MEDCO FORUM®

PRESENTING INNOVATIVE PRODUCTS & SERVICES TO HEALTHCARE PROFESSIONALS

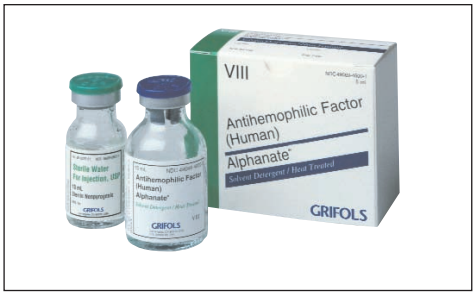
VOLUME 12 NUMBER 60 DECEMBER 2005

REPRINT

TREATMENT OPTIONS OF HEMOPHILIA A PATIENTS WITH INHIBITORS

Over the past four decades there have been significant changes in the treatments offered to patients with hemophilia and the risk of transmission of viral disorders has been nearly eliminated in recent years. Hemophilia affects approximately 400,000 people worldwide. Hemophilia A (Factor VIII deficiency) is more common than hemophilia B (Factor IX deficiency), representing 80 to 85 percent of the total cases. While relatively rare, hemophilia is a complex disorder in terms of diagnosis and management.

The main treatment for hemophilia A involves infusing the missing clotting factor, Factor VIII (FVIII), with the goal of keeping the levels of clotting factors in the blood high enough that bleeding will not occur. Dose and frequency depend on the severity of the bleeding problem. However, in some patients with hemophilia A, therapeutically administered FVIII can stimulate the production of antibodies (inhibitors) which react with FVIII to render it ineffective.(*1*) Development of inhibitory antibodies is the most common and serious complication resulting from treatment of hemophilia and causes major clinical and economic consequences. According to Margaret Heisel Kurth, MD, Co-Director, Hemophilia and Thrombosis Center at University of Minnesota Medical Center (Minneapolis, MN), "Inhibitor formation occurs in approximately 15 to 30 percent of individuals with hemophilia A and approximately 1 to 4 percent in individuals with hemophilia B. Inhibitors tend to occur early, typically affecting some people in the first 50 to 100 days after exposure to transfused factors, but have also been seen later in life when there are changes in the factor product that is administered. There is also now data suggesting that inhibitors may occur as early as the first 20 to 50 exposure days." When inhibitors are present in large amounts, patients may require very high and expensive quantities of transfused clotting factors to stem bleeding and sometimes even that may not be effective. Dr. Heisel Kurth says, "This is a huge problem. These patients are likely to develop long-term complications from bleeding episodes. If you want to change the quality of life for these people, you need to get rid of the inhibitors."



The elements involved in the management of patients with inhibitors consist of the treatment of bleeding episodes and efforts to eliminate inhibitor production through the induction of immune tolerance. To treat a bleeding episode in patients with FVIII inhibitors, an activated prothrombin-complex concentrate can be given in doses once or twice daily depending on the severity of the bleed. In addition, recombinant VIIa is licensed for the treatment of severe bleeding in these patients. An advantage of a recombinant product is the extra margin of protection with respect to transmission of viral infections. Although the growth medium from which recombinant products are manufactured may be a source of contaminant growth as well, evidencing why further purification and virus inactivation procedures are needed. It is, however, extremely expensive and likely to limit its use to situations where other products have failed. Dr. Heisel Kurth says, "Neither one of these treatments work perfectly. Some patients will not respond to either one, some patients will respond but not that well, and some patients will respond pretty well. The bottom line is if inhibitors remain, over the years patients are going to gradually have bleeds that don't respond well and risk long-term damage to their joints or other chronic health issues."

Immune Tolerance Induction (ITI) therapy, which involves the frequent administration of higher doses of factor concentrate to tolerize the immune system so that the antibody is no longer produced, has been generally accepted as the best available treatment and will permit resumption of standard dosing schedules.(*2*) Dr. Heisel Kurth says, "ITI therapy is successful in ~ 80 % of patients with inhibitors, with the average time to tolerance at about 18 months. Some people use a high dose daily factor, some people use a lower dose and give it three times per week. The advantage of using the lower dose is that it's cheaper and less traumatic for the patients. The daily higher dose requires a lot of patient care and it is extremely expensive. There is some evidence that the high dose may get patients tolerized more quickly."

Alphanate® Antihemophilic Factor (Human), manufactured by Grifols Biologicals Inc. (Los Angeles, CA), contains a high purity Factor VIII concentrate and is indicated for the prevention and control of bleeding in patients with hemophilia A or acquired Factor VIII deficiency. While Alphanate is not specifically

licensed for the treatment of inhibitors, it does have a number of features which make it a suitable product for further clinical investigation in ITI. Utilization of FVIII/VWF (von Willebrand Factor) concentrate has been suggested as a means to increase the success rate of ITI, shorten the duration of ITI, and decrease the quantity of factor concentrate used. Recent laboratory studies find that since the large VWF protein is bound to FVIII it occupies some of the same binding sites on FVIII targeted by the FVIII inhibitors.(*3*) In other words the VWF blocks some of the binding sites targeted by the antibody (inhibitor). A retrospective analysis of 8 patients who received FVIII/VWF concentrate as part of an ITI therapy regimen from 1993-2004 demonstrated that FVIII/VWF concentrate was successful in attaining immune tolerance in 5 out of 8 patients with high titer factor VIII inhibitors who had failed immune tolerance utilizing recombinant or monoclonal FVIII, were having a poor response to standard ITI therapy, or who were considered at high risk for failing standard immune tolerance.(*4*) Tolerance was defined as having a Bethesda titer of <1 BU/ml, >66% recovery of factor VIII, and/or a half-life of 6 hours or greater. In addition, one patient achieved partial tolerization and another is in the process of being successfully tolerized. Only one patient failed ITI therapy with FVIII/VWF concentrate. The majority of the patients were given Alphanate. This data further demonstrated that if tolerance can be achieved with FVIII/VWF concentrate, it can result in a major cost savings as the authors of the study found the FVIII/VWF concentrate to be about 50 to 66 percent of the cost of recombinant factor VIII.(*5*)

Jonathan Bernstein, MD, Hemophilia Treatment Center of Las Vegas (Las Vegas, NV), says that most of the Alphanate he uses is in patients who are combo-deficient--both Factor VIII and Von Willebrand Factor. "If you have a combination patient, you can't just treat them with a regular Factor VIII product—you need a von Willebrand Factor-containing product, and Alphanate is one of those products. I do have a large number of patients who are [deficient in] both, in which case this works perfectly for them. In addition, in a situation where you are looking at a person who has either an inhibitor or breaks down factor at a higher rate, the combination of the Factor VIII and von Willebrand factor in Alphanate may decrease turnover of the actual factor. This may save a ton of money in the long run because you may not have to use Factor VII or Factor VIII bypass products, all of which are more expensive than regular product."

Antihemophilic Factor (Human) is a constituent of normal plasma and is required for clotting. The administration of Alphanate temporarily increases the plasma level of the clotting factor, thus minimizing the hazard of hemorrhage.(*6*,*7*) Following the administration of Alphanate during clinical trails, the mean in vivo half life of Factor VIII observed in 12 adult subjects with severe hemophilia A was 17.9 + 9.6 hours. In this same study, the in vivo recovery was 96.7 + 14.5% at 10 minutes post infusion.(*6*) Recovery at 10 minutes post infusion was also determined as 2.4 + 0.4 IU FVIII rise/dL plasma per IU FVIII infused/kg body weight.(*8*)

Alphanate is prepared from pooled human plasma by cryoprecipitation of the Factor VIII, fraction solubilization, and further purification employing heparin-coupled, cross-linked agarose which has an affinity to the heparin binding domain of VWF/FVIII:C complex.(*9*) The product is treated with a mixture of tri (n-butyl) phosphate (TNBP) and polysorbate 80 to reduce the risks of transmission of viral infection. In order to provide an additional safeguard against potential non-lipid enveloped viral contaminants, the product is also subjected to 80º C heat treatment step for 72 hours. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products. Alphanate contains Albumin (Human) as a stabilizer, resulting in a final container concentrate with a specific activity of at least 5 IU FVIII:C/mg total protein. Prior to the addition of the Albumin (Human) stabilizer, the specific activity is significantly higher.

The solvent detergent treatment process has been shown by Horowitz, et al., to provide a high level of virus kill without compromising protein structure and function.(*10*) The susceptibility of human pathogenic viruses such as the human immunodeficiency viruses, hepatitis viruses, as well as marker viruses such as sindbis virus and vesicular stomatitis virus (VSV), to inactivation by organic solvent detergent treatment has been discussed in the literature.(*11*)

All Grifols products are subjected to rigorous donor screening, testing, viral inactivation and purification processes to enhance their quality and safety.

For more information about Alphanate® or Grifols USA, contact 888-GRIFOLS (888-474-3657), send a fax to 323-343-1806, visit the company's website at www.grifolsusa.com, email: john.gross@us.grifols.com, or contact a company representative at ASH Booth #2244.

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