Transfusion and Apheresis Science 56 (2017) 45–49

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Mechanisms of action of intravenous immunoglobulin

Benjamin Chaigne[a,b], Luc Mouthon[a,b,*]

[a] Université Paris Descartes, Faculté de Médecine, Service de Médecine Interne, Centre de référence pour les vascularites nécrosantes et la sclérodermie systémique, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris, France
[b] Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France

ARTICLE INFO

Keywords:
Intravenous immunoglobulins
Substitution
Immunomodulation
Auto-immune diseases

ABSTRACT

Taking advantage of the "World Apheresis Association/Société Française d'Hémaphérèse" meeting held in Paris in April 2016, this article reviews the current knowledge on the mechanisms of action of intravenous immunoglobulins. Immunoglobulins are a plasma-derived drug, which have been initially used as a replacement therapy for patients with antibody deficiency. Since 1980 they have also been used for their anti-inflammatory and immunomodulating efficacy in auto-immune diseases. Herein, we review the requirements for their production and composition before giving a specific attention to their mechanisms of action including substitution and immunomodulation.

Contents

1. Introduction

Intravenous immunoglobulin (IVIg) are liquid or freeze-dried therapeutic preparations, sterile, containing human G isotype immunoglobulins (Ig) made from a pool of plasma of healthy blood donors. In addition to their initial use as a replacement therapy for patients with antibody deficiency, it has been highlighted by Imbach et al. in 1980 that IVIg infused at high doses have a therapeutic efficacy in patients with autoimmune thrombocytopenia [1]. Since then their use as anti-inflammatory and immunomodulating therapy has been discussed in many systemic inflammatory and/or autoimmune diseases. However IVIg are approved in the treatment of a limited number of diseases. In 2015, in the entire world, 151.6 tonns of Ig (including subctuanous Ig) were used among which 19.4 tons were used for new indications [2]. Herein we reviewed the current knowledge on the mechanisms of action of IVIg.

* Corresponding author at: Service de Médecine Interne, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France.
E-mail address: luc.mouthon@aphp.fr (L. Mouthon).

http://dx.doi.org/10.1016/j.transci.2016.12.017
1473-0502/

Table 1
European Medical Agency (EMEA) guidelines for the preparation of intravenous immunoglobulins [3].

Quality of preparations	Quality control
-Inactivation of infectious agents include one or two steps -Absence of transmission of infection -Absence of side effectfs related to products used for virus inactivation -Prekallikreine activator <35 UI/mL -Absence of agglutination of anti-A and anti-B hemaglutinins at a dilution of 1/64 -Thrombin generation test	-Anti-complement activity ≥ 50 % -Total protein content ≥ 90% -monomere/dimere ≥90 % -Polymeres/agregates <3 % -≥2 antibodies (viral & bacterial) concentration - ≥3 times over that of the pool of plasma -distribution of IgG sub-classes identical to that of normal human plasma -functional Fc portion -Anti-HBs Ag Abs: titer >0,5 UI/g of Ig

2. Production and composition

2.1. Production

Since January 1995, Ig have had a drug status of blood-derived stable drug. As a result their composition and production follow the guidelines of the European Agency. These include requirements for the number of donnors, a guarantee of safety of the preparation and a control of the quality (Table 1). Thus, it is established that IVIg preparations are obtained from a plasma pool of more than 1000 healthy individuals, regular blood donors. They must not transmit infectious agents, they must have a defined concentration of 50 g/L of Ig, they must contain at least two antibody specificities (antiviral and antibacterial), for which there is an international standard or a reference preparation, and identified in a concentration of at least 3 times higher than that of the original plasma pool. Finally, preparations of Ig can not exhibit thrombogenic activity (procoagulant) and IgG contained in the preparations must be intact and have a functional crystallizable constant fragment (Fc).

This regulation is guaranteed by standards in solubility, pH, osmolality, content and protein composition, molecular weight, of anticomplementary activity, prekallikreinic activity, content of anti-A and anti-B hemagglutinin, anti-D antibodies, antibodies against the hepatitis B surface antigen, IgA, water content, sterility, satisfaction pyrogenic test or bacterial endotoxins, preservation and labeling [3].

Like any stable product derived from blood, IVIg may be potentially responsible for the transmission of infectious agents. Viral safety of IVIg is also regulated and verified at different stages of their preparation for donor selection, plasma fractionation and viral inactivation methods (acid pH, solvent-detergent treatment, pasteurization, nanofiltration). Thus, no transmission of HIV, hepatitis A virus or hepatitis B virus, has been reported. However, before 1995, cases of transmission of hepatitis C virus have been reported following IVIg treatment. Although the risk of transmission of prion is possible, no case of Creutzfeldt-Jakob disease has been reported. To further limit the risk of transmitting any infectious agent, particularly Parvovirus B19 and prions, a nanofiltration process to 35 or 20 nm was added in the manufacturing process of the IVIg (Fig. 1).

2.2. Composition

The composition of IgG in IVIg preparation is similar to that of normal human serum. It is almost exclusively intact IgG with a half-life of 3–4 weeks and the subclasses distribution is comparable to that of normal human plasma. Preparations of IVIg have a wide spectrum of reactivities directed against external antigens including viral and bacterial, autoantigens (natural autoantibodies) and antibodies (anti-idiotypic antibodies). The preparations of IVIg should contain less than 5% of aggregated IgG, not more than 7% of F (ab′) 2 IgG and, according to commercial formulations, from 0.06 to 40 mg of IgA protein.

Even if their production as well as their composition is regulated by specific guidelines and recommandations, the use of multiple donnors and the small intervariability in the process of production cannot guarantee that two prepations of IVIg are perfectly similar. This observation has to be taken into account when characterizing their mechanisms of action wich are multiple and intricated.

Table 2
Supposed immunomodulating mechanisms of intravenous immunoglobulins (adapted from [7]).

- Saturation and modulation of the expression of Fcγ receptors
- Binding of sialylated-IgG to DC-Sign
- Saturation of neonatal Fc receptors
- Modulation of dendritic cells
- Expansion of regulatory T cells
- Decreasing pro-inflammatory effects of monocytes
- Decreasing the interferon-α response
- Inhibition of the complement activation cascade
- Neutralization of chemokines and/or cytokines
- Inhibition of apoptosis
- Neutralization of auto-antibodies

2.3. Differences among IVIg preparations

We have compared the biological characteristics of five liquid IVIg preparations licensed in Europe and observed important differences among these IVIg preparations for anti-A and anti-B haemagglutinins, IgG antibody repertoires, IgA and factor XI and factor XII content and complement activation [4]. We provide evidence for a high degree of heterogeneity of biological and biochemical properties among IVIg preparations tested.

3. IVIg mechanisms: substitution

In immune deficiencies, IVIg infusions have a double functions. First they resolve the lack of antibacterial or antivial antibodies and second they stimulate the adaptative immune response. IgG are able to bind to bacterial or viral microrganims and microbial toxins. Following this binding, the pathogens is either directly neutralized or the bounded-IgG are opsonized also leading to the clearance of the pathogen. Thus, it appears that the substitutive efficacy of an IVIg preparation depends on the number of donors involved in the production pool: the more the number of donors are, the greater the ability to substitute the immune deficiency is.

Furthermore, it has been shown that IVIg had a role on the maturation of dendritic cells (DC). In X-linked agammaglobulinemia, where the maturation of DC from monocytes is limited, infusions of IVIg enable the production of anti-CD40 natural autoantibodies and the differentiation of DC [5]. It has also been demonstrated *in vitro* that in the presence of IVIg, there is a differentiation and a maturation of DC from patients with common variable immunodeficiency [6]. IVIg infusion induce the overexpression of CD1a which characterize the maturation status of DC. The stimulation of the expression of receptors involved in the costimulation of T lymphocytes such as CD80, CD86 and CD40, has also been reported following IVIg infusions.

4. IVIg mechanisms: immunomodulation

IVIg mechanisms of action in immunomodulation are numerous and entangled (Table 2) [7].