Clinical Commentary Review

The Nuts and Bolts of Immunoglobulin Treatment for Antibody Deficiency

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Immunoglobulin therapy is a key element in the management of most patients with primary immunodeficiency disease. Allergist/immunologists should be familiar with the appropriate evaluation of candidates for immunoglobulin, the characteristics of immunoglobulin products, and how to use them to provide the best care to their patients. Available immunoglobulin products appear to be equally efficacious, but they are not interchangeable. Minimizing the risk of serious adverse events and controlling minor side effects is important to ideal patient care. Immunoglobulin may be administered intravenously or subcutaneously. Individualizing the choice of immunoglobulin product, mode of administration, and site of care can optimize the clinical outcome and minimize the burden of care. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1076-81)

Key words: *Antibody deficiency; Immunodeficiency; Immunoglobulin replacement*

IgG replacement has been a key element in the treatment of primary immunodeficiency disease (PIDD) since Bruton's reports of brothers with recurrent pneumococcal bacteremia and absent gamma globulins in the early 1950s.[1] Although Bruton treated his patients subcutaneously, later with the addition of a "spreading factor,"[2] immunoglobulin, intramuscular (IGIM) became the norm in the United States. Immunoglobulin replacement significantly decreased bacteremias, but recurrent respiratory tract infections continued to be a major cause of morbidity and premature mortality because of the low IGIM dose, usually 100 mg/kg every 3 weeks. The introduction, in 1981, of immunoglobulin, intravenous (IGIV) allowed for significantly higher doses, revolutionizing the care of patients with PIDD. A dose-response relationship was appreciated almost immediately.[3]

In the United States, IGIV became the standard of care, whereas immunoglobulin, subcutaneous (IGSC) was routine in Scandinavia. Berger et al[4] resurrected IGSC in 1982, but this route was seldom used in the United States until a specific IGSC product was approved in 2006.[5] More recently, hyaluronidase-facilitated IGSC (immunoglobulin, hyaluronidase facilitated [IGHy]) has expanded the options.[6]

WHY SHOULD ALLERGIST/IMMUNOLOGISTS KNOW ABOUT IMMUNOGLOBULIN THERAPY?

Immunoglobulin is among the most complex of the drugs commonly prescribed by allergist/immunologists. To optimize their patients' care, prescribers should understand the indications, modes of administration, the selection of a particular product, and the potential for mild and life-threatening adverse events (AEs). In the absence of this knowledge, the prescribing physician may not make the best choices or, worse yet, may cede the decisions to a health care provider who has little or no knowledge of the patient and who may be influenced by factors other than the patient's best interest. Living with PIDD is burdensome because of recurrent infections and comorbid conditions.[7] It is important to individualize immunoglobulin administration to minimize the added burden caused by the treatment and associated AEs.

INDICATIONS

This review only considers immunoglobulin therapy for PIDD. Because antibody production defects are an element of most PIDDs, immunoglobulin replacement is the cornerstone of treatment for these disorders. Although many immunodeficiency phenotypes and approximately 300 immunodeficiency genotypes have been identified, not all patients with infection problems or even those with defined PIDDs should be treated with immunoglobulin replacement.

There should be no controversy about immunoglobulin treatment for genetically diagnosed patients with a well-described PIDD such as X-linked agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, or others. The appropriateness of immunoglobulin replacement is less straightforward for those patients whose diagnosis is based on their clinical presentation and nongenetic laboratory evaluation. Patients should be considered for immunoglobulin therapy on the basis of a history of severe, or recurrent, or unusually complicated, or poorly responsive bacterial infections and laboratory evidence of an antibody production disorder.[8]

Most immunologists agree that a minimal antibody deficiency evaluation should include measurement of IgA, IgG, and IgM levels. Many will order an IgE because some patients who are

Medical City Children's Hospital and Allergy Partners of North Texas, Dallas, Texas
This study was supported by Allergy Partners of North Texas.
Conflicts of interest: R. L. Wasserman has consultancy arrangements with Shires, ADMA Biologics, Inc., Bioplasma Laboratories, CSL Behring, Kedrion, Grifols, Therapure, and Prometic; has received 1 or more grants from or has 1 or more grants pending with Shires, Octapharma, Bioplasma Laboratories, and Therapure; has received 1 or more payments for lecturing from or is on the speakers' bureau for Shires and CSL Behring; and has received 1 or more payments for the development of educational presentations for Shires.
Received for publication June 14, 2016; revised September 14, 2016; accepted for publication September 21, 2016.
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.09.011

Abbreviations used
AE- Adverse event
AUC- Area under the time/concentration curve
IGHy- Immunoglobulin, hyaluronidase facilitated
IGIM- Immunoglobulin, intramuscular
IGIV- Immunoglobulin, intravenous
IGSC- Immunoglobulin, subcutaneous
ISR- Infusion-site reaction
IV- Intravenous
PIDD- Primary immunodeficiency disease

deficient in protective antibody production are able to make allergic antibody that may contribute to symptoms. Neither serum IgD concentration nor IgA subclasses correlate with infection risk and should not be measured. Similarly, IgG subclass determinations have poor sensitivity and specificity as markers of clinically important antibody production defects. Because many patients produce nonfunctional immunoglobulin or are able to generate an antibody response only to some antigens, the evaluation should include measurement of the response to protein and carbohydrate antigens.[8] Diphtheria and tetanus toxoids are the most commonly tested antiprotein responses, and pneumococcal polysaccharide vaccine (PNEUMOVAX®23) is most often used to test the anticarbohydrate response. The use of vaccines in the diagnosis of immunodeficiency has been reviewed.[9]

The appropriate diagnosis and treatment of patients with an infection history suggestive of an immunodeficiency, IgG concentration that is near normal or normal, and a less than robust response to vaccination are controversial.[10] Although disagreement exists regarding the serum IgG concentration below which treatment is mandated (ie, <500 mg/dL, <400 mg/dL, <300 mg/dL, <200 mg/dL) as well as the definition of a normal response to vaccine, the infection history is the most important data element. These issues are more fully discussed elsewhere.[8] Nevertheless, it is very important to obtain these studies because virtually all third-party payers will require these data as part of their approval process. Notably, the definition of an appropriate immunodeficiency evaluation has evolved significantly over the past 60 years and will certainly continue to evolve as the understanding of the host defense system deepens.

IMMUNOGLOBULIN PRODUCTS

All immunoglobulin products comprise at least 90% to 95% IgG. The US Food and Drug Administration (FDA) terms these products "Immune Globulin X% (Human)" and abbreviates them as IGHy, IGIM, IGSC, and IGIV, relating to the various modes of administration for which a product is approved. Different manufacturers have used synonymous variations such as IVIG and IVIg.

Because there are no prospective studies comparing available immunoglobulin products, comparisons of study reports should be made with caution. Most immunologists regard immunoglobulin products as equivalent, especially with regard to efficacy, but not generic because of differences in the way individual patients tolerate particular products. All immunoglobulins are derived from recovered (ie, blood donations) or source (ie, pharesis donors) plasma from a minimum of 1500 but as many as tens of thousands of donors. Isolation of the IgG component of plasma usually begins with a cold ethanol precipitation

TABLE I. Characteristics of immunoglobulin products

Characteristic	Comments
Concentration IV	One product may be used at 3%, 6%, 9%, or 12%. All others are either 5% or 10%
Concentration subcutaneous	10%-20%
Stabilizers	Carbohydrates such as sucrose or maltose Amphophilic amino acids; glycine or proline
Sodium content	Zero to twice normal saline
Osmolality	Near isosmolal to 1074 mosm
Lyophylized or liquid	Liquid preparations do not require reconstitution
Storage	Most products have some room temperature storage stability
IgA concentration	A few patients with IgA level of <7mg/dL have been reported to make IgE anti-IgA that has caused anaphylaxis. This is a very infrequent occurrence. Products with a very low IgA content are preferred for these patients. Contaminating IgA provides no therapeutic benefit

followed by additional steps to reduce contamination and eliminate or inactivate blood-borne pathogens. The products differ in the isolation process, pathogen removal steps, and excipients or stabilizers (Table I) (for product-specific details, see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The FDA mandates at least 3 pathogen inactivation/removal steps. There have been no reports of blood-borne infection (including HIV and prion disease) attributed to an immunoglobulin product sold in the United States in more than 20 years.[11]

IMMUNOGLOBULIN DOSING

The relationship between immunoglobulin dose and clinical outcome has been recognized for at least 30 years.[3,12] More recently, Orange et al[13] have shown, using meta-analysis, that increasing the dose of IGIV by 100 mg/kg/mo increases the trough IgG level by 121 mg/dL and decreases the incidence of pneumonia by 27% (Figure 1).

The goal of therapy, however, should be neither the achievement of a particular serum IgG concentration nor the prevention of all infections. Rather, immunoglobulin therapy should minimize serious infections and decrease the rate of all infections to approximately that seen in the normal population.[14] The concept of individualized biologic troughs, initially based on 2 patients whose infections increased when their IgG trough levels fell below a certain level that was different for each patient,[15] and supported by long-term observation of a large cohort of patients with common variable immunodeficiency and X-linked agammaglobulinemia,[14] has become widely accepted.

For decades, immunologists have used IgG trough levels (drawn immediately before a dose of immunoglobulin) as a surrogate marker for efficacy and as a guide to adjust dose. When an IGSC product was developed, the US FDA established a standard requiring that the area under the time/concentration curve (AUC) be at least 80% of the AUC achieved with intravenous (IV) administration (Figure 2). This concept, derived from small molecule pharmacokinetics, posits, in absence of data relating AUC to infection prevention, that the exposure to IgG over time is important to treatment efficacy. Nevertheless, because the IGSC AUC is substantially less than the IGIV AUC,