CHAPTER 21

INTRAVENOUS IMMUNOGLOBULIN TREATMENT

Belma Türsen, MD, Erdinç Terzi, MD

Introduction

The intravenous administration of exogenous pooled human immunoglobulin (intravenous immunoglobulin -IVIG) was originally licensed as antibody replacement therapy in patients with primary immunodeficiencies. IVIG has been used in the treatment of various dermatological diseases, including pemphigus vulgaris, bullous pemphigoid and toxic epidermal necrolysis. The new criteria have formalized the eligibility requirements for several dermatological disorders. This may increase access to intravenous immunoglobulin for treatment for these conditions. However, there remain stringent eligibility criteria with which dermatologists need to be acquainted. In some conditions, dermatology review is mandated by these criteria while in other conditions with skin manifestations, referral to other specialists is required. Intravenous immunoglobulin is a fractionated blood product manufactured from pooled human plasma. Introduced in the late 1970s, IVIG rapidly overtook the use of intramuscular preparations as a replacement therapy in primary and secondary immunodeficiencies. Intravenous immunoglobulin is increasingly important as replacement therapy in immunodeficiency and as an immunomodulatory agent in autoimmune diseases and transplantation. In general, replacement therapy is indicated for patients who have primary or secondary immunodeficiency diseases with a history of recurrent or severe infection and deficient or absent antibody production. When used as immunomodulatory therapy, IVIG can interrupt the pathological immune responses that result in a wide range of human diseases, including various disease processes which involve the immune system, the nervous system, the blood and blood-forming organs, and the skin. There is a continuing increase in the clinical indications for IVIG resulting in double-digit annual increases in the volume used over the last 10 years.[1-3]

Composition of IVIG

Since the early 1980s, immunoglobulin products approved for intravenous administration have been available in the United States. Plasma pools yielding IVIG range from 4000 L to 50,000 L and contain plasma from 1000 and 15,000 donors. Thus, each aliquot of IVIG contains a polyclonal mixture of antibodies from different donors that it contains antibodies with a multiple antigenic specificities. The pooled preparations of immunoglobulin are made up of more than 95% IgG and small amounts of IgM and IgA. There are multiple commercial preparations of human immunoglobulin available for purchase in the United States. These products are distributed as either lyophilized powders or liquid concentrates. Lyophilized powders require reconstitution, whereas liquid concentrates do not. Sugars are often added to IVIG preparations to stabilize the product and prevent re-aggregation. Because IVIG is a blood product it carries an inherent risk of transmitting infectious diseases. Multiple steps are taken to minimize this risk during preparation, beginning with careful donor selection. The second line of defense is screening of single plasma donations for HCV, HBV, HIV, and HBs antigen. In addition, PCR testing on plasma mini-pools or on the entire pool for fractionation has now been introduced. Processing of pooled donations then consists of a variety of viral inactivation or removal steps including treatment with solvent/detergent, polyethylene glycol, enzymatic treatment with pepsin or trypsin, pasteurization, acidification, nanofiltration, treatment with caprylate, and depth filtration. An important thing to remember is that commercial IVIG products are not generic or identical. Differences in production methodologies impact the product's pharmacologic and physiologic profile and these, in turn, impact tolerability and efficacy. Important aspects of individual products that may affect clinical tolerability include volume load, osmolality, sodium content, sugar content, pH, and IgA content. Thus, the decision to use one product over the others is not trivial, as small differences may affect individual clinical outcomes.[2,3]

Mechanism of action of IVIG

The mechanism of action of IVIG is complex and is not clearly understood. In many autoimmune bullous diseases, administration of IVIG has been shown to be associated with a decrease in serum levels of pathogenic autoantibodies. In all of the dermatologic diseases presented in this article, however, the therapeutic effects on IVIG include: Functional blockade of Fc

blistering diseases. In this statement it is suggested that IVIG be considered for treating autoimmune blistering diseases in several situations, including if there is failure of conventional therapy to control the disease, the patients experience significant adverse effects as a result of conventional therapies, and there are significant contraindications to the use of standard therapies. Until randomized controlled studies are performed, we believe that these recommendations should be considered for use of IVIG in all diseases in which it has been shown to be efficacious. However, immediate IVIG use should be considered in situations where the disease is rapidly progressive and/or life-threatening, such as with toxic epidermal necrolysis. IVIG was originally licensed as antibody replacement therapy in patients with primary immunodeficiencies and there are currently eight FDA-approved uses for this agent. Despite a current lack of FDA approval, off-label treatment of a multitude of dermatologic disorders with IVIG has shown exciting potential for this unique treatment modality. The diseases successfully treated with IVIG include autoimmune bullous diseases, connective tissue diseases, vasculitides, toxic epidermal necrolysis, and infectious disorders like streptococcal toxic shock syndrome. Currently the biggest drawback in the consideration of IVIG therapy in dermatologic disorders is the lack of randomized controlled trials. Nevertheless, there is a significant body of evidence demonstrating the efficacy of IVIG in patients with dermatologic disorders that are resistant to treatment with standard agents. In summary, IVIG constitutes a valuable and potentially life-saving agent in managing patients with a variety of dermatologic disorders under the appropriate circumstances.

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