

Properties and action mechanisms of intravenous gammaglobulin

Propriedades e mecanismos de ação da gamaglobulina intravenosa

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ABSTRACT

Intravenous immunoglobulins (IVIg) preparations have been used as a substitutive therapy for primary and secondary immunodeficiencies for many years; now it is well known that IVIg can have two other important and opposite functions: pro and anti-inflammatory, depending on its concentration. Low doses of IVIg exert proinflammatory activities, that require complement activation or binding via Fc fragment of IgG to IgG Fcγ specific receptors present on effector cells of innate immunity. On the other hand, administration of high IVIg doses has anti-inflammatory activity. This manuscript presents a revision of how IVIg IgG mediated these effects, how and upon which cells from the immune system acts, their capacity to scavenging complement fragments, the recently demonstrated anti-inflammatory activity of variable minor sialylated portion of IgG molecules and finally, the importance of genetic variation and expression of Fcγ receptors. To comprehend the mechanism of action of IVIg is fundamental, not only to obtain further improvements on therapeutic effectiveness, but also to discover new and unexpected capacities of this biological bomb known as IVIg.

Key-words: Immunologic Deficiency Syndromes. Gammaglobulin. Replacement Therapy. Immune Function.

Introduction

Human immunoglobulin was used for the first time in 1950 as a substitutive therapy in a patient with primary agammaglobulinemia.¹ It was not until the 1980s when improvements on the plasmatic fractionation allowed to develop molecules with an intravenous use (IVIg), allowing a much larger amount of infusion and therefore a wider therapeutic role than the IDP, applied, as well, in an important number of autoimmune diseases, inflammatory disorders and a wide range of off-label indications.² Gamma globulin is made from

human plasma and therefore its production is limited, affecting its price and making it an expensive good. It is a safe drug, suffering multiple viral inactivation processes, increasingly stringent, but not exempt of some risks, not only intrinsic to the product but also individual features of the patient, so it should be used under strict conditions with a clear therapeutic indication.³

IVIg contain polyspecific and polyclonal immunoglobulins, derived from fractionated pools of plasma from hundreds of healthy donors. They are constituted almost exclusively of IgG molecules. In the IVIGs one can detect antibodies to foreign antigens, natural

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autoantibodies and to idiotypic antibodies. The first IVIG application was as a substitutive therapy in primary and secondary immunodeficiencies. Nowadays we know the importance of pro and anti-inflammatory effects of gammaglobulin depending on the applied use.

Activities of IVIG

Substitutive

The mechanism of action as a substitutive molecule in primary and secondary immunodeficiencies has been comprehended for many years now.⁴ The IgG obtained from the plasma fractioning of hundreds of normal individuals, have the intrinsic capacity to recognize and eliminate foreign and pathogen specific antigens, when infused to a patient lacking this immunoglobulin.

Pro and anti-inflammatory activities

IgG molecules have been able to produce pro and anti-inflammatory effects depending upon its concentration. Infusion of high doses of IVIG has an important anti-inflammatory role and represents an efficient treatment for many autoimmune diseases. It is well known that the use of IVIG therapy is licensed for idiopathic thrombocytopenia purpura, Kawasaki diseases between others and the off-label used has increase during the years. Several mechanisms could explain the anti-inflammatory activity of IVIg, but by now the most relevant contributor to this activities are the Fc fragments of IgG.^{5,6} The neonatal FcR (FcRn) is an important regulator of the IgG function, they bind to the CH3 domain of IgG in acidic conditions. The importance of the FcRn receptor lies upon it ensuring the characteristic long half-life of IgG (2-3 weeks); if FcRn is not present the IgG half-life moves for a few hours and lowers the antigen-specific IgG capacity bind to the target. Blokage of IgG FcRn is a system to interfere with pro-inflammatory activity of IgG. It is also know that blocking FcγR interferes with the pro-inflammatory activity of IgG in many autoimmune diseases. Moreover, in vivo studies demonstrated that the sugar chain attached to the CH2 IgG domains shows and important anti-inflammatory activity, present and active in IVIG treatments. The Fcγ receptor with anti-inflammatory activity was the inhibitory FcγRIIB, the upregulation of this receptor was another way to inhibit the pro-inflammatory activity of IgG.

The pro-inflammatory activity of low IVIG doses needs complement activation or union of IgG Fc fragments to the FcγR presents in cells of the innate immune system; after, activation of different signalling pathways occurs, intracellular calcium increases and cell activation takes place.

Impact of IVIG on immune function

Recent observations demonstrated the effects of IVIG therapy on different cells of the immune system, dendritic cell (DC), monocyte/macrophages, granulocytes, natural killer (NK) and T and B lymphocytes, belongs to adaptive as well as in innate immune responses.⁷

At a dose used to treat autoimmune or inflammatory diseases (high doses), IVIG inhibits the differentiation and maturation of DC cells; expression of HLA, CD80 and CD86, essential for a suitable antigen presentation to T cells, is inhibited by IVIG, this could be an explanation to the positive activity of IVIG therapy in Lupus erythematosus and other autoimmune and inflammatory diseases as chronic inflammatory demyelinating polyradiculoneuropathy.⁸ Nevertheless, an opposite action seems to be the result of lower IVIG doses, when used as substitutive therapy in primary immunodeficiencies; common variable immunodeficiency (CVID) patients, presented repetitive infections and abnormal susceptibility to autoimmune diseases, associated to impaired DC functions. IVIG infusions partially restored immature DC phenotypes, and up regulated the expression of CD40, CD80 and CD86 molecules in CVID patients. X-linked agammaglobulinaemia (XLA) patients presented immature DC populations, an addition of IVIG to autologous XLA serum, naturally devoided of immunoglobulins, partially restores the characteristics of a mature DC phenotype, increasing the expression of maturation related molecules. This research suggests the importance of immunoglobulin on the correct functioning of the DC. During this process, anti-CD40 antibodies found in IVG partially intervene.⁹

IVIG also exert their anti-inflammatory activity through monocytes and macrophages; one mechanism is inducing IL-1 antagonist receptor production (IL-1RA), a potent anti-inflammatory molecule by monocytes, that would consequently block IL-1. IVIG also lowers serum levels of tumour necrosis factor (TNF-alpha) and IL-1β, and modified the transcription of different inflammatory genes as FcγRs and the heterocomplex S100A8/A9.¹⁰

IVIG effects on adaptive immune response was mediated through T and B lymphocytes. These effects not only included the Fc γ blockade, but also a possible suppression of autoreactive B lymphocytes and the neutralization of survival and proliferation B cell factors as B cell activating factor (BAFF) or the proliferation-inducing ligand (APRIL).

Paramount control mechanisms of autoimmune phenomena, were induced through IVIG- B lymphocytes interaction. As example, IVIG induce de novo production of IgG antibodies against different self and non self antigens derived from a only one individual B cell subset. The interaction of anti-idiotypic antibodies with IgG or IgM present in the B cell membrane may down-regulated autoantibodies production.¹¹ Recent reports confirm previous data on blood B and NK cell decrease after IVIG infusions in women with recurrent spontaneous abortion, modulation of LFA-1 and or restricted treatment effects on pregnant women immune system was described.¹² In another hand it is also demonstrated in vitro, that IVIG induce the differentiation of B lymphocytes and IgG secretion.¹³

It is well know that IVIG supress many T cell functions. How this supressive effect is mediated has not been fully elucidated, two mechanism affecting the supressive effects of Tregs were recently described, the expansion of CD4+CD25+ FOXP3+ T cells and an important increase in their suppressive activity, after IVIG infusion.¹⁴

It is well known that IVIG interact with multiple cells and molecules from the immune system, innate and adaptive immunity are involved and that makes clear support to the beneficial IVIG treatment effects.

Scavenging of complement products by IVIG, is well established, and is present in all four IgG subclasses. Binding to potentially dangerous complement fragments to IgG molecules prevents the deposition of these fragments on their target tissues and inhibits secondary tissue destruction together with inflammation phenomena.¹⁵

Recently, it was demonstrated that pro and anti-inflammatory activities of IVIG are related to the specific sugar moiety residues attached to the constant domain of Fc IgG fragments. The number of glycosylation variants present on IgG molecules, their function and which pathways intervene in these activities are currently being unveiled and may add new capacities to this increasingly surprising proteins.¹⁶

Conclusions

Knowledge of the mechanisms of action and properties of IVIG has increase exponentially in recent years; describing their pro and anti-inflammatory activities have opened the possibility of new therapeutic applications, the production of more effective molecules and, in a near future, an emerging but real production of recombinant IVIG products. These old folks named IVIG have surely in store some new and interesting therapeutic applications, free of significant side effects.

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RESUMO

As preparações de imunoglobulinas intravenosas (IVIG) têm sido utilizadas como terapia substitutiva para imunodeficiências primárias e secundárias durante muitos anos; agora é sabido que a IVIG pode ter duas outras funções importantes e opostas: pró e anti-inflamatória, dependendo da sua concentração. Em baixas doses a IVIG exerce atividades pró-inflamatórias, que requerem uma ativação do complemento ou uma ligação via fragmento Fc de IgG para IgG Fc γ receptores específicos presentes nas células efectoras da imunidade inata. Doutro lado, a administração de altas doses de IVIG provoca uma atividade anti-inflamatória. Este manuscrito apresenta uma revisão de como a IVIG IgG mediou nestes efeitos, como e sobre quais células do Sistema imune atua, a sua capacidade para limparem fragmentos do complemento, a atividade anti-inflamatória recentemente demonstrada de porção sializada menor variável de moléculas de IgG e, finalmente, a importância da variação genética e expressão de receptores Fc γ . Conhecer o mecanismo de ação da IVIG é fundamental para obtermos, não só uma melhoria na eficácia terapêutica, mais também para descobrirmos novas e surpreendentes capacidades desta bomba biológica chamada IVIG.

Palavras-chave: Síndromes de Deficiência Imunológica. Gamaglobulina. Terapia de Reposição. Função Imunológica.

References

1. Bruton OC. Agammaglobulinemia. *Pediatrics* 1952; 9 (6):722-28.
2. Committee for medical products for human use, EMEA. CPMP/BPWG/859/95 revision Core SPC for human Normal Immunoglobulin (IVIg) for Intravenous administration. <http://www.emea.europa.eu/pdfs/human/bpwg/085995.2008>
3. Ballow M. Safety of IVIG therapy and infusion related adverse events. *Immunol Res* 2007; 38:122-32.
4. Durandy A, Wahn V, Petteway S, Gelfand EW. Immunoglobulin replacement therapy in primary antibody deficiency diseases-maximizing succes. *Int Arch Immunol* 2005; 136:217-29.
5. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. *Nat Rev Immunol* 2008;8:34-47.
6. Lazar GA, Dang W, Karki S, Vafa O, Peng JS, Hyun L, et al. Engineered antibody Fc variants with enhanced effector function. *Proc Natl Acad Sci USA* 2006;103:4005-10.
7. Tha-In T, Bayry J, Metselaar HJ, Kaveri SV, Kwekkeboom J. Modulation of the cellular immune system by intravenous immunoglobulin. *Trens Immunol* 2008; 29:608-15.
8. Bayry J, Lacroix-Desmazes S, Carbonneil C, Misra N, Donkova V, Pashov A, et al. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. *Blood* 2003; 101:758-65.
9. Gurcan Hm, Ahmed AR. Efficacy of various intravenous immunoglobulin therapy protocols in autoimmune and chronic inflammatory disorders. *Ann Pharmacother* 2007; 41:812-23.
10. Seite JF, Shoenfeld Y, Youinou P, Hillion S. What are the contents of the magic draft IVIG?. *Autoimmun Rev* 2008; 435-9.
11. Lemieux R, Bazin R, Néron S. Therapeutic intravenous immunoglobulins, *Mol Immunol* 2005; 42: 839-48.
12. Moraru M, Carbone J, Alecsandru D, Castillo-Rama M, García-Segovia A, Gil J, et al. Intravenous immunoglobulin treatment increased live birth rate in a Spanish cohort of women with recurrent reproductive failure and expanded CD56(+) cells. *Am J reprod Immunol* 2012; 68:75-84.
13. de Grandmont MJ, Racine C, Roy A, Lemieux R, Néron S.. Intravenous immunoglobulins induce the in vitro differentiation of human B lymphocytes and the secretion of IgG. *Blood* 2003; 101: 3065-73.
14. Kessel A, Ammuri H, Peri R, Pavlotzky ER, Blank M, Shoenfeld Y, Toubi E. Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function. *J Immunol* 2007; 179: 5571-5
15. Basta M. Ambivalent effect of immunoglobulins on the complement system: activation versus inhibition. *Mol Immunol* 2008. 45:4073-9.
16. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science*;313:670-3.