Immunoglobulin Replacement Therapy in Children

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KEYWORDS

- Intravenous immunoglobulin therapy
- Subcutaneous immunoglobulin therapy
- Primary immunodeficiency diseases

The benefit of immunoglobulin (IG) replacement in primary antibody deficiencies (AD) is unquestionable. Many of these congenital disorders present early in life and this therapy is often first implemented in the young. For many of these children, IG infusions will remain a requirement for the foreseeable future. No other therapy has demonstrated to be as efficacious as IG in reducing the number and severity of infectious complications in pediatric patients with AD. The consensus among pediatric immunologists is that, when combined with close clinical monitoring, timely and appropriate IG replacement could ultimately extend the life expectancy of these young patients to approach that of the general population.

The general concerns surrounding IG therapy affect adults and children equally. Issues regarding efficacy in the ever-expanding applications of IG, the predicted shortages of this drug, and the rising costs of therapy have been comprehensively addressed in a number of recent reviews.[1–5] This article focuses on the indications of IG replacement in children, with an emphasis on the specific diagnostic problems encountered in this population. Also presented is an overview of the practical aspects of IG administration in the pediatric setting, including the recognition and management of adverse reactions. Finally, briefly discussed is the advent of subcutaneous IG, a therapeutic IG modality with the potential to have a great impact in the quality of life of children with AD and their families.

INTRAVENOUS IMMUNOGLOBULIN FOR ANTIBODY REPLACEMENT THERAPY

Intravenous immunoglobulin (IVIG) is a fractionated blood product made from pooled human plasma. Available in the United States since the early 1980s, it rapidly

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substituted the use of intramuscular preparations as replacement therapy in AD states. Because it is manufactured from plasma from thousands of individuals, IVIG contains a mixture of antibodies against a wide spectrum of infectious pathogens. The concentration of antibodies against hepatitis B, diphtheria, measles, tetanus, and polio in the final product must comply with Food and Drug Administration requirements. Titers against other pathogens, including those that more frequently affect patients with AD, such as *Streptococcus pneumonia* and *Haemophilus influenzae* subtype B, are presently not regulated by the FDA. These titers can vary significantly among different products and even from batch to batch.[6,7]

To comply with World Health Organization and FDA guidelines, more than 90% protein content in commercial IVIG should be monomeric IgG with a distribution of IgG subclasses close to that in normal plasma.[8,9] Traces of IgM and IgA are present in all products, but the content of the latter can vary significantly between manufacturers depending on the method of IgG purification followed. Other immunomodulatory proteins, such as cytokines, soluble CD4 and CD8 and CD40, and HLA molecules are also present in varying amounts.[1,10] The risk of transmission of infectious pathogens by this blood-derived product is minimized by the careful selection of donors, plasma antibody screening, and various procedures of viral inactivation.

Since the early 1990s the distinction between IVIG products has increased because of refinements in manufacturing.[11] Most of these products have proved to be efficacious in the treatment of AD when compared with historical untreated controls or patients treated with intramuscular IG. The methods of purification, viral inactivation, and the addition of stabilizers vary between different manufacturers and can affect the clinical performance of the different products. Physicians need to be aware of these differences because that could influence their decision in selecting the appropriate product for each individual patient. Further, no one IVIG product currently on the market has approval for all of the FDA-sanctioned indications.

There are notably few studies comparing side by side the efficacy of different IVIG products.[12] In one such study, patients treated with an IVIG product prepared with a less harsh method of viral inactivation had fewer infections that those who received a solvent-detergent treated IVIG.[13] Differences in efficacy between IVIG preparations have also been reported in children with Kawasaki disease.[14]

Production methods not only can affect efficacy but also tolerability. High sodium and sucrose-containing products, for instance, may be contraindicated in patients with marginal cardiac or renal function. This is also an important consideration in neonates and infants. Reduced blood volumes and immature renal function puts this population particularly at risk of developing electrolytic imbalances or volume overload. For these patients, IVIG products with a higher protein concentration, low osmolarity, and neutral pH constitute the best option. IVIG with products with reduced IgA content may be preferred in patients with IgA deficiency who are still able to produce antibodies of IgE or IgG isotype, because these patients are at risk of developing anaphylactic-type reactions when they receive IgA containing blood products.[15]

IMMUNOGLOBULIN REPLACEMENT IN CHILDREN

In general, IG replacement therapy is indicated for patients with primary or secondary AD only if they have recurrent or severe infections and defective antibody production. The efficacy of IVIG in this setting is primarily related to the well-known attributes of IgG antibodies to neutralize bacterial toxins, superantigens, and viruses; activate complement; and promote phagocytosis and antibody-mediated cytotoxicity.