

HEPATITIS B IMMUNE

Use in Liver Transplantation and Preventing Recurrence

BY KYM H. KILBOURNE

AS A HIGHLY SPECIALIZED IMMUNE GLOBULIN THERAPY, hepatitis B immune globulin (HBIG) is something most people have never heard of, let alone have ever needed. It doesn't grab headlines like a new cancer medicine for children and is not as relatable as RhoD immune globulin (covered previously in the *Source*), which has helped millions of expectant mothers. However, for those who know the product, and who were there from its earliest stages of development and witnessed the impact it has had on so many lives, two things are clear: HBIG plays an important role in liver transplantation and is life-saving. The people who work with the therapy are extremely proud to have such an extraordinary effect on people's lives.

Lifesaving immune globulins (Ig) are used to treat various disorders. They contain numerous specific antibodies to neutralize infectious agents that are damaging to the human body. Some immune globulins contain a much higher concentration (titer) of antibodies against a specific virus or other substance. Distinct immune globulins with high titers that "fight" against those viruses or substances include hepatitis B, cytomegalovirus, varizella-zoster, Rhesus, tetanus, rabies and many more.

Most of us remember receiving vaccinations as a child or when our children were immunized against certain viruses. These vaccinations are necessary to boost the human immune system to produce specific antibodies against potential threats from those viruses. When an individual becomes infected with a virus, the immune system responds with the massive production of specific antibodies to fight this infection. When you measure the concentration in the individual's plasma, higher titers will be present. Individuals who have higher titers either as a result of vaccinations or as a natural occurrence are

ideal donors to collect the specific plasma needed to manufacture these high-titer immune globulins (hyper-immunes).



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Hepatitis B immune globulin (HBIG) is one of them and is prepared from donors who have been vaccinated.

Obtaining Plasma

Kirsten Seidel, the medical director for CSL Plasma in Germany, explains that the collection program for plasma used to manufacture HBIG is fairly straightforward. Today, most donors are immunized against hepatitis B as children, and donors are offered a booster to participate in the special plasma collection program, which represents a very small percentage of plasma collections. Typically, donors are between the ages of 18 and 30, and in Germany the collections take place in regular donation centers. In the U.S., collections vary and can take place in a specialty plasma collection center as well.

Seidel explains that HBIG is used in a patient who is exposed to hepatitis B, but has never had an active immunization. The therapy binds the antigen—the hepatitis B antibodies injected or infused bind the virus that is coming into the bloodstream and form an immune complex, which is removed from the body.

GLOBULIN (HBIg)

of Hepatitis B

HBIg is administered to neutralize hepatitis B (HBV) infection in a person who has not received an active immunization or whose immune system is suppressed. If an individual is not immunized against HBV and is not given HBIg after exposure to the virus, he or she can develop hepatitis B, which can severely damage the liver and lead to end stage liver disease years to decades later requiring a liver transplant.

“Prior to the availability of HBIg, if you were accidentally exposed to blood, you were potentially exposed to hepatitis,” said Bob Suarez, former Director of International Sales for Biotest Pharmaceuticals, who worked with the the therapy for 17 years. There was no treatment to prevent the development of the disease, and one could only hope that the amount of antigen transmitted was not high enough to cause it to develop. “Imagine individuals waiting for two to six months to see if they develop hepatitis or not. It was absolutely horrendous,” Suarez added.

Today, in the Western World, most children and individuals in the medical profession or other high-risk professions are immunized against HBV by active vaccines. This practice may be different in developing countries. When HBIg is used prophylactically, it should immediately be administered after a patient who has not been immunized, is exposed to HBV.

The therapy also is used, in combination with other drugs, to prevent hepatitis B recurrence following liver transplantation resulting from residual HBV in the patient's blood. Data have shown that the use of HBIg to prevent HBV recurrence following liver





HBIg is produced through the same highly complex fractionation process used to produce other plasma-derived therapies, although in a much smaller volume.

transplantation has improved patient outcomes and post transplant survival according to Daniel Samphir, the product manager for HBIg for Cangene Corporation, one of several manufacturers of HBIg. In fact, Dr. Thomas Achtstetter, director of Medical Marketing with Biotest Ag in Germany, explains that HBV-liver transplantation could not successfully be performed before the introduction of HBIg for HBV-reinfection prophylaxis. He adds that this is the most important indication for intravenous HBIg and without the therapy, HBV-reinfection of the transplant liver was 100 percent.

Today the “gold-standard” is the combination prophylaxis consisting of iv/sc HBIg and a virostatic drug. (A subcutaneous product entered the market in 2010 in Europe and provides another option that facilitates greater compliance among patients who require

the lifelong treatment.) Both pharmaceuticals complement each other and thus offer the optimal protection from HBV-reinfection of the liver transplant. In fact, today there is no measurable difference between regular liver transplant in terms of survival rates during the first year, according to Dr. Achtstetter. He adds that it is no longer a very risky transplant, and that survival rates while excellent, depend on reinfection prophylaxis.

The typical number of HBV-related liver transplants fluctuates annually; over the past five years 150 to 300 transplant procedures were performed annually in the United States. In Canada, the number of transplants is much smaller. In Germany, there were a total of 1,100 liver transplants last year with about 5 to 8 percent for hepatitis B. Dr. Achtstetter adds that in general, one can say that in the western industrialized countries (Europe, the U.S. and Canada) 3 to 5 percent of the annual liver transplants are due to HBV-induced liver failure (either liver cirrhosis or hepatocellular carcinomas).

Hepatitis B Vaccine

The hepatitis B vaccine became available in the U.S. in 1982, and in 1986 and 1989 two recombinant therapies were introduced. With the availability of the new vaccine, many believed that the need for HBIg would disappear. Suarez explains that the situa-

tion proved to be quite the contrary. With the availability of the vaccine, it was now possible for active immunization against HBV, in addition to the passive immunization provided by HBIg. But many high-risk individuals did not become vaccinated in the early days of its availability and were infected with the virus, thus requiring injections of HBIg. A lack of education and knowledge, coupled with the expense of producing this highly specialized biologic were contributing factors. Further, there were incidences in the U.S. when hospitals failed to immunize their employees due to expense until it became required in 1991 by the Occupational Safety and Health Administration (OSHA) through its Occupational Exposure to Bloodborne Pathogens Standard.

While HBIg use in liver transplantation is the most significant indication today, hepatitis B is endemic in Africa and most Asian countries. However HBIg is not readily accessible there due to inadequate reimbursement.

“I hope someday newborns there will be given HBIg and active immunizations as routine practice” Seidel adds. But neither active nor passive immunization is the standard of care in those countries. ☞

SPECIAL THANKS to *Daniel Samphir, Dr. Kirsten Seidel, Iliana Carlisle, Dr. Thomas Achtstetter and Bob Suarez*

KYM H. KILBOURNE is PPTA’s Director, Public Affairs, North America.



Cartrell, Jr. (pictured left) and his father both donate for the HBIg program. Alicia (right) has donated for the HBIg program at a Cangene center in California for six years.



Brad has donated for two years at the Cangene center in Frederick, Maryland.



Additional Resources

The Changing Epidemiology of Hepatitis B in the United States: Need for Alternative Vaccination Strategies, *Journal of the American Medical Association*, 1990, M. Alter, et al.

Liver transplantation in HBs antigen (HBsAg) carriers: Prevention of hepatitis B virus (HBV) recurrence by passive immunization, *Journal of Hepatology*, 1991, R. Müller, et al.

Liver Transplantation in European Patients with the Hepatitis B Surface Antigen, *New England Journal of Medicine*, 1993, D. Samuel, et al.

Immunomodulating Effects of IVIG: New Insights in Mechanisms of Action, *H. Metselaar, Plasma Protein Forum*, 2011.



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