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Mechanisms of action and historical facts on the use of intravenous immunoglobulins in systemic lupus erythematosus

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ABSTRACT

The current existing therapies for severe cases of systemic lupus erythematosus (SLE) patients are still limited. Intravenous immunoglobulin (IVIGs), which are purified from the plasma of thousands of healthy human donors, have been profiled as efficacious and life-saving options for SLE patients refractory to conventional therapy. The specific mechanism of action by which IVIGs generate immunomodulation in SLE is not currently understood. In this manuscript, we reviewed some of the hypothesis that have been postulated to explain the IVIG effects, including those on T and B cell intracellular signalling and activation, as well as the interferon signalling pathways involved in the detection of nucleic acids and the defective removal of immune complexes and debris.

1. Introduction

Autoimmune diseases affect 5%–10% of the population in developed countries and are important causes of morbidity and mortality, which can increase medical attention costs that are comparable with those of cancer and cardiovascular disease [1]. Systemic lupus erythematosus (SLE) is the prototype disease that can affect any organ or tissue but predominantly the joints, skin, nervous system, kidneys and bone marrow [2]. The pathophysiology of SLE has not been completely understood, but genetic, immunologic, hormonal and environmental factors comprise the 'mosaic of autoimmunity" [3]. This multifactorial consideration can help explain the individual differences in the clinical presentation of the disease [4].

The different treatments used for the management of SLE comprise immunosuppressor agents, including hydroxychloroquine [5], azathioprine [6], methotrexate [7], cyclophosphamide [8] and mycophenolate mofetil [6], among others [9]. Most of these drugs do not have strong evidence of effectiveness and have non-specific mechanisms of action [9]. Randomised clinical trials on biologic therapy have shown advantageous results for diseases, such as rheumatoid arthritis (RA) [10–12], spondyloarthropathies [13,14] and inflammatory bowel disease [15]. In contrast, these therapies have been less effective or non-effective for SLE [16], with the exception of belimumab, which is a monoclonal antibody directed against the B cell activating factor (BAFF) and had demonstrated efficacy in a group of patients with non-severe SLE [17]. Therefore, the current existing therapies for SLE patients are still limited [2].

In the last decade, intravenous immunoglobulins (IVIGs) have been profiled as efficacious and life-saving options for SLE patients refractory to conventional therapy. This refractoriness to therapy is usually related with severe immunosuppressive states that can increase the risk for infections and, consequently, increase mortality rates [18]. Therefore, IVIGs are not only potent immunomodulators, but these are also protective agents against the frequent infections that these patients are susceptible to develop [19–21]. The specific mechanism of action by which IVIGs generate immunomodulation in SLE is not currently understood. In this manuscript, we reviewed some of the hypotheses that have been postulated to explain this IVIG effect.

2. A historical perspective on the use and indications of intravenous immunoglobulin

Administration of IVIGs as a therapeutic tool was used for the first time in the first third of the 20th century to treat some infectious diseases and had been known as curative serum, as developed by Von Behring and Kitasato [22]. This treatment saved the lives of many children who suffered from diphtheria and several World War I soldiers who suffered from tetanus [22,23]. Thereafter, it was used for the

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prevention and treatment of infections, such as poliomyelitis, measles, mumps, whooping cough and hepatitis A [24,25]. Since the 1950s, IVIGs became the standard treatment that had a direct impact on the survival rates of patients with antibody deficiencies, such as agammaglobulinemia and hypogammaglobulinemia [26,27].

Studies on the immunomodulatory activity of IVIGs started in the 1970's, when Barandun et al observed a decrease in the signs and symptoms of a patient with primary immunodeficiency and haemolytic anaemia; simultaneously, they used IVIGs on a child with immune thrombocytopenic purpura (ITP) and varicella and observed an increase in platelet count [23,27]. Imbach et al took these findings to perform a clinical trial on children with acute and chronic ITP and achieved successful results, as demonstrated by normalisation of the platelet count in almost all patients treated with IVIGs [28]. Around 1981, the commercialisation of IVIGs allowed the performance of similar studies and others that demonstrated the beneficial effects of IVIGs for different autoimmune disorders, including organ-specific and systemic diseases [23]. Therefore, in the 1990s, therapy with immunoglobulins started to be standardised for disorders, such as ITP, Kawasaki disease, Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy [23,28]. IVIGs have also been used, but less frequently, in dermatomyositis/polymyositis, systemic sclerosis, catastrophic anti-phospholipid syndrome and as bridging therapy in some cases of ANCA-associated vasculitis, as well as some autoimmune degenerative diseases [29–34]. In the last decades, some clinical trials, most of these were non-controlled studies, have shown the potential of IVIGs in decreasing the disease activity in SLE patients and discoid lupus patients [31,35,36].

3. IGIV preparations, doses and mechanisms of action

IVIGs is a preparation of purified human plasma that had been sterilised from thousands of healthy donors and comprise 95% intact immunoglobulin G, immunoglobulin A and traces of immunoglobulin M molecules [37]. IVIGs also contain immunomodulatory peptides (i.e. CD4, CD8 and CD95) and diverse cytokines, such as IL-1, IL-2, IL-4, IL-10 and TGF-β [38]. The standard preparations of IVIGs contain polyreactive natural antibodies, mainly anti-idiopathic antibodies, that are capable of neutralising auto-antibodies, such as anti-DNA, anti-phospholipid, anti-ganglioside, anti-glycolipids, anti-intrinsic factor, anti-thyroglobulin, anti-microsomal, anti-platelet, anti-Sm and antibodies against exogenous antigens [39]. The dose used for the treatment of inflammatory and autoimmune disorders is four- to five-fold higher than the dose used in patients with immune deficiencies [40]. The frequently used dose is 2 g/kg body weight for two to five days, and this had been shown to increase the serum levels of IgG to about 2500–3500 mg/dL [41]. IVIGs were thought to exert immunomodulatory and anti-inflammatory effects by acting on the different pathways involved in the innate and adaptive immune systems. However, these mechanisms are not well understood [40].

Although the aetiology of SLE involves genetic and environmental factors, some immunologic factors are now starting to be better defined. We will focus on the possible mechanisms of action by which IVIGs play an immunomodulatory role in each of the three pathophysiologic pathways associated with SLE: 1) T cell and B cell intracellular signalling; 2) interferon signalling pathways that are involved in the detection of nucleic acids or in the production and response to interferon and 3) the defective removal of immune complexes and other debris [42] (Figs. 1 and 2).

4. Mechanisms of action of IVIGS in t cell and b cell INTRACELULAR signalling

4.1. Expansion of the diversity in T cells

In acute and chronic viral infections, as well as in some immunodeficiencies, the T cell diversity is reduced; in these conditions, only a selected number of clones expands by homeostatic proliferation and produces a normal number of lymphocytes with abnormal diversity [43]. Patients with autoimmune disorders have the same limitations, with an overexpression of expanded oligoclonal T cells, including TCRs with identical rearrangements among different patients with autoimmune diseases [44,45]. This has been demonstrated by evaluation of the complementarity-determining region 3 (CDR3) length spectratyping [46] and the use of next-generation sequencing to determine the CDR3 of the rearranged TCRβ loci in the peripheral blood lymphocytes of patients with SLE [47]. This study showed a marked oligoclonality in the Vβ chain of the TCR, affecting 17 of the 23 Vβ families analysed.

Initially, T cell diversity was thought to depend on the interaction between T cell precursors and thymic epithelial cells. However, a study on murine models showed that T cell diversity was brought about by B cells and immunoglobulins [48]. The authors showed that T cell diversity was reduced from 1.1×10^8 to 6×10^2 in mice without B cells and immunoglobulins. Adoptive B cell transfer or administration of immunoglobulin to these mice increased the diversity of the thymocytes by eight-fold. On the other hand, adoptive monoclonal B cell transfer or administration of monoclonal immunoglobulin did not show any increase in the diversity. In conclusion, their results showed that the T cell diversity increased only with polyclonal immunoglobulin administration and no when monoclonal immunoglobulin was administered [48,49].

A study on 15 SLE patients with oligoclonality of TCR repertoires and 16 healthy controls showed that the TCR diversity was increased after administration of IVIGs, supporting the hypothesis that IVIGs induce diversification of TCR repertoires [50]. Interestingly, the improvement of the individual repertoire in two of the four Vβ families was strongly correlated with a greater average density of CD25 on the surface of regulatory T cells FoxP3+ (Tregs); this finding suggested the hypothesis that during IVIG therapy, Tregs contribute substantially to control and limit the expansion of T cell clones [50].

4.2. Cell count and Treg function

CD4+, CD25+, FoxP3+ Tregs were described in the 1990s as a specialised subpopulation of T cells that keep the immune system homeostasis and tolerance to auto-antigens, playing a key role in the prevention of auto-immunity [51]. Different studies have described a decrease in the Tregs count and suppressor activity on effector T cells in patients with SLE, in comparison with healthy controls. Moreover, Tregs count was reported to have an inverse correlation with clinical disease activity and antibody titers [52–54]. Previous reports suggested that the effectiveness of IVIG therapy can be explained, in part, by the repair of Treg deficit and function. This ability of IVIGs to affect the induction of Tregs had been demonstrated in both human and animal models [55].

In 1981, the first approach on T and B cell culture from children treated with IVIGs was reported and showed significant suppressor effects [56]. Subsequent in vitro studies showed that polyclonal IgG was capable of direct interaction with Tregs to induce up-regulation of intracellular FoxP3, TGF-β and IL-10, when it was administered to healthy human CD4+ T cells in culture, compared with single CD4+ T cells or monoclonal IgG. Additionally, the suppressive effect of Tregs on effector T cells was increased in the cell culture with polyclonal IgG [55]. Recently, a study on eight Kawasaki disease patients with a decreased pool of Tregs during the acute phase of the disease revealed that IVIG treatment significantly increased the expression of FoxP3, reaching a normal Tregs count that was comparable with that in healthy controls [57].

SLE patients treated with IVIGs were also reported to have a significant increase in the Tregs count [58]. Furthermore, IVIGs have been demonstrated to induce differentiation of naïve Tregs FoxP3+ CD25− to activated Tregs FoxP3+ CD25+, upgrading the suppressive activity

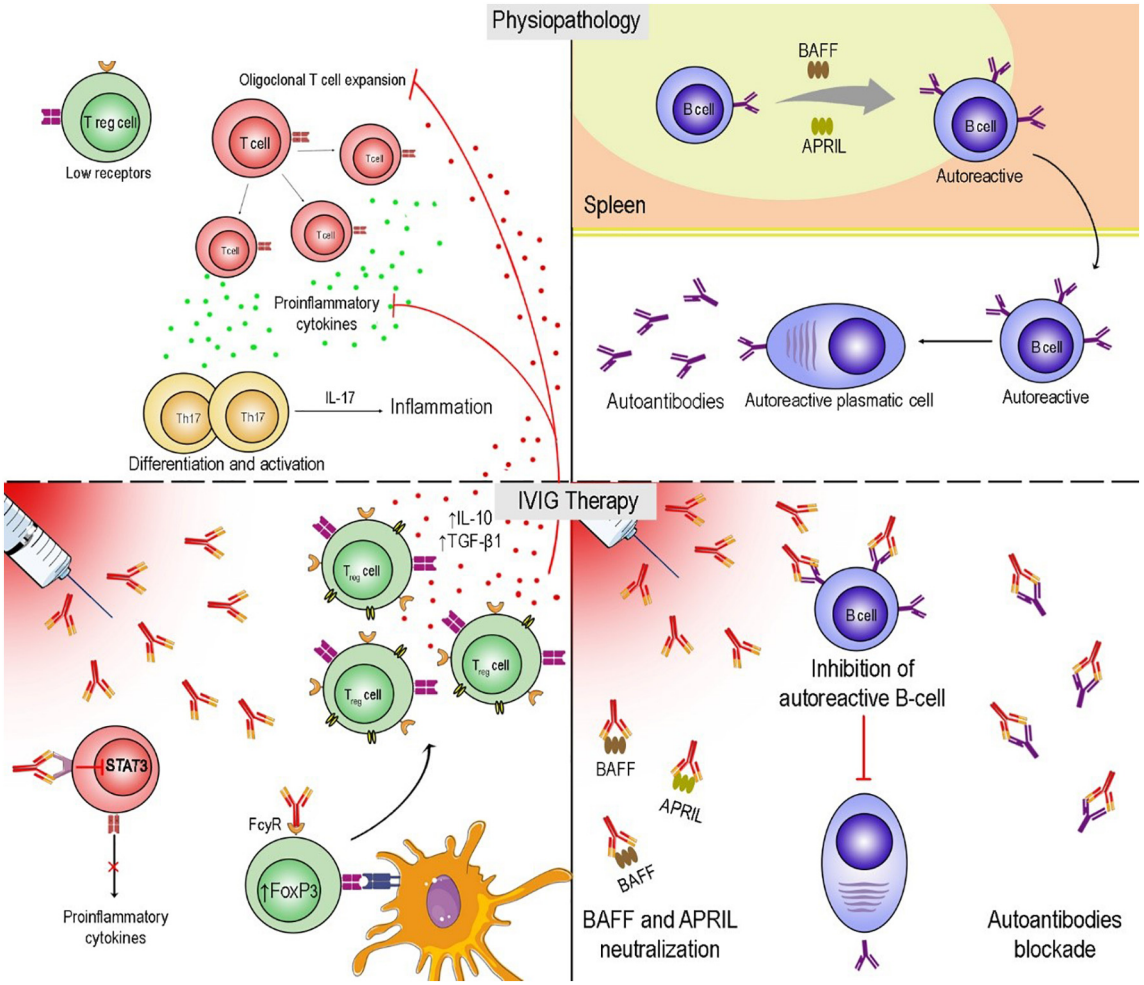

Fig. 1. Mechanism of IVIG over the intracellular signalling in T-cells and B-cells in SLE.
At the top of the figure it is described part of the physiopathology of Lupus, (*left*) it can be observed that a decrease in a T-reg cells number and their suppressor activity conduce to an oligoclonal T-cell expansion that increase the production of proinflammatory cytokines that over stimulate the Th17 cells. On the other hand, (*right*) under the stimulus of cytokines as BAFF and APRIL, autoreactive B-cells differences to an autoantibody-producing plasma cells. When the IVIG is supplied (*bottom figure*) the T-reg cell increased their regulator function inhibiting the oligoclonal T-cell growth and the secretion of proinflammatory cytokines avoiding the stimulation of Th17 cells. Meanwhile, the mechanisms of IVIG to inhibit the autoreactive B-cells and the production of autoantibodies is by a direct linkage to BAFF and APRIL blocking its stimulating function.

on effector T cells and decreasing the production of pro-inflammatory cytokines [58].

The use of IVIGs has been associated with an increase in the Tregs function in other autoimmune and inflammatory disorders, such as Still's disease and RA [59,60]; the results were mainly on the effector T cell subtypes Th1 and Th17, which are responsible for the inflammatory response in most autoimmune disorders, including SLE [61–63]. One of the possible mechanisms by which IVIGs increase the suppressive Treg response is by increasing ZAP70 phosphorylation, as demonstrated in a murine model of skin transplant with totally incompatible MHC [64]. In particular, IVIGs were shown to be capable of binding to the Treg membrane surface, in a FcγR-independent or -dependent manner, probably through TCR stimulation or by motif activator receptors, such as ITAM [64]. This action triggers the ZAP70 signalling pathway that is mediated by SRC kinase, resulting in better allogenic T cell suppression for the prevention of graft rejection [64,65].

4.3. Down-regulation of pro-inflammatory cytokines and up-regulation of anti-inflammatory cytokines

Compared with healthy controls, SLE patients have an evident dysregulation of cytokine profiles, with a significantly higher expression of type I interferons and inflammatory cytokines (i.e. IL-17, IL-6, IL-12 and IL-10) and a tendency for reduced TGF-β and IFN-γ levels [66]. Circulating cytokines, such as BAFF and APRIL, have also been implicated in the pathogenesis of SLE, and some immunomodulatory therapies have tried to address these molecules and their pathways [67].

IVIGs can affect the balance of cytokine production, mainly by down-regulating pro-inflammatory cytokines and up-regulating inhibitory cytokines [68]. Therefore, IVIGs reduced in a 70–95% the concentration of IL-2 in the supernatant of T cells culture stimulated by mitogens. Moreover, IVIGs did not alter the levels of IL-2 mRNA or lead to the accumulation of luciferase, when the gene was bonded to IL-2 promoters; this indicated that inhibition of IL-2 production by IVIGs was at a post-transcriptional level. Therefore, IVIGs could stimulate a negative regulatory effect on the proliferation and differentiation of auto-reactive effector T cells in SLE patients [69].

Another study detected high levels of TGF-β1 and TGF-β2 in children with immune-mediated disorders after treatment with IVIGs [70]. Considering that TGF-β is a potent immunosuppressive multifunctional cytokine, an increase in the level of this molecule could be an additional mechanism that explains the immunoregulatory effects of IVIG therapy [71]. Moreover, inhibition of the differentiation and amplification of

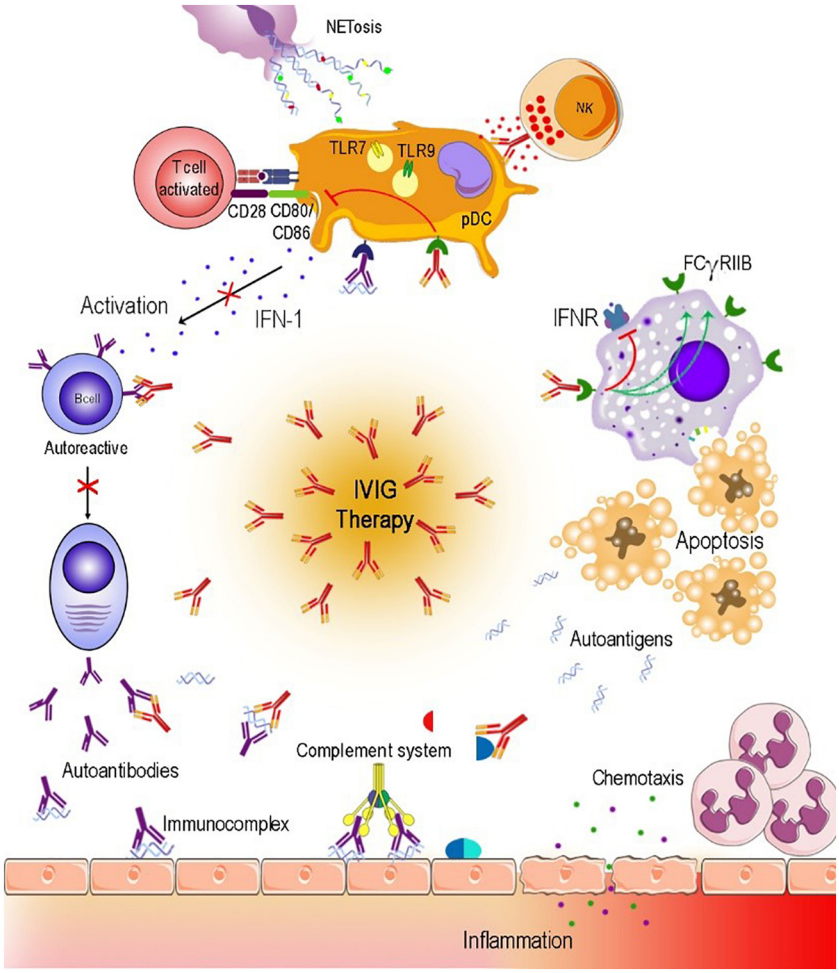

Fig. 2. IVIG in the regulation of IFN-1 and the clearance of apoptotic cells.
The therapy with IVIG inhibits the *IFN-1* release by plasmatic dendritic cells (pDC) through a direct blockade of the *FcγRIIB* receptor, limiting the pDC activation mediated by the co-stimulation of T-cells. Moreover, this inhibition do not permit the B-cell activation and the subsequent release of auto-antibodies. The IVIG are able to bind to the *FcγRIIB* receptor in macrophages as well, this produce an over expression of the *FcγRIIB* receptor as a possibility of autocrine regulation of *IFN-1*. Furthermore, the complement system, is inhibited by direct junction of IVIG to complement proteins and the circulating immunocomplex, this restrict their deposits on the endothelium and decreasing the inflammatory process.

Th17 cells and inhibition of the production of IL-17A, IL-17F, IL-21 and CCL20 cytokines were shown to be similar with the induced by other inhibitors, such as IFN-β [72]. The mechanism of this suppression has been attributed to the ability of IVIGs to bind to T cells via the Fab domain, inhibiting the sustained phosphorylation of STAT3, which is needed for the overactive function of Th17 cells in SLE patients [73].

On the other hand, overproduction of BAFF and APRIL in SLE is well-known to allow over-activation of auto-reactive B cells and their differentiation to plasma cells that produce auto-antibodies [74]. Some studies have evaluated the possibility that BAFF and APRIL antagonists can be found in IVIG preparations and influence B cell survival pathways, indicating that IVIGs are capable of binding BAFF and APRIL and confirming the presence of natural auto-antibodies against BAFF and APRIL. IVIGs can potentially prevent that BAFF saves auto-reactive B cells from deletion, promoting the therapeutic immunomodulation of IVIGs in SLE [75].

4.4. Suppression of auto-reactive B cell expansion

Auto-reactive B cells to endogen DNA are therapeutic targets in SLE. The loss of tolerance of these cells in SLE is mainly stimulated by BAFF and APRIL, which are critical factors for homeostasis and proliferation during the development of B cells and during deletion of auto-reactive cells. The serum levels of BAFF were reported to be higher in SLE patients than in healthy controls [76]. Elevated levels of BAFF and activating molecules, such as TLR9, may reduce the precision of clone selection and allow auto-reactive clones to persist in the peripheral blood, thereby, facilitating activation of these cells and production of auto-antibodies [77]. IVIGs suppress auto-reactive B cell expansion in a Fab-dependent manner that involves replacement of the anti-idiopathic network and the B-cell mediated inhibition by receptor idiotypes [78].

4.5. Increase in glucocorticoid receptor affinity

Glucocorticoids (GC) are usually considered the first-line therapy for SLE and their effects are predominantly mediated by the classic glucocorticoid receptor (GR) [79]. The alternative splicing in exon 9 during the transcription of GR generates two mRNA transcripts with high homology, producing two GR isoforms (i.e. GRα and GRβ) [80]. The GRα isoform mainly works as a transcription factor-activating ligand, whereas the GRβ isoform does not bind to a ligand, resides mostly in the nucleus and has an antagonist effect to the GRα isoform. GRβ expression can be induced by pro-inflammatory cytokines and other immune activators, which can decrease the GRα:GRβ ratio and cause GC resistance [81]. In asthma patients, monthly administration of IVIGs for six months was shown to significantly reduce the required GC doses and the number of hospitalisations in GC-sensitive and GC-resistant patients, possibly by increasing the binding affinity of GC to their receptors [82]. Although the mechanism of action of this effect on GCs is not understood yet, IVIG-mediated pro-inflammatory cytokine reduction may be one possible explanation [41].

5. Interferon signalling pathways implicated in the detection and production of nucleic acids and response to interferon

Type I and II IFN have emerged as the key molecules in the pathogenesis of SLE; their up-regulation usually precedes the development of auto-antibodies. Type I IFN is produced mostly by plasmacytoid

dendritic cells (pDC), which are increased in SLE patients [83]. Dysregulated function of this pro-inflammatory cytokine and others promote B cell differentiation and loss of tolerance [84]. TLR7 and TLR9 conduce neutrophils into NETosis and the formation of immune complexes as important mediators of IFN response by stimulating pDC [85]. Overproduction of IFN allows B cell activation via BAFF stimuli, decrease in Treg function and plasma cell induction [86]. The kidney mesangial cells in SLE patients are capable of producing IFN, and animal models have shown that exogenous IFNα administered to SLE patients can exacerbate the disease [87,88].

5.1. Cellular signalling suppression in dendritic cells

IVIGs suppress auto-antibody-mediated inflammation by induction and activation of molecules, such as FcγRIIB, and the negative regulator signalling pathways; these inhibit down-stream co-stimulatory molecules, such as CD80, CD86 and CD40 in dendritic cells and monocytes; decreasing type I IFN production; attenuate adaptive immunity response and decrease auto-antibody production [89,90]. IVIGs can also sensitise phagocytic and dendritic cells to the action of clodronate liposomes to reduce the production of IFN [91].

5.2. Decreased dendritic cell count and blockade of the IFN-γ signalling pathway

Some researchers reported that administration of IVIGs could mediate the identification of dendritic cells by NK cells, in the same way that immunoglobulin detects some epitopes to form a cell–immunoglobulin complex, which is then detected by NK cells via FcγRIII to induce the destruction of mature dendritic cells through a cytotoxic effector mechanism [92]. In addition, IVIGs have been demonstrated to block IFN-γ signalling and the expression of its genetic signature. IFN-γ inhibition is mediated by suppression of IFN-γ receptor subunit IFNGR2 expression via soluble immune complexes and its recognition by FcγRIII. These data suggested that inhibition of IFN-γ-induced macrophage responses contributes to the anti-inflammatory properties of IVIGs [93].

6. Mechanisms of action of IVIGS in the defective elimination of immune complexes and other cellular debris

SLE patients are well-known to have alterations in apoptosis and elimination of nuclear debris, which are related with infections, ultraviolet light exposure and cytokine function; these increase the exposure of nuclear auto-antigens [94]. When the apoptotic cell burden exceeds the body's ability to eliminate them, immune responses against endogen DNA and other auto-antigens can be elicited and allow the formation of auto-reactive B cells, which will become plasma cells that will secrete auto-antibodies that will form immune complexes with auto-antigens [95]. Immune complexes activate the complement system and can be detected by Fcγ receptors, leading to inflammation [96].

6.1. Complement protein neutralisation

Immunoglobulins play a key role in complement system regulation, with an ambivalent behaviour of activation and inhibition. Immunoglobulins can generate fragments that help eradicate invasive microorganisms but can also inhibit the action of these activated fragments on the host cells. The activation or inhibition effect depends on the antibody specificity. Meanwhile, clonal-specific antibodies or auto-antigens trigger the excessive formation of complement fragments, and the rest of the circulating antibodies that lack complement serve as modulators. However, this regulatory effect can be saturated, and administration of IVIGs is necessary to prevent deposition of these fragments and cellular destruction secondary to local inflammation [97].

6.2. Immune complex neutralisation and up-regulation of FcγRIIB

The IgG of IVIGs can induce the formation of large quantities of immune complexes that exceed the auto-antibody–auto-antigen relation and block the host Fcγ receptors to avoid the secondary activation of inflammatory cells [98]. IVIGs are also capable of up-regulating FcγRIIB, which is a low-affinity inhibitory receptor that is expressed on activated macrophages. This facilitates modulation of these effector cells and reduces pro-inflammatory responses; this mechanism could explain the resistance to the beneficial immunomodulatory effects of IVIG in ITP and RA animal models, in which FcγRIIB was suppressed [99].

Another widely defined mechanism of IVIGs is the down-regulation of anti-idiopathic antibodies that interact with B cells and the neutralisation of pathogenic idiotypes. This anti-idiopathic antibodies can improve the clinical manifestations by inhibiting the binding of auto-antibodies to their corresponding auto-antigen in vitro and in vivo [100].

7. New perspectives in the immunomodulatory mechanisms of IVIGS

7.1. IVIGs sialylation patterns

The glycosylation patterns of IgG in IVIG preparations interfere with its pro-inflammatory and/or anti-inflammatory responses. As demonstrated in murine models of inflammation, non-glycosylated IVIGs do not have any immunomodulatory effect [101–104]. The anti-inflammatory activity of IVIGs has been suggested to be mainly mediated by antibodies that contain terminal bonds of α2, which is a 6-linked sialic acid in the glycan Fc region of residue Asn297, that binds to a specific type C lectin antibody receptor for sialylated Fc (i.e. SIGN-R1) [105]. This protein is expressed in the macrophages in the splenic marginal zone; loss of SIGN-R1 during a splenectomy or genetic deletion of SIGN-R1 can reduce the anti-inflammatory activity of IVIGs [105,106]. The binding of sialylated recombinant IVIGs to SIGN-R1 up-regulates FcγRIIB in inflammatory cells, leading to antibody-mediated attenuation of inflammation [106].

Binding of Fcγ receptors through maintenance of the open conformation of the heavy chains is essential to IgG antibody glycosylation. This pre-requisite of glycosylation explains why non-glycosylated antibodies do not trigger its effects in vivo [103]. The structure of the carbohydrate bonded to the Fc region can be critical for antigen elimination and complement activation [107]. IgG molecules contain glycans in the CH2 domain of the Fc fragment (N-glycosylation). This glycosylation is heterogeneous, because different terminal carbohydrates can be bonded, including sialic acid, fucose, *N*-acetylglucosamine and mannose; these glycans can affect IgG binding to FcγRIIIA and allow cytotoxicity (ADCC) [108]. On the other hand, when galactose is bonded to the antibody, its binding to C1q is affected and modulates complement-dependent cytotoxicity [109]. IVIG administration could replace the levels of IgG that has abundant sialic acid glycosylation, which is significantly reduced in the acute phase of inflammatory diseases. Therefore, reduction of the inflammatory activity increases the immunomodulatory effect on the up-regulation of FcγRIIB. This receptor is expressed exclusively in B cells and works as a negative regulator of BCR activation, suppressing the effector function of auto-antibodies [41]. The use of recombinant sialylated Fc IgG1 demonstrated the anti-inflammatory properties of IVIGs in C57BL/6 murine models of RA [105]. Recently Bartsch et al. demonstrated that the specificity of sialylated antibody to the different antigens had a great immunomodulatory impact, as shown in RA murine models exposed to specific collagen antibodies, that needed low doses of sialylated IgG to produce a decrease in disease progression [110]. This evidence suggested that sialylated IgG is capable of attenuating the progression of autoimmune disorders [111].

Table 1
Summary of the multimodal mechanisms of action of IVIGs in SLE, based on murine and human studies.

Mechanisms of action of IVIGs in intracellular signalling in T and B cells
• Expansion of the diversity in T cells • Increase in the Treg cell count and suppressive function • Down-regulation of pro-inflammatory cytokines • Up-regulation of anti-inflammatory cytokines • Suppression of auto-reactive B cell expansion • Increase in glucocorticoid receptor affinity
Mechanisms of action of IVIGs in the interferon signalling pathway
• Suppression of cellular signalling in dendritic cells • Decreased dendritic cell count • Decrease in IFN-γ signalling pathway blockade
Mechanisms of action of IVIGs in the defective elimination of immune complexes and other cellular debris
• Complement protein neutralisation • Immune complex neutralisation • Up-regulation of FcgRIIB

8. Conclusion

Review of evidence from diverse publications enabled us to elucidate the multimodal mechanisms of action of IVIGs in autoimmune disorders, specifically in SLE; in particular, we found out the effects of IVIGs can encompass all the main pathophysiologic pathways in SLE (Table 1). However, the current evidence was based on experimental studies. In the near future, sialylated IVIGs are attractive and potential therapeutic options for autoimmune disorders.

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