (HBV) positive orthotopic liver transplant (OLT) recipients. However, this use is off-label, i.e. not approved by the FDA. The question arises what data (retrospective and prospective) would be needed for approval of HBIGIV preparations for this indication.

**BACKGROUND**

The current standard of care for HBV +ve OLT recipients includes treatment with HBIGIV and antiviral drugs, based on a consensus of treating physicians that the combination is effective in preventing recurrent liver disease due to HBV, and more effective than either product alone. For this reason, manufacturers are seeking approval of HBIGIV preparations for use in OLT. However, the pathway to licensure of HBIGIV as treatment to prevent recurrent HBV liver disease following OLT is complex because current standard of care involves combination treatment. The challenge is to design appropriate clinical trials that will generate data that can be used for licensure.

Initial 5-year survival rate for patients undergoing OLT for HBV was 50% (Terrill et al, Liver Transplantation 2002, 8:S74-81). A European consortium of liver transplant programs reported the largest experience with HBIG (this is an i.m. preparation used i.v. off-label) monotherapy in 1993. This study of 334 liver transplant recipients with HBV found that patients treated with HBIG for at least 6 months post transplantation had a significantly lower rate of recurrent HBV (36%) compared with patients receiving no prophylaxis (75%) (Samuel et al NEJM 1993;329:1842-7). Studies with smaller cohorts yielded similar results. According to Terrault et al recurrence without HBIG prophylaxis was 76% (21/28), and 19% (4/24). Using combination prophylaxis with HBIG and lamivudine the rate of recurrent HBV can be reduced to less than 10% (Lok, Liver Transplantation, 2002;8: S67-73). The problems of previous trials were that they were mainly retrospective in nature and generally had low patient numbers.

**DISCUSSION**

FDA seeks the advice of the committee on three related issues, namely 1) the scientific validity for use of suppression of emergence of detectable HbsAg serologically as a primary clinical end-point in trials of HBIGIV; 2) the overall design of clinical trials needed to establish safety and efficacy of HBIGIV for prevention of reactivation HBV disease in OLT; and 3) the design of PK studies needed to establish potency of HBIGIV as part of the efficacy standard. FDA's current thinking on these issues is as follows:

**Suppression of HBsAg as a Clinical End-point:** FDA agrees with some experts who believe that hepatitis B surface antigen (HbsAg) levels in serum are the most reliable marker for determining whether clinically significant disease has recurred in the grafted liver. As such, FDA proposes to accept suppression of reemergence of HBsAg as a primary clinical end-point in studies of HBIGIV in OLT. FDA seeks concurrence of the Committee with this approach.

**Design of studies:** In order to establish safety and efficacy of HBIGIV for prevention of reactivation HBV disease in OLT, it would be conventional to propose a clinical trial with HBIGIV as a single therapeutic agent compared either with placebo or a known active treatment regimen. However, prospective trials in subjects with HBV would be ethically and practically difficult to perform at this time because of the perceived additional benefit from antiviral drugs. Nevertheless, data from trials that were done in the past using HBIGIV alone may be sufficient to satisfy current criteria for licensure if they show superiority to historical controls that did not use HBIGIV. For prospective trials it may be possible to measure the clinical benefit of HBIGIV by comparing the outcome of regimens that include HBIGIV along with an antiviral drug to historical controls that used the same antiviral regimen alone, provided that the antiviral regimen has been shown to be effective for this indication. FDA seeks the advice of the Committee on these possible approaches.

**Use of PK studies to support efficacy of HBIGIV:** In addition to collecting safety and efficacy data, pharmacokinetic data are required for licensure of immune globulin products. For approval of hyperimmune globulins PK studies can be performed in normal volunteers and/or in the target population. Presence of even low concentration of HbsAg in the circulation may interfere with accurate determination of HBIGIV in the serum of patients following OLT. Therefore it may be necessary to perform these studies in normal volunteers using historical controls for HBIGIV until an approved product becomes available as a comparator. For HBIG (i.m. administration) an approved product is available as a comparator. In the case of HBIGIV in OLT, there are unresolved questions regarding the necessary dosage regimen to insure efficacy. FDA believes that PK data should be collected at time points more than 3 months after transplantation, because prior to that time HBIGIV pharmacokinetic parameters may vary considerably. This is due to higher levels of HbsAg being present in the peri-operative period and immune complex formation between HbsAg and HBIGIV. Also, there is evidence that HBIGIV trough levels need to be maintained at minimal levels in order to avoid HBV recurrence. FDA seeks the advice of the Committee to clarify the scope of PK studies that should be performed to support licensure of HBIGIV for prevention of HBV disease in OLT.

## **QUESTIONS FOR THE COMMITTEE**

1. In clinical trials to show efficacy for HBIGIV treatment, can the end-point "HBsAg seronegativity" be used as the primary clinical end-point for licensure?

2. Is an open label study during the maintenance period (i.e., excluding the peri-transplant period) following OLT sufficient for licensure? The study would compare
  - a. Either HBIGIV with an historic control of no treatment for 12 months
  - b. Or HBIGIV + lamivudine (or other antivirals) for 24 months with an historical control of lamivudine (or other appropriate antiviral) alone
  
3. What PK studies are required for licensure?
  - a. To test the quality of the immune globulin in normal volunteers compared to historical data until an approve comparator HBIG/HBIGIV becomes available.
  - b. To collect data that can be used to establish the frequency and level of dosing by studying the target population, i.e., PK in HBsAg +ve OLT recipients during the maintenance period following transplant.
  - c. To determine whether trough levels are useful in titrating the HBIGIV dose in individual patients