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Intravenous immunoglobulins in immunodeficiencies: more than mere replacement therapy

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Summary

Intravenous immunoglobulin (IVIG) is a therapeutic compound prepared from pools of plasma obtained from several thousand healthy blood donors. For more than 20 years, IVIG has been used in the treatment of a wide range of primary and secondary immunodeficiencies. IVIG now represents a standard therapeutic option for most antibody deficiencies. Routinely, IVIG is used in patients with X-linked agammaglobulinaemia (XLA), common variable immunodeficiency (CVID), X-linked hyper-IgM, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and selective IgG class deficiency. In addition, IVIG is used extensively in the treatment of a wide variety of autoimmune disorders. IVIG is administered at distinct doses in the two clinical settings: whereas immunodeficient patients are treated with replacement levels of IVIG, patients with autoimmune and inflammatory diseases are administered with very high doses of IVIG. Several lines of experimental evidence gathered in the recent years suggest that the therapeutic beneficial effect of IVIG in immunodeficiencies reflects an active role for IVIG, rather than a mere passive transfer of antibodies.

Keywords: autoimmune diseases; inflammatory diseases, intravenous immunoglobulin; immunodeficiency

Intravenous immunoglobulin (IVIG) is prepared from pools of plasma obtained from several thousand healthy blood donors. The large donor pool ensures the diversity of antibody repertoires that include antibody specificities to a wide spectrum of antigens. IVIG contains a sampling from the complete array of variable regions of antibodies similar to those present in normal human serum [1]. Antibodies that occur in the absence of pathological conditions or deliberate immunizations are referred to as natural antibodies (NAb), and IVIG represents a privileged source of natural antibodies. NAb have been attributed with a variety of functions, including first-line defence against pathogens [2–4]. The presence of antibodies to recurrently occurring pathogens may thus be critical for the replacement therapy of patients with humoral immune deficiencies.

For more than 20 years, IVIG has been used in the treatment of agammaglobulinaemia [1,5]. IVIG is now standard therapy for most primary immunodeficiencies (PID) [6]. Most routinely, IVIG is used in patients with X-linked agammaglobulinaemia (XLA), common variable immunodeficiency, X-linked hyper-immunoglobulin (Ig)M, severe combined immunodeficiency, Wiskott–Aldrich syndrome and selective IgG class deficiency. In addition, IVIG is used extensively in the treatment of an increasing number of autoimmune and inflammatory disorders.

IVIG is administered at distinct doses in the two clinical settings, whereas immunodeficient patients are treated with replacement levels of IVIG and patients with autoimmune and inflammatory diseases are administered with very high doses of IVIG. The peak plasma IgG level reached in immunodeficient patients following infusion of IVIG when administered as a 'replacement therapy' is 12–14 mg/ml, compared to 25–35 mg/ml when administered as a 'high-dose' immunomodulatory agent in autoimmune and inflammatory disorders. In autoimmune and inflammatory diseases, several mutually non-exclusive mechanisms have been put forward to explain the immunomodulatory effects [1,7–13]. Thus, IVIG exerts its immunoregulatory functions at multiple levels, implicating modulation of expression and function of Fc receptors, interference with complement activation and the cytokine profiles, modulation of idiotype network and cell proliferation. While some of these effects may explain the rapid and passive neutralization of pathogenic autoantibodies, clinically the beneficial effects of IVIG are observed well beyond the half-life of infused IgG, suggesting that its effect may not be due merely to a passive

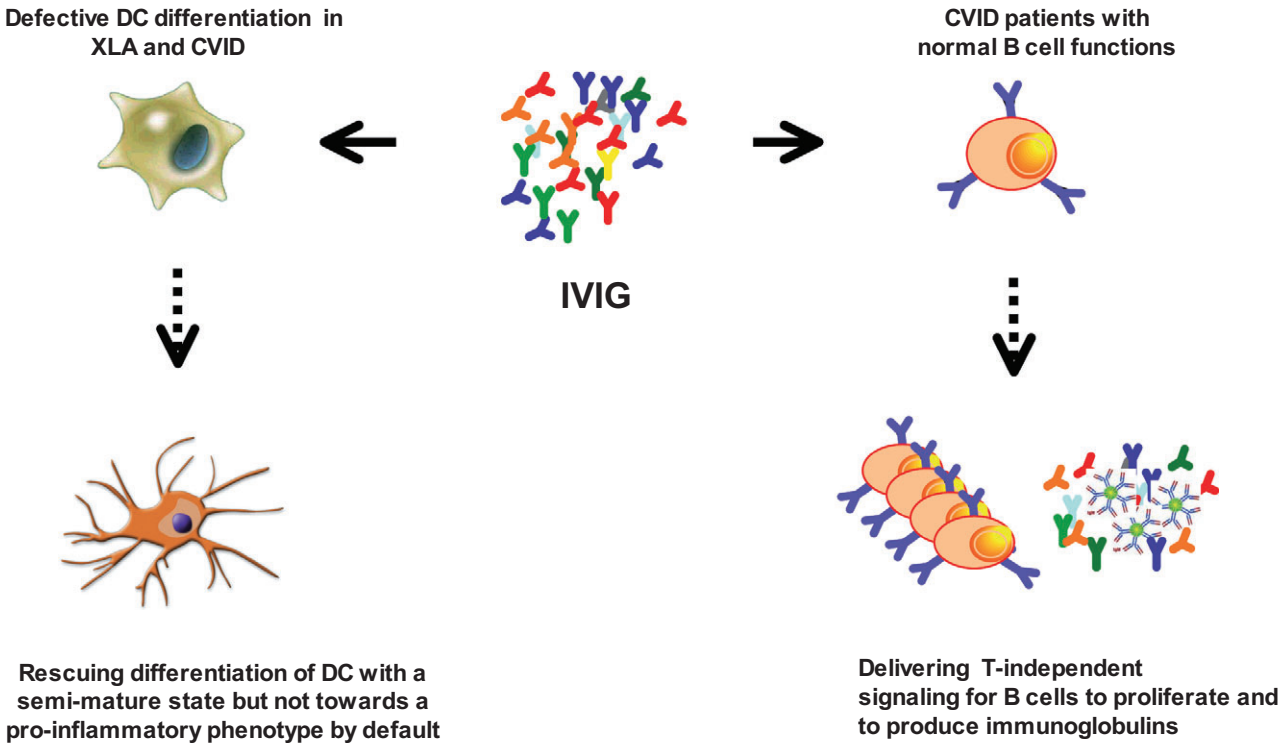

Fig. 1. Possible mechanisms of action of intravenous immunoglobulin (IVIG) in primary immunodeficiency.

clearance or competition with pathogenic autoantibodies. These observations open the possibility that IVIG therapy induces significant modifications in the cellular compartment of the immune system [14,15]. Several recent findings have emphasized the effects of IVIG on different cells of the innate and adaptive compartments of the immune system, including dendritic cells (DC), the monocyte/macrophage system, granulocytes, natural killer cells, subsets of T cells, in particular the regulatory T cell (T) subset, and B cells. Together, these findings may help to explain the beneficial effects of IVIG in autoimmune and inflammatory disorders due to dysregulated cellular immunity.

In immunodeficiencies, IVIG is generally believed to replace the missing antibodies and thereby prevent recurrent infections. However, several lines of experimental evidence gathered recently provide a basis for an active role for IVIG in immunodeficiency [16–19]. This renewed view is based on findings of the studies on the effect of natural antibodies in IVIG preparations on various cellular compartments of the immune system of patients with XLA and CVID (Fig. 1).

We have observed previously that peripheral blood monocytes of XLA patients are defective in their differentiation towards DC, as evidenced by lower expression of CD1a and CD83, compared with DC of healthy controls [16]. The patients' cells also expressed lower levels of CD80, CD86, human leucocyte antigen D-related (HLA-DR), CD11c and CD40 compared to DC from healthy donors. Further, BDCA 1^+ myeloid DC of XLA patients also showed decreased levels of HLA-DR and CD11c than that of healthy donors. However, the DC of XLA patients are not intrinsically defective and are able to respond to appropriate maturation signalling, as observed by their ability to up-regulate the maturation markers upon incubation with CD40L-transfected fibroblasts.

Interestingly, DC of XLA patients who were incubated with physiological levels of IVIG (12–13 mg/ml; 0·03 mM IVIG) reconstituted in autologous plasma during the differentiation phase expressed higher-level maturation markers compared to DC cultured without *in vitro* addition of IVIG. These data indicate that the defective differentiation of DC in XLA patients with XLA is due, at least in part, to the low levels of circulating antibodies and that IVIG at replacement dose can correct this defect to an appreciable extent. The maturation of DC induced by NAbs within IVIG is accompanied by an increased interleukin (IL)-10 and decreased IL-12 production, suggesting that maturation of DC does not lead to T helper type 1 (Th1) differentiation by default [20]. Thus, contrary to the suppressive effect on differentiation, maturation and function of DC at 'high dose' [21], IVIG exercises rather a stimulatory effect on maturation of DC at replacement 'low' dose. Interestingly, similar findings are observed with DC of CVID patients [17,22–25]. IVIG corrected the defective phenotypes of DC from CVID patients. Thus, adherent monocytes of CVID patients cultured for 6 days, supplemented with IL-4 and recombinant human granulocyte–macrophage colony-stimulating factor

(rhGM-CSF) in the presence of autologous plasma reconstituted *in vitro* with 10 mg/ml of IVIG, showed an up-regulated expression of CD1a and co-stimulatory molecules CD80, CD86 and compared to DC in the presence of autologous plasma alone [17]. In view of the critical role of DC in the predisposition to several pathological conditions, the stimulatory effect of IVIG may be of importance in the understanding of its role in PIDs accompanied by autoimmune manifestations. In fact, higher susceptibility to recurrent infections and the occurrence of autoimmunity in CVID patients may be accounted for by the defective DC functions [17,26,27]. A beneficial effect of IVIG in autoinflammatory manifestations following infusion of IVIG in immunodeficiencies, accompanied by restored phenotypes of DC, support the active role of IVIG through interactions with the cellular compartment.

Interaction of IVIG with the cellular compartment in immunocompromised situations also includes the B cells. We have demonstrated recently that IVIG induces proliferation and immunoglobulin synthesis from B cells of some of the CVID patients. Thus, at concentrations equivalent to that of 'replacement dose' (10 mg/ml), IVIG induced proliferation of B lymphocytes, indicating that antibodies within IVIG interact actively with B cells of the CVID patients [28]. In parallel, the B cells from these patients responded actively to IVIG through secretion of IgM and IgG.

Intriguingly, IVIG-mediated B cell stimulation is not associated with induction of B cell effector cytokine interferon (IFN)-γ and of transcription factor T-bet. Further, IVIG inhibits production of the inflammatory cytokine IL-6 by B cells. These results demonstrate that although a 'replacement dose' of IVIG can activate the B cells to proliferate and synthesize immunoglobulins independently of T cells, it is accompanied by an inhibition of the inflammatory cytokine responses in primary immunodeficient patients [28]. Together, the results indicate that in patients with immunodeficiencies, IVIG exerts an effect more than mere substitution of antibodies against pathogenic microbes; it rectifies the defective signalling and induces an optimal functioning of cellular compartment, thus re-establishing immune homeostasis.

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