Intravenous Immunoglobulins

Subjects: Others

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Intravenous immunoglobulins (IVIG) are blood preparations pooled from the plasma of donors that have been first employed as replacement therapy in immunodeficiency. IVIG interact at multiple levels with the different components of the immune system and exert their activity against infections. Passive immunotherapy includes convalescent plasma from subjects who have recovered from infection, hyperimmune globulin formulations with a high titer of neutralizing antibodies, and monoclonal antibodies (mAbs). IVIG are used for the prevention and treatment of several infections, especially in immunocompromised patients, or in case of a poorly responsive immune system. The evolution of IVIG from a source of passive immunity to a powerful immunomodulatory/anti-inflammatory agent results in extensive applications in autoimmune diseases. IVIG composition depends on the antibodies of the donor population and the alterations of protein structure due to the processing of plasma.

Keywords: autoimmunity ; infection ; intravenous immunoglobulins ; SARS-CoV-2 ; virus

1. Introduction

Intravenous immunoglobulins (IVIG) are a blood preparation pooled from the plasma of tens of thousands of donors who underwent plasmapheresis in order to obtain a very high concentration of immunoglobulins (Ig). The most abundant component of IVIG is IgG, usually over 95%, although other fractions of Ig can be present as well. Various IVIG formulations are commercially available and differ in terms of concentration, Ig content (Ig isotypes, IgG, IgM, IgA, and IgE), and other characteristics [1][2].

IVIG were first employed to treat immunodeficiencies in the 1950s and are currently licensed for the treatment of primary immunodeficiencies (PIDs) with impaired antibody production, secondary immunodeficiencies with recurrent infections, antibody deficiency, or proven specific antibody failure (PSAF) [3]. Following the first evidence on the ability of IVIG to reduce the rate of infections in immunocompromised patients, reports have been published suggesting beneficial effects in idiopathic thrombocytopenic purpura (ITP). Data have been accumulated on several other autoimmune diseases and inflammatory conditions supporting the current license of IVIG treatment in patients with ITP, Guillain-Barré syndrome, Kawasaki disease, chronic inflammatory demyelinating disease, and multifocal motor neuropathy. Beyond their licensed indications, the off-label use of IVIG is very common as well, in clinical practice, in specific conditions including severe inflammatory myopathies, myastenia gravis, Lambert-Eaton myastenic syndrome, Lyell's syndrome, and others. However, because of the rarity of most of these diseases, useful large studies and randomized clinical trials (RCTs) are awaited [3][4][5].

IVIG contain structurally and functionally intact Ig with half-lives of approximately 18–32 days, (similar to native IgG) and a normal proportion of subclasses: 95% monomeric IgG, small amounts of dimers, variable amounts of IgA and IgM. IVIG may also contain traces of soluble molecules including human leukocyte antigen (HLA) and cytokines. They do not contain high molecular weight immune complexes and contaminants such as vasomotor peptides and endotoxins. IVIG are subjected to industrial manipulation, processes of inactivation, and chemical and physical removal of bacteria and viruses. IVIG products may differ in their pharmaceutical properties (osmolality, pH, sodium content, stabilizer, IgA content) which can affect safety and tolerability [6].

2. Mechanisms of Immunomodulatory Action

IVIG interact at multiple levels with the different components of the immune system [7][8]. Indeed, beyond the antigen-specific effects, IVIG exert anti-inflammatory activity through the interactions between the Fc domain of the IgG and their receptors (FcγRs) [9]. In autoimmune diseases characterized by thrombocytopenia mediated by the presence of antiplatelet antibodies, IVIG probably induce the blockade of FcγRs present on monocytes and macrophages involved in the mechanism of antibody-dependent cytotoxicity and phagocytosis of autoantibody-coated platelets. The Fc-dependent immunomodulation exerted by IVIG can also involve alternative cellular mechanisms. In fact, IVIG induce the expression

of FcγRIIB inhibitory receptors with consequent inhibition of B-cell activation and induction of anergy and/or apoptosis through the phosphorylation of intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM) domains. Another proposed mechanism of action concerns the saturation of “neonatal” Fc receptors (FcRn), which involves an accelerated clearance of circulating pathogenic antibodies [10]. IVIG also allow the neutralization of circulating autoantibodies through the anti-idiotype antibodies contained in them: the interaction between IVIG and B-cell receptor idiotypes is at the basis of the ability of IVIG to regulate self-reactive B cell clones in vivo. In fact, IVIG are able to induce a block in the proliferation of B cells: this seems to be due to the differentiation of a subset of non-proliferating IgG secreting B cells [11]. IVIG exert their immunosuppressive effect at the level of dendritic cells, inhibiting the expression of HLA and CD80/CD86 molecules as well as the production of interleukin (IL)-2 [11]. It has been postulated that the modulation effect of the cytokine network, with the induction of the production of anti-inflammatory cytokines (such as IL-10), represents the main anti-inflammatory action of IVIG in vivo [12]. IVIG interfere with the activated complement components and the formation of the membrane attack complex (MAC) through the binding of C3b and C4b and, consequently, avoiding the interaction of these components with cellular targets [13]. Natural anti-C3b antibodies have been revealed able to inhibit the activity of C5 convertase in vitro [13].

Another anti-inflammatory mechanism of IVIG seems to be mediated by the pool of IgG with α-2,6 sialylated terminal residues (sFc) at Fc [14]. These sFc binds the dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) receptor on the cell surface of macrophages and the mouse counterpart SIGN-R1 (specific intracellular adhesion molecule-grabbing non-integrin R1). Through these interactions, sFc promotes the expression of cytokines and immunosuppressive receptors (FcγRIIB). According to this model, the anti-inflammatory effects of IVIG treatment are weaker in the knockout mouse model for SIGN-R1 but can be restored in the knock-in model with human DC-SIGN. Studies suggest the presence of other surface lectins as alternative ligands for the Fc fragment of IgG [8][15]. Immunomodulatory activities of IVIG also include the Tregitope “(regulatory T-cell epitopes present in IgG)” mechanism in tolerance induction mainly through the modulation of the regulatory T-cell axis, Tregs-cytokine expression, reduction of IL-17, and enhancement of the suppressive function of Tregs [16]. IVIG can promote the suppressive function of the T regulatory cells, probably thanks to the mediation of dendritic cells [17][18][19][20]. In addition, it has been shown that they have an inhibitory effect on the differentiation and amplification of T helper (Th)17 cells, reducing inflammatory cytokines and other pro-inflammatory mediators’ production, thereby interfering with the maintenance of chronic inflammatory response [21]. IVIG can induce apoptosis of B and T cells through the activation of Fas receptor, are able to block the binding between T cells and superantigens, to control self-reactivity and induce tolerance, and to inhibit the differentiation and maturation of dendritic cells.

3. Therapeutic Indications in Rheumatology

The Food and Drug Administration (FDA) has approved the use of IVIG for the treatment of PIDs since the 1980s. The therapeutic goal in these conditions is to reach a serum IgG level in the recipient > 5 g/dL, before the next infusion, although this threshold value and its potential “protective” effect is still debated [22]. The recommended dose is 400–600 mg/kg approximately every 2–4 weeks, with an inter-infusion interval that varies from patient to patient. The therapeutic benefits of IVIG in this context were initially traced to the ability to deliver specific antibodies to recipients unable to produce them-particularly antibodies to encapsulated microorganisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. However, simultaneously, data emerged on IVIG efficacy in improving autoimmune hematological complications (such as ITP) [23]. Subsequent studies showed that high doses of IVIG were able to provide a significant rise in the platelet count and often a resolution of clinical features in children with ITP. Extensive use of IVIG was thus promoted in other autoimmune diseases.

To date, IVIG are used in the treatment of a broad spectrum of severe rheumatological diseases including dermatomyositis (DM) and systemic vasculitides, such as KD, ANCA-positive small vessels vasculitides (AAV) [24][25][26][27][28]. In this context, several studies support the efficacy of high-dose IVIG in the therapy of eosinophilic granulomatosis with polyangiitis (EGPA), mainly in patients with neurological and/or cardiovascular complications [29][30].

IVIG treatment is also applied in clinical practice in systemic lupus erythematosus (SLE), polymyositis (PM), anti-phospholipid antibody syndrome (APS), and others [5]. In such pathological conditions, the IVIG dosage is usually 2 g/kg administered over 2–5 consecutive days.

IVIG are currently used for the treatment of patients with severe SLE who do not respond to other immunosuppressive drugs or as a steroid-sparing agent, mainly in patients with lupus nephritis [30]. Case reports and open-label trials describe that high-dose IVIG are effective in improving numerous clinical manifestations in SLE patients including neuro-SLE [31]. IVIG can represent a first-line therapy in cases of neuro-SLE, in patients who are not candidates for other immunosuppressants such as cyclophosphamide, or in patients with concomitant infections [31][32]. Many therapeutic

interventions are available to treat patients with PM and DM including corticosteroids, immunosuppressive drugs, and plasmapheresis: evidence documents that IVIG represent an efficacious therapy replacing or reducing steroid and immunosuppressive medications in PM/DM patients, mainly in induction for refractory cases or when immunosuppressive drugs are contraindicated [33].

IVIG represent a key treatment to manage APS refractory to conventional therapy [34][35]. Furthermore, in pregnant women with primary or secondary APS to SLE, various therapeutic protocols with IVIG have been successfully applied over the years with safety and efficacy on mothers and newborns [36][37][38][39].

4. Anti-Viral Aspects of IVIG

IVIG is a well-known treatment for a variety of diseases not only as a replacement therapy but also for its efficacy against infections and its anti-inflammatory and immune-modulating effects in autoimmune disorders [40][41][42]. The anti-viral effects of Ig include their activity in preventing cell penetration and activating innate immune system cells and the complement pathways [42]. Preparations of IVIG that are obtained from healthy donors contain various polyclonal Ig directed against a wide variety of antigens.

IVIG are currently used for the prevention and treatment of several infections, especially in immunocompromised patients, or in the case of severe and poorly responsive autoimmune disease (Table 1) [42]. The administration of IVIG finds indication in infections of subjects with an impaired immune system or as a substitute treatment for patients with hypogammaglobulinemia (primary or secondary deficiency) to prevent or treat common opportunistic viral and bacterial infections [43][44][45]. IVIG composition depends on the antibody composition of the donor population [46][47]. However, IVIG usually present significant activities against different viruses, like cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), hepatitis A virus (HAV), respiratory syncytial viral (RSV), Epstein-Barr virus (EBV), measles, mumps, rubella, parvovirus B19 [48], and polyomavirus BK [49]. IVIG may also be effective in treating drug-resistant or severe CMV, parvovirus B19, and polyomavirus BK infections in post-transplant patients [50][51]. Several case reports have described the successful use of IVIG in the treatment of anemia caused by chronic parvovirus B19 infection. IVIG therapy has been shown to clear viremia and to improve symptoms and cytokine dysregulation in parvovirus B19–associated chronic fatigue. Parvovirus B19 infection is highly prevalent in the general population, IVIG contain a significant anti–parvovirus B19 concentration and are considered the only specific treatment of the viral infection.

IVIG, especially the so-called “hyperimmune preparations”, i.e., Ig collected from donors with high titers of desired antibodies, are still used for the treatment of a variety of infectious diseases and infection-related disorders (botulism, CMV, hepatitis B, rabies, tetanus) [39][52]. In transplant patients, the use of IVIG (400 mg/kg on days 1, 2, and 7 and 200 mg/kg on day 14) combined with antiviral drugs such as acyclovir and gancyclovir, seems to prevent CMV related complications, such as pneumonitis, whereas either treatment alone does not [52][53][54]. In the meanwhile, the same combination does not seem to give benefit in case of CMV gastrointestinal involvement [55][56]. IVIG were also used as prophylaxis for VZV infection in newborns exposed to the virus after birth and were effective for the treatment of a disseminated VZV infection [57][58]. In addition, IVIG seem to reduce the recurrence of genital manifestations of HSV-2 [59]. Although they are efficacious in reducing the risk of secondary infection in HIV-infected children, they have no efficacy against HIV infection and should not be considered as antiviral therapy in HIV patients [39].

Among the viruses to which IVIG may exert defensive activity, there is also HAV: as reported, standard immunoglobulins preparations may be utilized in selected, susceptible patients for the prevention of HAV [60][61]. In a comparative study between HAV vaccine and IVIG for post-exposure prophylaxis, no significant difference, rather a slightly higher IVIG-induced protection, was observed [62].

Few data on immunodeficient patients treated with ribavirin combined with IVIG (500 mg/kg every other day) for the treatment of RSV pneumonitis are available. Survival rates in these series compared with those expected based on historical cohorts were encouraging, and suggested a benefit from IVIG as an adjunct therapy to ribavirin [63][64]. However, even a humanized monoclonal antibody has been approved and is available for immunodeficient patients [65][66][67].

Evidence documents the use of IVIG in EBV-related diseases including the prevention of EBV-associated post-transplant lymphoproliferative disease (PTLD), in association with acyclovir or ganciclovir [68], as well as in conservative treatment without etoposide in patients with hemophagocytic lymphohistiocytosis (EBV-HLH) [69]. Moreover, IVIG and plasma exchange are the standard therapy for acute inflammatory demyelinating polyneuropathy such as Guillain-Barré syndrome that has been linked to EBV, CMV, and other viruses [70].

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