Actas Dermosifiliogr. 2018;xxx(xx):xxx-xxx

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

PRACTICAL DERMATOLOGY

Dermatology and Immunoglobulin Therapy: Who to Treat and How to Administer Immunoglobulins☆

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Received 2 April 2017; accepted 5 November 2017

KEYWORDS
Intravenous immunoglobulin therapy;
Dermatology;
Dermatomyositis;
Autoimmune bullous diseases;
Toxic epidermal necrolysis

Abstract Intravenous immunoglobulin (IVIG) replacement therapy has been used in immune deficiency diseases for more than 50 years. The indications for this treatment have evolved, however, and IVIG therapy is now used in various diseases in which the immune system plays a prominent role. IVIG therapy has carved out a niche in dermatology for the treatment of such conditions as dermatomyositis, autoimmune bullous diseases, and toxic epidermal necrolysis. Special attention has been paid to this therapy in recent years. New guidelines have been published and should be taken into consideration in dermatology. This review provides a practical guide to IVIG use in our specialty.

PALABRAS CLAVE
Inmunoglobulinas intravenosas;
Dermatología;
Dermatomiositis;
Enfermedades autoinmunes ampollares;
Necrólisis epidérmica tóxica

Dermatología e inmunoglobulinas. ¿A quién y cómo administrarlas?

Resumen El uso de las inmunoglobulinas intravenosas en la medicina se remonta a hace más de 50 años, tras el uso como terapia sustitutiva en enfermedades inmunodeficientes. Sin embargo, las indicaciones de este tratamiento han evolucionado de tal manera que actualmente está dirigido a enfermedades donde el sistema inmune desempeña un papel relevante. En el campo de la dermatología se ha hecho un hueco interesante en algunas enfermedades, como la dermatomiositis, las enfermedades autoinmunes ampollares o la necrólisis epidérmica tóxica, entre otras. En los últimos años se ha prestado especial atención al uso de las inmunoglobulinas intravenosas, de hecho se han publicado recientemente nuevas guías sobre su uso, y qué consideraciones debemos tener en cuenta durante su uso en dermatología. Nuestra intención con este artículo es reflejar de una manera práctica el uso de las inmunoglobulinas intravenosas en la dermatología.

☆ Please cite this article as: Navarro-Triviño FJ, Pérez-López I, Ruíz-Villaverde R. Dermatología e inmunoglobulinas. ¿A quién y cómo administrarlas?. https://doi.org/10.1016/j.ad.2017.11.009
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Introduction

Immunoglobulins have been used for more than 50 years in the indication of primary and secondary immune system deficiencies. Their introduction in the treatment of different skin diseases is more recent, mainly because of the lack of randomized, controlled clinical trials and also because of the high costs. In 2008, the first guideline for the clinical use of intravenous immunoglobulin (IVIG) was published. Since then, publications have appeared in a wide range of journals describing their use for different conditions in isolated cases or in case series, culminating in recent guidelines. Between 3000 and 10 000 healthy donors are required to obtain an immunoglobulin concentrate. The production standards (World Health Organization 1982) were updated by the Committee for Propietary Medicinal Products of the European Medicines Agency (CPMP/BPWG/859/), with the aim of maintaining a higher level of quality and maximum safety in the manufacturing process. Plasma is incubated for at least 60 days to detect possible seroconversion of infectious agents (HBV, HCV, HIV, parvovirus B12, etc.). The functional integrity of the preparation is also tested for neutralizing antibodies and other immunomodulatory and inflammatory properties with the aim of detecting possible abnormalities in the function of these immunoglobulins. The national health agencies are responsible for regulating the manufacturing process as well as screening for viruses. Serum from donors positive for viral infections by polymerase chain reaction techniques or with abnormal immunoglobulin function is directly discarded to maintain the quality of the product.

Commercial IVIG preparations contain physiological quantities of all immunoglobulins except IgA, given that this immunoglobulin is responsible for anaphylactic reactions. The levels of this immunoglobulin should be kept as low as possible.

The bioavailability of IVIG is 100% at the time of infusion and 70% to 80% at 24 hours. On the fifth day, 50% of administered product has been cleared. Although the half-life is estimated between 18 and 32 days, conditions such as fever or infections increase catabolism and, therefore, decrease the half-life. IVIG can pass through the placenta and is excreted in breast milk. In terms of mechanism of action, the Fc region of IgG can change signaling and transduction signs in cells that express Fcγ receptors on their surface, thus inducing both immune-mediated and anti-inflammatory changes. However, the mechanism of action of IVIG has not been fully clarified in in vivo studies. Recently, Pérez et al.[1] published a very complete review of existing evidence of the use of IVIG in humans. The review aimed to provide the reader with a practical grounding in the use of this treatment in dermatology.

Main Indications for Intravenous Immunoglobulins in Dermatology

Although the list of skin diseases in which IVIG therapy has been reported as a treatment option is quite extensive (Table 1), use was almost always off label. Nevertheless, good outcomes have been reported in some cases. In this article, we highlight the most relevant publications with the corresponding level of evidence and strength of recommendation (Table 1).

Table 1 Main Skin Diseases for Which IVIG Can be of Use.

Main Off Label Indications for Use of IVIG in Dermatology	Other Indications
Dermatomyositis	Atopic dermatitis
Autoimmune bullous diseases	Autoimmune urticaria
Kawasaki disease	Lupus erythematosus
Toxic epidermal necrolysis	Systemic sclerosis
Scleromyxedema	ANCA-associated vasculitis
Pyoderma gangrenosum	Behçet disease
Livedoid vasculopathy	Kaposi sarcoma

Dermatomyositis

Level of Evidence IIA, Strength of Recommendation B

Of all the skin diseases described in this article, dermatomyositis, along with autoimmune blistering diseases, is perhaps the one with the highest level of evidence for efficacy. Placebo-controlled studies[2] and multiple case series[3] have been published, reporting satisfactory outcomes. IVIG is indicated as first-line therapy in cases of dermatomyositis with severe muscular involvement (fulminant myolysis), inclusion body myositis, and polymyositis.[4] Cases of juvenile dermatomyositis,[5] idiopathic dermatomyositis, and paraneoplastic dermatomyositis have been described with good response to treatment. IVIG is administered as adjuvant therapy, never as monotherapy, in patients who have not responded adequately to systemic corticosteroids after 1 month or in patients who experience worsening of muscle symptoms on decreasing the corticosteroid dose. The posology is described in Table 2. These agents are also useful in the treatment of skin manifestations associated with dermatomyositis, particularly when these are severe and extensive, even when muscular involvement is not present,[6] or in the treatment of dystrophic calcinosis[7] and calcinosis refractory to multiple immunosuppressants.[8] Good outcomes have also been reported in severe edematous dermatomyositis[9] and in dermatomyositis panniculitis.[10] According to the systematic review by Callander et al.,[11] IVIG therapy is an interesting alternative in the treatment of amyopathic dermatomyositis, as reported in isolated cases.[12] In the treatment of juvenile dermatomyositis, IVIG therapy occupies a position as an effective and safe alternative,[13] particularly when administered subcutaneously.[14] This route of administration represents a major breakthrough in terms of safety and low rate of side effects, and it also reduces the number of school days missed.

Autoimmune Blistering Diseases

Level of Evidence III, Strength of Recommendation C

Autoimmune blistering diseases are the second group of diseases in which IVIG therapy is an interesting treatment alternative,[15,16] particularly in the severe forms and forms refractory to systemic glucocorticosteroids in combina-