Intravenous immunoglobulin: pharmacological properties and use in polyneuropathies

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Abstract

Introduction: Intravenous immunoglobulin (IVIg) is increasingly used for the treatment of autoimmune and systemic inflammatory diseases with both licensed and off-label indications. The mechanism of action is complex and not fully understood, involving the neutralization of pathological antibodies, Fc receptor blockade, complement inhibition, immunoregulation of dendritic cells, B cells and T cells and the modulation of apoptosis.

Areas covered: First, this review describes the pharmacological properties of IVIg, including the composition, mechanism of action, and adverse events. The second part gives an overview of some of the immune-mediated polyneuropathies, with special focus on the pathomechanism and clinical trials assessing the efficacy of IVIg. A literature search on PubMed was performed using the terms IVIg, IVIg preparations, side effects, mechanism of action, clinical trials, GBS, CIDP.

Expert opinion: Challenges associated with IVIg therapy and the treatment possibilities for immune-mediated polyneuropathies are discussed. The availability of IVIg is limited, the expenses are high, and, in several diseases, a chronic therapy is necessary to maintain the immunomodulatory effect. The better understanding of the mechanism of action of IVIg could open the possibility of the development of disease-specific, targeted immune therapies.

Keywords: IVIg, CIDP, GBS, anti-idiotype antibodies, anti-ganglioside antibodies, sialylation, IgG molecule, Fc receptors.

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1. Introduction

Intravenous immunoglobulin (IVIg) is prepared from plasma collected and pooled from several thousands of healthy donors. IVIg therapy was first used as a substitution therapy in primary and secondary immunodeficiencies [1]. In the early 1980s, Imbach successfully used high doses of polyclonal IgG to treat immune thrombocytopenic purpura (ITP) in children with immune deficiency [2]. Since then, the spectrum of autoimmune diseases treated with IVIg has been expanding continuously. Besides the licensed indications that can vary from country to country depending on the local regulatory authorities, several off-label indications exist covering hematological, dermatological, neurological, and oncological indications. The list of diseases that can be treated with IVIg is presented in Table 1 [3, 4].

This review includes a description of the composition, pharmacokinetics, and mechanisms of action of IVIg. The second part of the paper provides an overview of the immune-mediated polyneuropathies in which IVIg is a first-line therapy, with special focus on the pathomechanism of the diseases, the mechanisms of action of IVIg, and of the main results of clinical trials supporting the evidence of its efficacy.

2. Composition of IVIg

IVIg is a complex preparation pooled from a minimum of 1000 and up to 60,000 donors, depending on the manufacturer [5], which contains antibodies against a multitude of antigens. As a result of pooling, a diversity of antibody specificities is obtained. IVIg predominantly contains polyclonal immunoglobulin G (IgG), and low quantities of IgA and IgM. The IgG molecule comprises two heavy and two light chains (Figure 1). Both chain types have hypervariable regions that form the antigen-binding sites (Fab). When exposed to an antigen, B cells with complementary binding sites are selected and stimulated to secrete antibodies against the antigen. These antibodies

themselves function as an antigen. The unique antigen-binding site is called the *idiotype*, whereas the antibody secreted against the idiotype and capable of blocking it is referred to as the *anti-idiotype* [6, 7]. The anti-idiotypes can block the antigen-binding site of the pathological antibody. IVIg preparations contain many idiotypes and antibodies against several receptors as well. See Table 2 for details [8, 9].

At first, IVIg was used in a concentration of 5%, but subsequently, formulations with higher concentrations of 10-12% were also developed, which permitted the lowering of the volume load and the shortening of the time of administration. Formulations for subcutaneous use **(SCIg)** are available since the 1980s, which permit steadier IgG levels and a more favorable systemic side effect profile, **except for the higher incidence of local reactions.** Several brands of IVIg are available, with each considered to be a distinct product with a unique composition and different excipients. The products differ with regard to the production process, viral inactivation, purification, IgA content, **sodium content,** and the applied stabilizers, and are associated with different risks of adverse effects, depending predominantly on the IgA content, the osmolarity, and the stabilizers used.

In recent years, significant advances have been achieved in the production process of IVIg preparations with regard to purity, pathogen inactivation, and stabilization. Cold alcohol fractionation is used to isolate the immunoglobulin-containing plasma fraction, which is further purified through multiple steps of precipitation and can also be combined with ion-exchange chromatography, processes resulting in a highly purified polyvalent IgG product (>95%). Pathogens are removed by manipulations including fatty acid/alcohol treatment, low pH, solvent-detergent treatment, pasteurization, and nanofiltration. Beside maltose, sucrose, and glucose, amino acids such as glycine and proline can also be used as stabilizers [10].

The liquid products and the reconstituted solutions of lyophilized products are stored in refrigerators, and are to be brought to room temperature before use. Microwave and other heating procedures are not recommended, as they can denature the product. Shaking and

mixing should be avoided, as they can cause excessive foaming. The product should be carefully inspected before use to avoid administration of a solution that is not completely dissolved and contains visible particles and aggregates [10].

There are insufficient data on the efficacy and the cost-effectiveness from head-to-head randomized clinical trials to prove the superiority of one brand over the other; therefore, the choice of the brand in the daily practice depends on the characteristics of the product and the risk factors of the particular patient [5].

The choice of route of administration should be based on the clinical setting. It depends on the clinical characteristics of the patient, the preference of the patient, the site of care, the experience of the medical staff, and insurance coverage [11]. Although in immunodeficiencies, SCIg and IVIg are both approved (a.k.a. 'on-label') therapies, in autoimmune diseases, particularly in inflammatory neuropathies, IVIg is the preferred product, presumably due to the fact that it was more extensively studied and its efficacy is evidence-based. Notably, however, the results of some clinical trials with SCIg are promising [12].

3. Pharmacokinetics

The dose of IVIg used for the treatment of immunodeficient conditions is 0.4**–0.6 g/kg, administered every 3 to 4 weeks. Once the diagnosis is set, a continuous replacement therapy is to be initiated, which should not be interrupted. Some patients require higher doses of up to 0.8 g/kg. Doses exceeding this level have not been evaluated [13].** The total dose used in autoimmune/inflammatory diseases is 2 g/kg, administered in 2-5 consecutive days. This dose was introduced to clinical practice after the observation of a dramatic increase in the platelet count in a patient with concomitant immunodeficiency and ITP [2]. The initial dose is followed by maintenance infusions in doses of 1-2 g/kg every 3-4 weeks. The doses are generally adjusted according to the clinical response, and no antibody measurements are used. Individualized therapy is needed for each patient with respect to the applied doses (g/kg/month) and the intervals of

administration.

Intravenous infusion in a dose of 2 g/kg results in a 4-fold increase in the serum IgG levels. After 48-72 hours, the serum IgG levels drop by 50% as a result of the distribution in the extracellular fluid [14]. IgG is then catabolized and has a half-life (T1/2) of maximum 21-30 days, depending upon the activity of the neonatal Fc receptors (FcRns) [15]. At low pH conditions, circulating IgG in the serum is endocytosed by myeloid cells and endothelial cells, bound to FcRns and recycled to the surface of the cells [16].

The IVIg antibodies compete with pathological autoantibodies for the FcRn binding sites. Animal models of immune disorders, such as that of ITP and bullous pemphigoid, show a reduction of the T1/2 of pathological autoantibodies after IVIg infusion [17, 18]; however, it is unclear to what extent this phenomenon is responsible for the anti-inflammatory effect of IVIg preparations. The exact role of FcRns in the therapeutic effect of IVIg is difficult to estimate. The reduction of the FcRns observed in experimental conditions in FcRn-deficient animals leads to a subsequent reduction in the T1/2 of autoantibodies, and interferes with the mechanisms leading to tissue inflammation; on the other hand, however, the T1/2 of IVIg preparations is also decreased in these animal models [16].

4. Pharmacodynamics - mechanism of action

The immunomodulatory mechanism of action of IVIg has not yet been fully elucidated. Several mechanisms have been proposed (Figure 2), some of which are presumed to be mediated through the binding of the constant fragment (Fc) to Fcγ receptors (FcγRs) on the target cells, whereas other proposed mechanisms are mediated by the variable (Fab) region of the IgG. Some of these mechanisms are dose-dependent and are attributed to a competition with pathological antibodies, whereas others are more complex and involve cellular networks and various molecular targets.

4.1. Fc pathway-mediated immunomodulatory effects of IVIg

The Fc fragment is essential for the initiation of inflammation and acts as an adaptor, linking the innate and adaptive immune responses. The innate humoral response is triggered by the activation of complement 1q (C1q) and that of the innate immune cells via the FcγRs. The FcγR family contains one inhibitory and several activating members, and an alteration of their balanced expression or function may result in inflammation [19]. IVIg modulates the expression of the inhibitory FcγRs and blocks the activating FcγRs on antigen presenting cells (APCs). FcγRs have a low affinity for monomeric IgG and can be better activated by multimeric IgG, such as that present in immune complexes. However, there are no IgG aggregates in IVIg preparations, and the proportion of IgG dimers is also low. The small relative amount of dimers and the low affinity of the receptors might be responsible for the high doses of IVIg required to achieve an immunosuppressive effect [8].

Dimers that occur in IVIg preparations are formed by idiotype-anti-idiotype antibody pairs, for which the site of interaction is localized to the distal part of the Fab fragments [20]. The content of dimers in IVIg preparations depends on age, the formulation, the stabilizers used, and the conditions of storage, and it varies between 5 and 15% [21]. An increased level of dimers in the IVIg preparations correlates with a higher incidence of side-effects [21, 22]. Experiments have demonstrated that dimers have increased self-reactive specificities compared to those of the monomeric fraction, and some of these antibodies are of value for the treatment of autoimmune and inflammatory diseases [22]. In CIDP patients, IVIg infusion has been evidenced to increase the serum dimer levels to an extent suggesting a spontaneous formation of new immune complexes. These newly formed dimers show immunoreactivity against peripheral axons and Schwann cells; however, the specific antigens could not be revealed yet. A high serum level of dimers detected following IVIg infusion correlates with a better clinical response to IVIg therapy, suggesting that post-infusion dimer levels might be used as biomarkers to identify IVIg responsive patients. Further analysis of dimers formed

after IVIg infusion could identify disease-specific antibodies [21].

The infusion of Fcγ fragments alone can block FcγRs and increase the platelet count in ITP patients. Particularly sialylated Fc fragments with a terminal alfa 2-6 sialylation of the Fc glycan exert anti-inflammatory properties [23, 24]. In patients with SLE, lower levels of sialylated IgG (saIgG) are detected, a phenomenon which can serve as a biomarker of the disease [25]. The saIgG represents only 1-2% of the total IgG in the therapeutic preparations and has a low affinity for the FcγRs, suggesting that not the blockade of the FcγRs but rather an action on other receptors is responsible for the inhibitory effect. Examples of such receptors are members of the sialic acid-binding immunoglobulin-like lectin (SIGLEC) receptor family, including the cluster of differentiation-22 (CD22) inhibitory receptor on B cells. These receptors have motifs capable of triggering cell inactivation, such as the intracellular immunoreceptor tyrosine-based inhibitory motifs (ITIMs) or ITIM-like motifs [8, 9, 26]. The saIVIg interacts with adhesion molecules (specific intercellular adhesion molecule-3-grabbing non-integrin, SIGN) on dendritic cells (DCs) and macrophages, leading to the overexpression of the inhibitory Fcγ RIIB and to a consequent stimulation of the immunosuppressive regulatory T cells (Tregs) [27]. Experimental evidence confirms that saIVIg Fc provides a protective effect in T cell-mediated and antibody-mediated autoimmune diseases [26]. Sialylation might induce conformational changes in IgG molecules that decrease the binding affinity to FcγRs, but increase that to other receptors, such as SIGNs [28, 29]. **Recent studies have questioned the role of the FcγRIIBs as well as of the sialylation of the Fc fragments in the anti-inflammatory effects of IVIg. A proposed mechanism based on experience from animal models postulates that sialylated Fc fragments may act on DC-SIGN receptors and promote the release of IL-33, a molecule which stimulates basophils that produce IL-4. The therapeutic effect of IVIg and the role of Fc fragments have been confirmed in a murine arthritis-model; however, the results did not support the involvement of sialylation or that of the basophils in the mechanism of action of IVIg therapy [30]. In line with this, in rheumatic patients, IVIg induced the release of IL-33, which was, however, not**

associated with the stimulation of basophils, and IL-4 could be hardly detected in the plasma of patients following IVIg therapy. The source of IL-33 was unclear, as its production could not be shown from DC-SIGN+ human innate cells. These results suggest that the therapeutic effect of IVIg is independent of sialylation and basophils [31]. In an *in vitro* study on human macrophages, the IVIg-induced inhibition of the phagocytosis of IgG-opsonized blood cells was independent of Fc sialylation and the upregulation of the FcγRIIBs, but improved when preparations with an increased binding capacity to the low-affinity FcγRs, such as the IgG dimers, were used [32].

The regulatory action on T cells and the effect on cytokines are presumed to be likewise sialylation-independent [33, 34].

4.2. Fc-independent mechanisms of action of IVIg

Mechanisms independent of the Fc pathway have also been proposed underlying the therapeutic action of IVIg; however, a co-operation of Fab and Fc regions in these mechanisms cannot be fully excluded.

4.2.1. Anti-idiotype antibodies

Antibodies in the IVIg preparations can neutralize toxins and pathogens as well as pathogenic antibodies with their F(ab') portion. *In vitro* experiments demonstrate that F(ab') or F(ab')2 IVIg fragments *per se* can neutralize autoantibodies. The anti-idiotype antibodies present in the IVIg preparations can neutralize pathological antibodies such as the anti-ganglioside antibodies in **Guillain-Barrė syndrome** (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), and the anti-acetylcholine receptor antibodies in myasthenia gravis. In certain autoimmune disorders with a deficiency in the idiotype network, IVIg therapy can restore the normal function. The idiotype-anti-idiotype interaction may presumably be a mechanism through which IVIg modifies the autoimmune disease process. The amount of anti-idiotype antibodies is very low in the IVIg preparations, suggesting the involvement of other more complex mechanisms in addition to a neutralizing action, such as an immune-modulating function or an inhibitory effect on B cells

through FcγIIRBs [7].

4.2.2. Anti-complement effect

Soluble IgG from the IVIg preparation competes with surface-bound IgG for C3b, and thereby inhibits the complement-mediated lysis of the target cells. This is of importance in complement-mediated diseases, such as GBS [35]. In dermatomyositis, IVIg forms complexes with C3 and hence prevents its activation. As a result, it prevents the formation of the C5b/C9 membrane attack complex (MAC) responsible for the inflammation of intramuscular capillaries [15]. Reductions in the expression of intercellular adhesion molecule (ICAM) and major histocompatibility complex (MHC) I were observed following IVIg treatment, and a down-regulation of cytokines, complement factors, and adhesion molecules was evidenced as well. IgG can also non-covalently bind to C3a and C5a, which results in the diminishment of the pro-inflammatory effects [36].

IVIg is capable of neutralizing anaphylatoxins, such as C3a and C5a, and of suppressing the complement-induced release of pro-inflammatory thromboxane B2 and histamine. The neutralization of C3a and C5a was observed to occur in cells treated with Fab and whole IVIg, and was found to be independent of the Fcγ fragments. In fact, both the F(ab')2 and the Fc fragments play roles in complement inhibition. C3b and C5b bind to the Fc region, whereas C3a and C5a are neutralized by the F(ab')2 fragments present in the IVIg, with the latter resulting in the inhibition of MAC formation and a subsequent damage to the target tissue [37].

4.2.3. Cell-penetrating antibodies

In addition to an FcR-mediated endocytosis, IVIg can be internalized also in an FcR-independent manner by immune cells. Cell-penetrating antibodies (CPAs) are known to play roles in certain autoimmune diseases. Among them, the anti-nuclear CPAs in SLE are capable of inducing apoptosis and modulating the expression of nuclear factors and cytokines [38]. However, a recent study showed that IgG present in the IVIg preparations can penetrate into a variety of cell lines in an energy-independent manner, in a process mediated by the F(ab') fragment. Up to 2% of IgGs in

IVIg have been demonstrated to be CPAs. These natural CPAs might modulate cellular activities; however, their exact role is still incompletely understood, necessitating further investigations [39].

4.3. IVIg alters dendritic cell and regulatory T cell function

IVIg can inhibit the maturation and differentiation of DCs and induces tolerogenic phenotypes, an effect mediated by both the Fab and the Fc fragments. The mechanism through which these effects occur have not yet been completely elucidated. IVIg is presumed to activate FcγR by triggering the immunoreceptor tyrosine-based activation motif (ITAM). The presence of FcγRIIB inhibitory receptors was found to be indispensable for these effects of IVIg in different autoimmune disorders. No interaction exists between this receptor and IVIg; however, the upregulation of the FcγRIIB on DCs and APCs is essential for the suppressive effect of IVIg on DC activation [40].

Tolerogenic DCs express a low amount of co-stimulatory molecules (CD40, CD80, and CD86), and are characterized by a reduced expression of MHC class II (and thereby a decreased ability to present antigens), an increased expression of co-inhibitory molecules (PD-L1, CTLA-4), and an increased production of inhibitory cytokines [41]. DCs present antigens to T cells. Naive T cells are induced via cell-cell contact and by soluble mediators provided by an APC, and receive signals via the T cell receptors (TCRs), costimulatory molecules, and cytokine receptors [26]. DCs act on naive T cells and induce their evolution into distinct T cell subsets. In animal experiments, IVIg inhibits the differentiation of CD4+ cells to T helper 1 (Th1) and Th17 cells, and induces an expansion of the immune-suppressor Treg cells [42-44]. Polyclonal IVIg predominantly targets CD11c+ DCs, a mechanism demonstrated to be sufficient for the peripheral induction of Tregs in IVIg-treated mice [45].

Tregs maintain tolerance to self-antigens and preserve the homeostasis of the immune system. Two main types of Tregs are distinguished: naturally occurring Tregs (nTregs), generated in the thymus, and peripherally induced Tregs (pTregs), originating in peripheral lymphoid tissues from CD4+ cells. Tregs express specific markers. The transcription factor, forkhead box P3

(FOXP3), provides anti-inflammatory functions and its expression enables the switch of T cells towards a regulatory phenotype. Other markers include CD25 (a high-affinity interleukin-2 (IL-2) receptor), human leukocyte antigen-DR (HLA-DR), CTLA-4, GARP, TIGIT, a CD28-related protein, and Fc receptor-like protein 3 (FCRL3; an Fc-receptor-like glycoprotein) [46].

IVIg administration increases the number as well as the suppressive function of Tregs. Treg induction by IVIg can be explained by a direct interaction of IgG with T cells and with other targets, such as APCs and cytokines. In cell cultures, IVIg increases the expression of FOXP3 [47, 48]; furthermore, epitopes from both the Fc and Fab fragments (Tregitopes) can activate FOXP3, resulting in Treg activation and expansion [49]. The prostaglandin E **(PGE)** pathway might also play a role in the IVIg-induced changes in Treg function, **as the IVIg-induced increase in the number of Tregs is associated with an increase in circulating PGE2 levels. PGE2 can inhibit natural killer (NK) cells, granulocytes, and macrophages, and impairs the ability of DCs to stimulate Th1 cells. PGE2 induces the expansion of Tregs and improves their immunosuppressive function [50].** Tregs can provide immunological tolerance in autoimmune diseases; however, Treg infusion therapy has not yet been successfully implemented; therefore, therapies targeting Treg expansion and activation are of increasing interest [51]. **The reciprocal regulation between the inhibition of Th1 and Th17 cells and the expansion of FOXP3+ Treg cells is independent of sialylation, according to results gained from an experimental autoimmune encephalitis (EAE) model [33]. Th17 cell expansion and activation might be inhibited by the Fab fragments, which could also induce Treg expansion through PGE2 [33]. In cell culture, IVIg and SCIg exerted inhibitory effects on T cell activation and suppressed several effector cytokines; however, these effects did not require sialylation and were independent of B cells or monocytes [34].**

4.4. Effects on cytokines and chemokines

IVIg exerts anti-inflammatory effect through a modulation of the production of cytokines and cytokine antagonists [52]. IVIg modulates cytokine production in monocytes, but also acts on T

helper cell types (Th1, Th2, and Th17). IVIg upregulates the production of inhibitory cytokine IL-10 in DCs, and downregulates pro-inflammatory cytokines, such as interferon-γ (IFNγ), tumor necrosis factor-α (TNFα), and IL-12 [53]. IVIg also acts on chemokines and influences chemokine receptor expression on circulating leukocytes, contributing to the homeostasis, recruitment and trafficking of inflammatory cells, including Tregs, to different tissues. IVIg treatment results in the downregulation of ICAM-1, complement C1q, IL-22, transforming growth factor-1 (TGF-1), and the upregulation of the chemokines, CXCL11 and CXCL and a number of immunoregulatory genes [52].

4.5. Effects on apoptosis

IVIg can inhibit cell activation and can even induce apoptosis in various different types of immune cells, including macrophages, NK cells, DCs, and T and B lymphocytes [54]. IVIg preparations contain agonist and antagonist antibodies to the CD95 receptor, and their effect proved to be dose-dependent in *in vitro* studies. While low doses inhibit CD95-mediated neutrophil apoptosis, the high doses induce it [55]. Anti-CD95 antibodies presumably have an immunomodulatory effect that depends on the applied IVIg dose, probably on the disease state, as well as on the proportion and avidity of the agonistic and antagonistic antibodies [56].

5. Adverse events and safety considerations

Adverse events are related to IVIg antigenicity, traces of IgA, the presence of aggregates, pathogenic antibodies, and molecules not removed during fractionation, such as procoagulants or kallikreins, and to the applied stabilizers. The side effect profile varies from one brand to another. Adverse events can be classified according to the localization (local and systemic), the severity (mild, moderate, and severe), as well as the occurrence (immediate, delayed, and late) [57]. See also Table 3.

Local side effects are rare, whereas systemic side effects occur in 20-40% of patients and 5-

15% of infusions [58], with higher rates (55% and 18% respectively) observed in doses of 1-2 g/kg [59].

Immediate side effects occur within 6 hours and are usually mild, with the exception of anaphylactic/anaphylactoid reactions, which can be life-threatening. Delayed reactions occur within 1 week, whereas late reactions, such as infections and interference with vaccine effectiveness, develop weeks or months after the infusions [57].

Side effects are mostly transient and mild, estimated to occur between 1 to 15% of infusions, and many of them can be reversed even by temporarily stopping or slowing the infusion [60]. The most frequently encountered adverse effects include headache, chills and fever, nausea, mild hypotension or hypertension, and mild arthralgias. According to a meta-analysis of randomized trials, headache, chills, fever, and nausea were reported in 82 out of 167 IVIg-treated participants, corresponding to a 49% of side effect rate, a frequency statistically indifferent from that observed in the groups treated with prednisolone or plasma exchange (PE). The severe side effects include aseptic meningitis, anaphylactic shock, thrombosis, stroke, and impairment of renal function. The incidence of severe adverse events was less than 0.5% for 26,000 infusions, and less than 4% in 2554 participants in a postmarketing pharmacovigilance study **[61]**. In randomized trials, the occurrence of serious side effects was 6%, and was not statistically significant as compared to that encountered in participants treated with prednisolone (7%), PE (12%), or placebo (7%). It is difficult to compare the side effects of different therapeutic regimens in clinical trials, as patients treated with PE are less in number compared to those treated with IVIg, rendering the results less accurate. On the other hand, most of the trials were not designed long enough for steroid-related side effects to develop [62].

5.1. Safety considerations

Risk factors for IVIg-related thrombotic adverse events include advanced age, immobilization, hyperviscosity, a history of arterial or venous thrombosis, the presence of cardiovascular risk factors, and indwelling vascular catheters; however, thrombosis can occur even

in the absence of any apparent risk factors. Mechanisms underlying IVIg-related thrombosis include hyperviscosity and the presence of procoagulant antibodies or coagulation factors, such as activated factor XI, in the IVIg preparation [63, 64]. IVIg-related thrombosis is arterial in 80% of the cases, and occurs within hours to days [57]. Venous thrombotic adverse events, such as deep venous thrombosis or pulmonary embolism, generally develop days to weeks after infusion [65]; furthermore, the occurrence of cerebral venous sinus thrombosis has also been reported [66]. A proper hydration and the administration of IVIg at the minimum dose effective and the minimum rate of infusion practicable are factors essential in the prevention of IVIg-related thrombosis [67].

Patients with IgA deficiency and with antibodies to IgA are at risk to develop anaphylactic reactions and hypersensitivity due **to the IgA present in IVIg products. In the newer preparations, however, only traces of IgA are present, and this problem is less prevalent** [68].

Hemolytic anemia is an adverse event developing due to intravascular hemolysis or an enhanced sequestration of red blood cells, and is associated with risk factors such as higher doses of IVIg applied, the presence of an underlying inflammation, and a non-O blood group [69]. **In a review on five cases of GBS and MFS, all three patients with non-O blood group developed hemolytic anemia requiring blood transfusion. The authors concluded that in these patients, the risk of hemolytic anemia is increased when high doses of IVIg are administered over a short interval of less than 2 weeks [70].**

In predisposed patients, acute renal failure, renal dysfunction, and nephrosis may occur more commonly in case the preparation contains sucrose or maltose. Slow infusion rate, monitoring of renal function, and adequate hydration need to be ensured [71].

Aseptic meningitis has also been reported as an IVIg-related adverse event; however, it is usually mild and resolves without sequelae [72]. **PRES may occasionally occur after IVIg infusion [73, 74]. This condition should be suspected in patients developing visual disturbances, confusion, and seizures following IVIg infusion, and the diagnosis can be confirmed by MRI. In such cases, improvement was reported with PE therapy [75, 76].**

Other possible side effects include vasospasm, vasculitis, enterocolitis, eczema, hyperproteinemia, hyponatremia, and mild leukopenia [72]. IVIg is a plasma product and, therefore, has the inherent potential risk of transmission of different infectious agents, such Parvovirus B19 or the prion protein; however, no cases of the latter have so far been reported [77]. IVIg preparations can influence the response to live virus vaccines. Though IVIg is not contraindicated in pregnant women, it should be used with caution. Each IVIg preparation is a different compound, and the safety considerations should be taken into account as regards the particular preparation.

6. Background and clinical evidence for the efficacy of IVIg in immune-mediated polyneuropathies

6.1. Guillain-Barrė syndrome

6.1.1. Clinical presentation.

GBS is an acute ascending-type symmetrical sensorimotor polyneuropathy. The incidence is 0.81-1.89 per 100,000 person-year [78]. Most of the cases are characterized by demyelination, termed acute inflammatory demyelinating polyneuropathy (AIDP), however, more severe axonal-type variants also exist. See Table 4 for the classification of immune-mediated polyneuropathies [79, 80]. Patients have predominantly motor signs, but pain and sensory impairments also frequently occur. Up to 10-20% of patients have signs of cranial nerve involvement and a comparable proportion of patients present with concomitant autonomic involvement, manifesting predominantly in tachycardia, hypertension, rapid changes in blood pressure, bladder dysfunction, and gastrointestinal dysfunction. Sudden death can also occur. The diagnosis is established on clinical grounds, supported by electroneurography (ENG), which also yields the type of nerve damage and, thereby, the subtype of GBS, and by the evidence of an elevated protein count without pleocytosis in the cerebrospinal fluid (CSF), a phenomenon also referred to as *albuminocytologic dissociation*. Serological evidence of the triggering infection and testing for anti-ganglioside

antibody also add to the diagnosis. The severity, the clinical course, and the outcome are variable, and about 20% of patients remain with some extent of long-term disability. Although GBS is considered a monophasic disease, about 5-10% of patients can succumb [79, 81].

6.1.2. Pathomechanism and mechanism of action of IVIg

The pathomechanism of GBS is complex and involves cellular and humoral mechanisms. The presumed background of GBS is the *molecular mimicry,* induced by a pathogen. Indeed, antibodies against Campylobacter jejuni or other pathogens, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), Mycoplasma pneumoniae, or Haemophilus influenzae, have been shown to cross-react with self-antigens [82, 83]. In a study, up to 43 % of patients had serologic evidence of an infection [84]. Patients with a proper anti-idiotype response can neutralize the antigen-binding site of the antibodies secreted against the pathogen; however, patients with an ineffective anti-idiotype response will continue to produce antibodies that will cross-react with the nerve tissue [15]. Antibodies against gangliosides have been detected in some 60% of GBS patients with evidence of previous infections [84].

Anti-GM1 and anti-GD1a antibodies were identified in acute motor axonal neuropathy (AMAN) patients [85], whereas anti-GQ1b antibodies were found in 65% of acute ataxic form and also in Miller Fisher syndrome (MFS) [86]. Antibodies against nodal proteins, such as neurofascin **(NF)** and gliomedin, were identified in **some** AMAN and AIDP patients [87]. **NF has a neuronal isoform (NF186) with a role in sodium channel clustering and a glial isoform (NF155) necessary for paranodal junction formation. Autoantibodies to NF can be detected in some 4% of patients with AIDP and CIDP. Most antibodies are of IgG1, IgG3, and IgG4 subtypes [88]. In 52 patients with GBS, the serum NF-IgG levels were significantly higher compared to controls. NF antibodies are presumed to impair sodium channel function, disrupt axonal conduction at the nodes, lead to axonal injury, and impair remyelination [89].** Anti-GM1 antibodies cause a reversible impairment of nodal function, affecting the axolemma. Antibodies

against Schwann cell antigens are presumed to be responsible for the classical GBS form, whereas antibodies against the axolemma are proposed to cause the axonal variants. The nodes of Ranvier may also be disrupted, thereby exposing axonal and myelin antigens, which lead to overlapping clinical forms. The binding of the pathogenic antibody is followed by complement activation and complement-mediated nerve cell damage [90]. **A decreased number and an altered function of Tregs are involved in the impairment of immunologic self-tolerance in GBS. Acute-phase AIDP and AMAN patients have been shown to exhibit reduced amount of Tregs. FOXP3 expression and the suppressive function of Tregs were found preserved in certain studies, suggesting that a reversible decrease of functionally intact Tregs can be responsible for the self-limited monophasic disease course [91]. More recent results revealed that not only the number of FOXP3+ Tregs is decreased, but their function is also defective. Furthermore, GBS patients have increased numbers of Th1, Th17, and Th22 cells, especially in the acute phase of the disease [92, 93]. The elevated Th22 cell count correlates with disease severity; however, it does not correlate with the subtype of the disease. GBS patients have higher levels of the pro-inflammatory molecules IL-17 and IL-22 [93].**

The therapeutic action of IVIg in GBS **is complex. It is partly attributed** to the reduction of the amount of pathological autoantibodies through *anti-idiotypes,* in a dose-dependent manner. Subsequently, no complement activation and hence complement-mediated cytotoxicity occur. **IVIg can prevent the binding of pathogenic antibodies, such as the anti-ganglioside antibodies, to the target antigen.** Other mechanisms, such saturation of FcRn, **alteration of FcR expression or an effect on the altered cytokine pathway might also be involved. In this respect, IVIg has been demonstrated to increase the amount of circulatory TGFβ in GBS patients. IVIg has also been shown to have an anti-complement effect; it decreases the serum levels of C1q and C4, and diminishes the complement activity** [11, **94**]. **IVIg has also been evidenced to modify T cell response in GBS [94, 95]. As discussed above, a reduction of Tregs and an imbalance of the regulation of the different T cell subtypes occurs in GBS. IVIg therapy significantly increases**

the number of Tregs in GBS patients along with the improvement of the neurological signs [91]. Furthermore, IVIg induces a proliferation of pre-existing FOXP3+ Treg cells and improves their suppressive function; however, after four weeks, the amount of Tregs returns to the pre-treatment levels [92]. On the other hand, IVIg therapy reduces the number of Th1, Th17, and Th22 cells, as well as the production of effector molecules, such as IL-17, IL-22, IFNγ, and GM-CSF [92, 93]. This results in a reciprocal regulation of Th1/Th17 and Treg, a process dependent on the up-regulation of the pro-inflammatory cytokine IL-10, capable of inhibiting Th17 cell function and stimulating Tregs. IVIg also interacts with DCs and consequently stimulates Tregs through different pathways, such as the induction of cyclooxygenase-2-dependent PGE2. In GBS patients, increased levels of PGE2 were observed following IVIg treatment [50]. IVIg may also neutralize inflammatory cytokines and can inhibit B cells, which effects might be of importance in the axonal forms of GBS [92].

6.1.2. Treatment of GBS

PE has been used in the treatment of GBS since the '80s. On the other hand, steroids have been proven to be ineffective [79]. The list of clinical trials that examined IVIg for the treatment of GBS is provided in Table 5 [96-105].

6.2. Chronic inflammatory demyelinating polyneuropathy

CIDP is a chronic, acquired, immune-mediated polyneuropathy, associated with a chronic progressive or relapsing-remitting course. CIDP is a rare disease, with a prevalence rate between 1 and 9 per 100,000 population, increasing with age [106].

6.2.1. Clinical presentation

The classic form of CIDP has a symmetric presentation with the motor involvement being more severe than the sensory symptoms. Weakness affects both proximal and distal muscles. Furthermore, up to 20% of patients have cranial nerve and bulbar involvement as well. The sensory signs include pain, and impaired vibration and position sense, leading to an ataxic gait. Autonomic

involvement may occur in more severe cases [80]. ENG and nerve biopsy show signs of demyelination, but the indication for the latter is getting restricted to cases with an unclear diagnosis. CSF analysis reveals albuminocytologic dissociation. There are several diagnostic criteria for CIDP; relying on the clinical presentation, ENG results and CSF analysis, the most widely used one is the European Federation of Neurological Societies (EFNS) criteria [107]. CIDP variants differ from the classical form in terms of clinical presentation, pathomechanism, ENG alterations, and the response to therapy [108].

6.2.2. Pathomechanism and mechanism of action of IVIg in CIDP The pathomechanism of CIDP has not yet been fully elucidated. An autoimmune inflammation is presumed to be responsible for the demyelination of the nerve roots and nerve trunks. Although, it is not clear weather the inflammation is the attributable to humoral or cellular immune mechanisms, they are presumed to act synergistically to cause damage to the peripheral nerves.

Demyelination, onion bulb formation, axonal degeneration, and perivascular/endoneurial macrophage and T cell infiltration can be detected in sural nerve biopsy specimens. Besides removing debris, macrophages play a role in the development of inflammation. An upregulation of MHC II molecules necessary for antigen presentation and that of the costimulatory molecules, B7-1 and B7-2, occurs in macrophages and other inflammatory cells. Furthermore, a secretion of pro-inflammatory cytokines has also been evidenced [80]. All these result in the activation of T cells. A clonal expansion of CD8+ cytotoxic T cells has been observed in sural nerve biopsy specimens; whereas, on the other hand, Tregs are reduced in number and are less effective [109, 110]. **In CIDP patients, the activation of cytotoxic CD8+ T cells is more pronounced than that of the CD4+ cells, suggesting an important role of CD8+ cells in the pathomechanism of the disease [95].**

Nerve biopsies reveal the disruption of the blood-nerve barrier (BNB), a phenomenon considered to be a critical step in the development of inflammation. Activated T cells adhere to endothelial cells via adhesion molecules (such VCAM-1 and ELAM-1) that are upregulated due to

the inflammatory process through the action of cytokines and chemokines. As a result, T cells cross the BNB and influence the permeability of molecules restricted in normal conditions, such as antibodies [80].

Immunoglobulins and complement deposits on Schwann cells can also be observed in biopsy specimens, as a proof of the involvement of humoral mechanisms. Although neither the presumed infectious trigger of the autoimmune response, nor the putative antigen on the Schwann cell or the myelin is known, the presence of anti-ganglioside antibodies as well as the beneficial effect of PE together support the essential role of antibody-mediated pathomechanism **[15].** Experimental evidence suggests that the target antigen might be located in the compact myelin (with potential targets including myelin proteins P0, P2, peripheral myelin protein 22 (PMP22), and connexin) or in the nodal, paranodal, or juxtaparanodal regions. Antibodies have been detected against the nodal cell adhesion molecules (CAMs) gliomedin and neurofascin-186 (NF186), as well as against the paranodal contactin-1/caspr-1 complexes bound to the glial neurofascin-155 (NF155) on the Schwann cells [90, 111, 112]. According to a study, 30% of patients have a serum IgG that can bind to the paranode or the node of Ranvier, and the disruption of nodal and paranodal region has also been detected in biopsy specimens [113].

There are CIDP patients with a severe form of the disease who exhibit antibodies of the IgG4 subtype to NF155 [114]. IgG4 antibodies are considered to be anti-inflammatory due to their reduced affinity to complement and Fc receptors; however, they can become pathogenic through an antigen-blocking mechanism via blocking the functions of the target antigen [111]. Patients carrying IgG4 auto-antibodies against contactin-1 generally present with a disease form characterized by a subacute onset, a severe disease course, sensory ataxia, and are associated with a poor response to IVIg and a better outcome with corticosteroid therapy, suggesting a different underlying pathomechanism [115]. **A dysregulation of the inhibitory FcγRIIB receptor expression occurs in CIDP patients. In untreated patients, the expression levels of FcγRIIB on B cells are lower than in healthy controls, and its upregulation does not occur or cannot be maintained as the**

cells develop from the naive state to memory cells. 43% of CIDP patients carry a rare FcγRIIB promoter polymorphism that results in a reduced promoter activity; however, its role in disease pathomechanism has not yet been fully elucidated [116].

As detailed above, IVIg therapy can theoretically interfere with several steps and mechanisms described in the above sections discussing the pathomechanism of CIDP. However, the symptomatic effect of IVIg lasts only for about 3 weeks in most of the CIDP cases, and repeated doses are needed at different time intervals for each patient. These dose-dependent effects suggest that IVIg might act through the action of anti-idiotype antibodies, **but several other mechanisms of action have been implicated. Indeed, IVIg therapy regulates FcRs in CIDP, as it upregulates FcγRIIB expression on B cells and monocytes, resulting in an anti-inflammatory effect [116]. Another effect of IVIg is the reduction of activated T cells, a cell type considered to play an important role in the pathogenesis of the disease [95]. In addition, IVIg also targets B cell-activating factor (BAFF), a molecule released from DCs, monocytes, and granulocytes, and plays essential roles in B cell homeostasis, maturation, survival, and antibody production, and can also regulate T cells. BAFF plays a role in several autoimmune diseases, as its overexpression leads to the survival of autoreactive B cells and to auto-antibody production. In CIDP patients, the serum level of BAFF is elevated [117, 118]; furthermore, IVIg reduces BAFF expression and transcription, inhibits BAFF release in monocytes, and diminishes elevated BAFF levels in the serum of CIDP patients. Its action on BAFF is implicated among the FcγR-independent mechanisms of action of IVIg [117]. IVIg preparations contain antibodies against BAFF, which can be responsible for the short-term decrease of BAFF levels detected after IVIg therapy. On the basis of this, BAFF levels could be used as biomarkers of therapeutic response [118].**

6.2.3. The treatment of CIDP

The therapy of CIDP includes corticosteroids, PE, IVIg, and immunosuppressive agents,

according to the EFNS guideline [107]. It is recommended to start with steroids or IVIg as first-line therapy, and switch to other therapeutic options in case of insufficient clinical response. Although steroids are considered as first-line therapy for CIDP, their efficacy has only been investigated in a single randomized-controlled trial (RCT) [119]. PE was shown to be effective in two RCTs in about 33-66% of patients; however, side effects related to the therapy itself or the maintenance of the venous access were frequently reported [120].

Several clinical trials proved the efficacy of IVIg for the treatment of CIDP. RCTs found comparable short-term efficacy of IVIg as compared to oral steroids [121] and to PE [122]. IVIg proved more efficacious as compared to placebo in earlier RCTs [123-126]. A meta-analysis comparing the effect of IVIg to placebo, corticosteroid therapy, and PE, concluded that the efficacy in terms of muscle strength and the reduction of disability is short-term, lasting only for 2-3 weeks [127].

The ICE trial was an RCT that compared the long-term efficacy and safety of IVIg-caprylate to placebo in a total of 117 patients with CIDP. It concluded that the overall short-term improvement achieved with IVIg, as regards the improvement in the Inflammatory Neuropathy Cause and Treatment (INCAT) score and other efficacy measures, was significantly better as compared to placebo. The extension study revealed the long-term efficacy of IVIg-caprylate given every 3 weeks as a maintenance therapy for patients with CIDP. On the other hand, therapy withdrawal increased the risk of a relapse. The study also showed that the loading dose of 2 g/kg and the maintenance dose of 1 g/kg can be given safely in short time frames of 2 and 1 day, respectively, that might also be a cost-saving approach [128].

The PRIMA study investigated efficacy and safety of Privigen in patients with CIDP in a prospective, single-arm, open-label Phase III trial. Patients received the standard induction dose of 2 g/kg and maintenance doses of 1 g/kg every 3 weeks. The responder rate was above 60%, and improvements could be observed in the INCAT score, the grip strength, and the Medical Research Council (MRC) sum score. The study also proved that patients who were non-responders after 6

weeks may respond later to IVIg therapy, and a longer period should be considered in order to declare a person non-responder to IVIg. Adverse events were mild to moderate, but cases of hemolysis occurred [129].

In 2013, an extensive meta-analysis evaluated the RCTs assessing the efficacy of IVIg for the treatment of CIDP. In this analysis, IVIg lead to a significant improvement in disability scores within 6 weeks of treatment initiation. In order to compare the results of the trials, the different disability scores applied were transformed into the modified Rankin score, and the overall result demonstrated an improvement in the IVIg-treated patients. Long-term benefit was revealed in only one trial included in the meta-analysis, which has already been discussed in detail above [128]. There was no significant difference between IVIg and PE, and between prednisolone and IVIg in terms of therapeutic benefit in CIDP [62].

A retrospective analysis of the effect of immune therapies in patients with CIDP carried out in Italy concluded that 69% of patients responded to the first-line therapy (corticosteroid therapy or IVIg), whereas 81% responded after switching the therapy in the case of a non-responder state. This study demonstrated that the lack of response to one therapy does not exclude a potential response to another immune therapy. The efficacy of IVIg was slightly higher as compared to corticosteroid therapy, whereas the side effect profile was more favorable as compared to PE [130].

A study conducted on 45 patients compared the efficacy and tolerability of IVIg (0.5 g/kg/day for 4 consecutive days) compared to intravenous methylprednisolone (0.5 g/day for 4 consecutive days) given monthly during a 6-month period. The study concluded that the number of patients having discontinued the therapy was higher in the methylprednisolone-treated group, though the occurrence of side effects did not differ in the two groups. The efficacy of IVIg was superior; however, the number of patients who worsened and required further therapy was higher in the IVIg group [131].

6.3. Disorders mimicking CIDP – multifocal motor neuropathy

There are disorders mimicking CIDP but considered as separate entities due to a different clinical presentation, specific pathophysiologic features, and a different response to therapy as compared to the classic form. Due to length limitations, only multifocal motor neuropathy (MMN) is described in detail in this paper, although other forms also respond to IVIg therapy [108] (Table 4).

MMN is a chronic immune-mediated neuropathy with an asymmetric presentation mostly involving distal upper limbs, without sensory involvement. ENG examination reveals multifocal motor conduction blocks, with preserved sensory conduction [131]. Up to 60% of patients have anti-GM1 IgM antibodies, the presence of which might correlate with disease severity [132, 133]. Over 60% of patients have antibodies against gliomedin or NF186, and some 10% of the anti-GM1-negative patients are positive for anti-NF186 antibodies [134]. Complement activation and an autoantibody-induced complement attack on ganglioside-rich nerve structures are presumed to underlie the pathological changes seen in the peripheral nerves [15]. MMN responds to IVIg therapy; however, it does not respond to PE or corticosteroid treatment [135, 136]. Axonal excitability improves after IVIg infusions, an effect waning in time, however. IVIg is presumed to act in MMN predominantly via complement inhibition [137]. Another possibility is that IVIg exerts its effect through a competitive mechanism by anti-idiotype antibodies. The T1/2 of IgM is short, as it is not recycled by the FcRn, and, therefore, IVIg presumably does not act via an increased catabolism of the pathological antibody. The effect of IVIg lasts for a few weeks, and maintenance therapy is needed for MMN patients.

7. Conclusions

IVIg has a complex but not fully elucidated mechanism of action. The beneficial effect last beyond the half-life, suggesting that it is not simply due to an enhanced passive clearance of or an interference with pathogenic antibodies, but to a complex mechanism involving complement inhibition, interference with the cytokine network, modulation of the expression of Fc receptors, as

well as an effect on DCs, T cells, and B cells. Though neither the specific mechanism of action of IVIg in autoimmune neuropathies nor the pathomechanism of all the affected diseases is fully understood, clinical trials have proven the efficacy of IVIg in these conditions. IVIg is generally well tolerated, being associated with only few severe side effects.

8. Expert opinion

IVIg therapy has a proven efficacy in the treatment of several autoimmune diseases; however, it is a costly and non-specific therapy with a limited access worldwide. IVIg treatment meets several challenges.

The relationship between pharmacokinetics and pharmacodynamics of IVIg in neuromuscular disorders is complex, and is presumed to depend on the mechanisms involved in the disease pathomechanism. This relationship is even more difficult to understand in light of the fact that neither the exact pathomechanism of some of the neurological diseases in which IVIg therapy has been proven to be effective, nor the mechanism of IVIg is fully understood. A rapid onset and the short-lasting, dose-dependent effect are presumed to be the consequence of the competition of the high concentrations of IVIg with the pathological antibody for the binding sites, whereas the late, longer-lasting, and less dose-dependent effect is presumed to be the result of more complex cellular (involving lymphocytes and APCs) and molecular interactions induced by IVIg. In cases where a rapid short-duration response is achieved, most probably due to antibody competition, it is likely that antibodies play the key role in the pathomechanism of the target tissue dysfunction (*i.e.,* nerve dysfunction, or neuromuscular junction dysfunction). Further research is necessary to better understand the mechanisms of action of IVIg and the pathomechanism of immune diseases.

Immune-mediated polyneuropathies are a heterogeneous group of disorders of the peripheral nervous system. Despite the considerable progress in the fields of supportive therapy and immunotherapy, GBS is still a life-threatening disease, which can result in permanent disability in as many as 20% of patients. The chronic forms are difficult to diagnose, and, especially in case of a

delay in the initiation of the therapy, a severe disability and an impairment of the quality of life can ensue. There is still much to do in order to improve the therapy for immune-mediated polyneuropathies. More easier to use diagnostic criteria for daily clinical practice even for non-neurologists might raise the clinical diagnostic yield. The continuous improvement of the prognostic factors in acute polyneuropathies is essential to aid the selection of patients that are at high risk of developing respiratory insufficiency and severe complications. In chronic polyneuropathies, the response to a therapy is sometimes difficult to assess, especially in case of a long-lasting disease with a severe disability at baseline. Future advancements in clinical outcome measures may improve the choice of more individualized therapy. Another challenge is the paucity of specific guidelines on how to tailor IVIg maintenance therapy, and when and how to start tapering the doses in order to offer an effective but also cost-effective therapy. What we see in clinical practice is that patients need an individualized therapy. Some patients experience a wearing off of the effect even before that could be expected on the basis of the T1/2 of IVIg, whereas, in other cases, the effect lasts longer and the patient requires less frequent maintenance infusions. On the basis of these, in a chronic disease such as CIDP, clinical studies are warranted to aid the tailoring of long-term therapy, with special focus on the delineation of the terms of dose reduction and interruption of IVIg treatment. More accurate clinical scores would be of use for the assessment of the therapeutic effect not only in clinical trials but also in the clinical setting. Biological markers of the disease might help to predict the clinical outcome and to identify patients for whom a good or longer-lasting response to IVIg therapy is expected. The revelation of possible correlations between therapy-related serum IgG levels and the observed clinical response might be of help in optimizing the doses and may reduce the expenses. Another approach could be to aim at maintaining a steady serum IgG level to compete with the pathological autoantibody.

The availability of IVIg is limited, the expenses are high, and, in several diseases, a chronic therapy is necessary to maintain the immunomodulatory effect. The better understanding of the mechanism of action of IVIg could open the possibility of the development of disease-specific,

targeted immune therapies, and non-plasma-derived medicines. Tregs can provide immunological tolerance in autoimmune diseases; therefore, therapies targeting Treg expansion and activation are of interest.

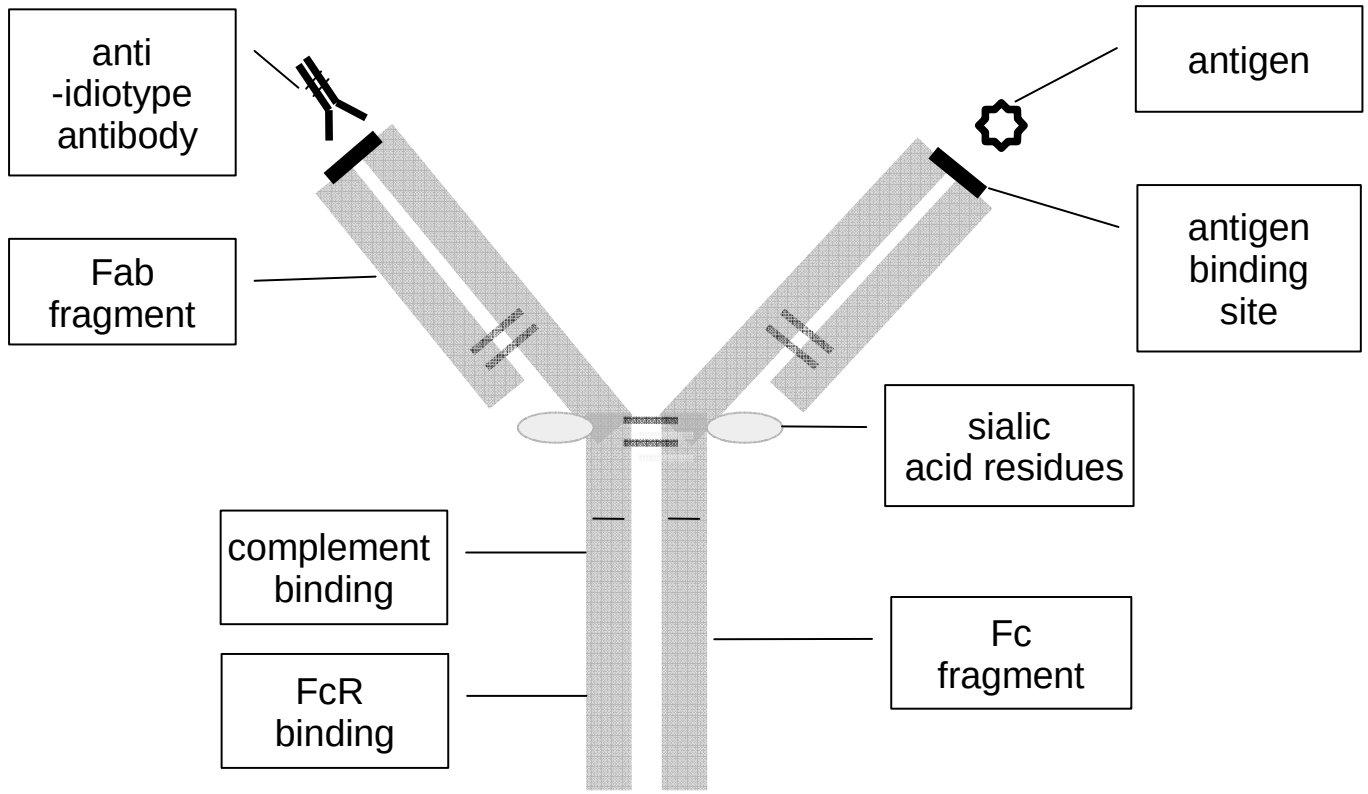
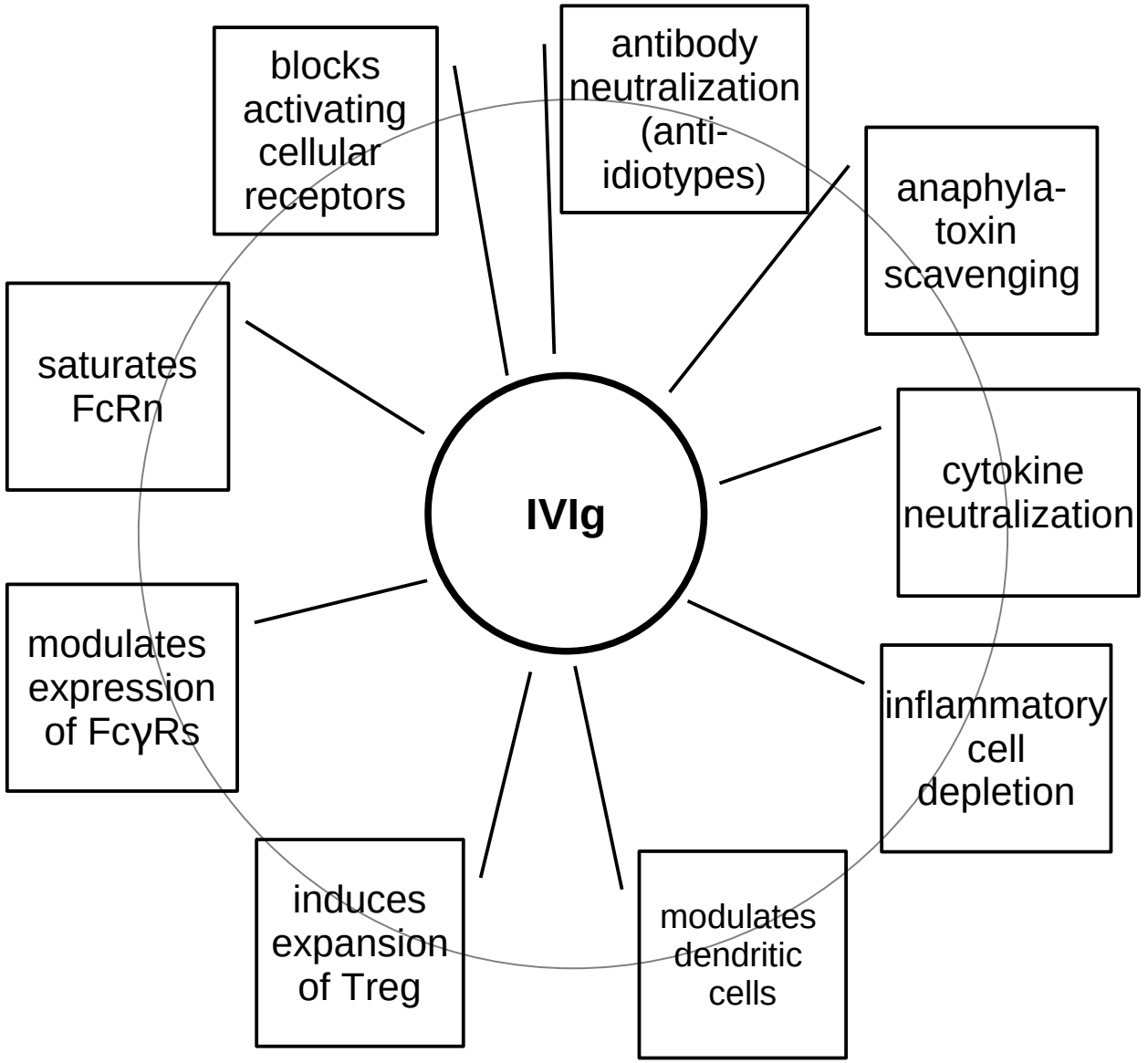


Figure 1. Immunoglobulin G molecule, schematic representation

Figure 2. Mechanism of action of IVIg



Neurological disorders • **CIDP** • **Guillain-Barré syndrome (GBS)** • **Multifocal motor neuropathy (MMN)** • Paraproteinemic (IgM) neuropathy • Dermatomyositis or polymyositis • Myasthenic exacerbation • Lambert-Eaton myasthenic syndrome (LEMS) • Multiple sclerosis, relapsing-remitting (RRMS) • Neuromyelitis optica (NMO) • Stiff-person syndrome • Lennox-Gastaut syndrome • Rasmussen syndrome Infectious diseases • **Pediatric HIV type 1 infection** • Lymphoproliferative disease, treatment of bacterial infections • CMV-pneumonitis in solid organ transplants • Enteroviral meningoencephalitis • Rotaviral enterocolitis • Staphylococcal toxic shock • Thrombocytopenia, secondary to HCV, HIV Other • Asthma (steroid-dependent) • Autoimmune uveitis • Graves' ophthalmopathy • Diabetes mellitus • Rheumatoid arthritis, severe form • Systemic lupus erythematosus • Systemic vasculitides • Recurrent pregnancy loss.	Hematological disorders • **Allogeneic bone marrow transplantation** • **Hematopoietic stem cell transplantation in patients above 20 years** • **Chronic lymphocytic leukemia** • **Common variable immunodeficiency (CVID)** • **Kidney transplantation with a high antibody recipient or with an ABO incompatible donor** • **Primary immunodeficiency disorders associated with defects in humoral immunity.** • **Idiopathic thrombocytopenic purpura (ITP)** • **Kawasaki disease** • Aplastic anemia • Autoimmune hemolytic anemia • Acquired factor VIII inhibitors • Acquired von Willebrand disease • Immune-mediated neutropenia • Refractoriness to platelet transfusion • Thrombotic thrombocytopenic purpura / hemolytic-uremic syndrome • Post-transfusion purpura • Fetomaternal alloimmune thrombocytopenia • Renal transplantation, prevention of acute humoral rejection • Monoclonal gammopathy Dermatologic diseases • Toxic epidermal necrolysis and Stevens-Johnson syndromeDelayed pressure urticaria • Autoimmune bullous diseases

Table 1. Conditions in which IVIg can be used. On-label indications are in bold letters.

Anti-idiotype antibodies against • anti-neutrophil cytoplasmic antibody • anti-DNA • anti-acetylcholine receptor • anti-factor VIII • anti-thyreoglobulin • anti-GAD • anti-ganglioside • anti-HLA
Antibodies against receptors, such as: • CD5 • CD95 (FAS) • CD95 ligand (FASL) • sialic acid-binding immunoglobulin-like lectin 8 (SIGLEC8) on eosinophils • SIGLEC9 on neutrophils • T cell receptors (TCRs)
Antibiodies against • blood group antigens • **cytokines** • B cell-activating factor (BAFF) • a proliferation-inducing ligand (APRIL) • adhesion molecules involved in leucocyte trafficking • anaphylatoxins (C3a, C5a)

Table 2. Antibodies present in IVIg preparations with potential importance in the immunomodulatory effect.

	Mild	*Moderate*	*Severe*
Immediate	local pain, swelling headache myalgia, arthralgia nausea, vomiting hypotension, hypertension tachycardia fever, chills fatigue	-	anaphylactic reactions
Delayed	neutropenia hyponatremia	headache aseptic meningitis anemia eczema	renal failure nephrosis tubular necrosis thrombosis colitis **PRES**
Late	-	interference with vaccines	infectious diseases

Table 3. IVIg-related adverse events. See text for references

Form	*Nerve conduction*	*Antibodies against*
Acute		
GBS (AIDP)	demyelinating	GM2, GQ1b, NF186
Miller Fisher syndrome	demyelinating	GQ1b, GT1a
acute motor axonal (AMAN)	axonal	GM1a, GM1b, GD1a, GalNAc-GD1a, NF186
acute motor and sensory axonal (AMSAN)	axonal	GM1, GD1a
pharyngeal-cervical-brachial variant	demyelinating	GQ1a
Chronic		
CIDP	demyelinating	Presumed: gliomedin, NF186, paranodal contactin-1/caspr-1 complex bound to glial NF155, NF155
pure motor CIDP	demyelinating	not known
sensory CIDP	demyelinating	not known
distal acquired demyelinating sensory (DADS)	demyelinating	MAG
multifocal acquired demyelinating sensory and motor (MADSAM) (Lewis Sumner)	demyelinating	not known
axonal variants	axonal	not known
focal CIDP	demyelinating	not known
CIDP mimics		
Multifocal motor neuropathy with conduction block (MMN)	demyelinating	GM1
Paraprotein associated CIDP	demyelinating/axonal	MAG, (IgM), not kown (IgG, IgA)
Chronic ataxic neuropathy with ophthalmoparesis, M protein, cold agglutinins and disialosyl ganglioside antibodies (CANOMAD)	demyelinating	disialosyl ganglioside
Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS)	demyelinating/axonal	not known (IgG, IgA paraprotein)

Table 4. Classification of immune-mediated polyneuropathies.

Comparison of IVIg vs supportive treatment or dexamethasone							
Type	*Number of patients (age)*	*Dose of IVIg*	*Comparator*	*Endpoint*	*Recovery time (d)*	*Result*	*Ref.*
Quasi-randomized, single-center, parallel-group	9 vs 9 (< 18 y)	1.0 g/k for 2 days	supportive treatment	days for unaided walking	15 vs 24.5	IVIg was superior	**99**
Randomized, single-center, parallel-group	20 vs16 (< 18 y)	0.2-0.3 g/kg for 5-6 days	dexamethasone (4-5 mg for 5-6 days)	days to improve on disability scale	17.1 vs 24.8 (IVIg vs dexamethasone)	IVIg was superior	**104**
Randomized, multicenter, parallel-group	14 vs 7 (< 18 y)	1.0 g/kg for 2 days	no treatment	days to improve on disability scale	8 vs 32	IVIg was superior	**100**

Comparison of IVIG vs PE							
Type	*Number of patients*	*Dose of IVIg*	*Dose of PE*	*Follow-up*	*Endpoint*	*Result*	*Ref*
Randomized, national, multicenter, parallel-group	150 adults and children	0.4 g/kg for 5 days	200-250 ml/kg	4 weeks	median days to improve one grade point: 27 vs 41	IVIg was superior	**103**
Randomized, single-center, parallel-group	50 adults	0.5 g/kg for 4 days	200-250 ml/kg	no data	multiple outcome measures	NS	**96**
Randomized, international, multicenter, parallel-group	379	0.4 g/kg for 5 days	250 ml/kg	4 weeks	improvement on a disability scale	NS	**102**
Randomized, multicenter, parallel-group	23 vs 24	0.4 g/kg for 5 days	200-250 ml/kg	4 weeks	improvement on a disability scale	NS	**101**
Randomized, multicenter, parallel-group	25 vs 26	0.4 g/kg for 5 days	200-250 ml/kg	4 weeks	improvement on a disability scale	NS	**97**
Randomized, single-center, parallel group, ICU	20 vs 21	0.4 g/kg for 5 days	200-250 ml/kg	4 weeks	median days in ICU: 13 vs 11	NS	**98**

Table 5. Main characteristics of clinical trails with IVIg

Conflict of interest

The authors declare that they have no conflict of interest and have received no payment in preparation of their manuscript.

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List of abbreviations

AIDP	acute inflammatory demyelinating polyneuropathy
AMAN	acute motor axonal neuropathy
APC	antigen presenting cell
C1q	complement 1q
CD22	cluster of differentiation-22
CIDP	chronic inflammatory demyelinating polyneuropathy
CMV	cytomegalovirus
CPA	cell-penetrating antibodies
CSF	cerebrospinal fluid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CXCL11	C-X-C motif chemokine 11
CXCL	chemokine (C-X-C motif) ligand
DC	dendritic cell
EBV	Epstein-Barr virus
EFNS	European Federation of Neurological Societies
ELAM-1	endothelial-leukocyte adhesion molecule-1
ENG	electroneurography
Fab	variable region
Fc	constant fragment
FcγR	Fcγ receptor
FcRn	neonatal Fc receptor
FCRL3	Fc receptor-like protein 3
FOXP3	transcription factor, forkhead box P3
GARP	glycoprotein A repetitions predominantand
GBS	Guillain-Barre syndrome
HLA-DR	human leukocyte antigen-DR
ICAM	intercellular adhesion molecule
IFNγ	interferon-γ
IgG	immunoglobulin G
INCAT	Inflammatory Neuropathy Cause and Treatment
ITAM	immunoreceptor tyrosine-based activation motif
ITIM	intracellular immunoreceptor tyrosine-based inhibitory motif

ITP	immune thrombocytopenic purpura
IVIg	intravenous immunoglobulin
MAC	membrane attack complex
MFS	Miller Fisher syndrome
MHC	major histocompatibility complex
MMN	multifocal motor neuropathy
MRC	Medical Research Council sum score.
NF186	neurofascin 186
NK cells	natural killer cells
PD-L1	Programmed death-ligand 1
RCT	randomized-controlled trial
SIGLEC	sialic acid-binding immunoglobulin-like lectin
SIGN	specific intercellular adhesion molecule-3-grabbing non-integrin
T1/2	half-life
TCR	T cell receptor
TGF-1	transforming growth factor-1
Th1	T helper cell 1
Th17	T helper cell 17
TIGIT	T cell immunoreceptor with Ig and ITIM domains
TNFα	tumor necrosis factor-α
Treg	regulatory T cell
VCAM-1	vascular cell adhesion molecule-1

Bullets

- IVIg is a blood product obtained from plasma pooled from thousands of healthy donors. IVIg is used in lower doses as a replacement therapy for immunodeficient patients and in doses of 1-2 g/kg for the suppression of autoimmune diseases. Besides the licensed indications, several *off-label* indications exist.
- IVIg has a complex mechanism of action, involving the neutralization and an enhanced clearance of pathological antibodies, Fc receptor blockade, complement inhibition, a decrease in the production of inflammatory cytokines, immunoregulation of DCs, B and T cells, an enhancement of Tregs, and the modulation of apoptosis.
- IVIg is generally well tolerated, with most of the side effects being mild and transient. Severe side effects, such as thrombosis, anaphylactic reaction, and kidney injury, can occur.
- Immune-mediated polyneuropathies are a heterogeneous group of diseases of the peripheral nervous system. Anti-ganglioside antibodies through molecular mimicry and complement activation play a role in the pathomechanism of GBS. The pathomechanism of CIDP is not fully understood, with both cellular and humoral mechanisms involved. Several clinical trials prove the efficacy and safety of IVIg in GBS and CIDP.
- Despite the considerable progress in both the supportive therapy and immunotherapy, GBS is still a life-threatening disease, resulting in a permanent disability in some 20% of the patients. The chronic forms are difficult to diagnose, and, especially in the case of a delay in the initiation of the therapy, a severe disability and an impairment of the quality of life can ensue. There is still much to do in order to improve the therapy for immune-mediated polyneuropathies.
- Understanding the exact mechanism of action of IVIg in these disorders might enable the design of more specific therapies.

Dear Mr David Owusu,

We have revised our manuscript entitled **'Intravenous immunoglobulin: pharmacological properties and use in polyneuropathies'** in accordance with the comments of the reviewers. We are pleased to accept all the suggestions.

Some aspects that were only shortly discussed or were not included in the original manuscript, either due to lack of space or other considerations, have now been discussed in the revised manuscript, along the recommendations of the reviewers. These supplementations considerably extended the length of the manuscript. Several new references have been added as suggested by the reviewers. The changes made in the text and the new references are highlighted in bold red letters. Hereby we provide a point-wise rebuttal to the comments of the editorial office and reviewers:

Comments of the editorial office:

1. Please can you confirm whether your figures and tables are original and have not previously been published, OR, provide me with a copy of permission to use from the original publisher. For any figures that require permission, please ensure that the figure caption is updated to acknowledge the source as per the original publisher's requirements

We declare that the figures and tables are original and have been specially created for this article.

Reviewer comments

Reviewer 1
General comments:

This article presents pharmacological properties and use o IGIV in polyneuropathies. This referee recommends augmenting the review by including the following references:

1. In Guillain-Barré syndrome patients, IGIV has been shown to modify T cell response
- *PMID: 25391612;*
- *PMID: 24899787;*
- *PMID: 25482074;*
- *PMID: 17997492*

The effects of IVIg on T cell response are now discussed in the revised manuscript. The papers recommended have been included in the references of our manuscript.

2. Fc sialylation- independent mechanisms of IGIV merits discussion and referencing
- *PMID: 25982320;*
- *PMID: 25012067;*
- *PMID: 25352126;*
- *PMID: 24760152;*
- *PMID: 24700174*

A new paragraph has now been included on the Fc sialylation-independent mechanisms of action of IVIg. The papers recommended have been included in the references of the revised manuscript.

Reviewer 2

General comments:

The paper is a review about the use and mechanisms of action of IVIg in immune mediated neuropathies. Generally the paper is well written and acceptable in length.
My main concern is that some aspects are not discussed in detail that includes also the discussion of relevant references that are not included in this version. So I strongly recommend addressing the following points:

1. page 5: Dimers are can also occur after IVIg infusion due to idiotypic.anti-idiotypic antibodies. A shot paragraph is needed here that include the following references:
• Schaub A, Wymann S, Heller M, Ghielmetti M, Beleznay Z, Stadler BM, Bolli R, Miescher S. Self-reactivity in the dimeric intravenous immunoglobulin fraction. Ann N Y Acad Sci. 2007 Sep;1110:681-93. PubMed PMID: 17911483.
• Ritter C, Bobylev I, Lehmann HC. Chronic inflammatory demyelinating polyneuropathy (CIDP): change of serum IgG dimer levels during treatment with intravenous immunoglobulins. J Neuroinflammation. 2015 Aug 14;12:148. doi: 10.1186/s12974-015-0361-1. PubMed PMID: 26268846; PubMed Central PMCID: PMC4535537.
• Tankersley DL. Dimer formation in immunoglobulin preparations and speculations on the mechanism of action of intravenous immune globulin in autoimmune diseases. Immunol Rev. 1994 Jun;139:159-72. Review. PubMed PMID: 7927410.

A paragraph has been included on dimer formation following IVIg infusion. The recommended papers are now cited in the revised manuscript.

2. Page 6: It is Guillain-Barré syndrome

The spelling has been corrected throughout the manuscript.

3. Page 10: Martin at el. needs a reference

A reference has been added

4. Page 11: IgA: I would change this sentence because in the newer IVIG preparations this problem is not prevalent anymore.

This sentence has been changed accordingly.

5. Page 11: Safety considerations:
• This paper need to be referenced as well (hemolytic anemia after IVIG in non-O blood types) O http://nn.neurology.org/content/1/4/e50.short?sid=b6345c13-f62b-4d0b-a3e8-2a866bf7a43e

This paper has been discussed in the revised manuscript and has been added to the reference list.

• PRES may occasionally occur after IVIg infusion. This needs to be added (also in the table3)
• Stetefeld HR, Lehmann HC, Fink GR, Burghaus L. Posterior reversible encephalopathy syndrome and stroke after intravenous immunoglobulin treatment in Miller-Fisher syndrome/Bickerstaff brain stem encephalitis overlap syndrome. J Stroke Cerebrovasc Dis. 2014 Oct;23(9):e423-5. doi:

10.1016/j.jstrokecerebrovasdis.2014.05.034. Epub 2014 Aug 20. PubMed PMID: 25149206.
• Belmouaz S, Desport E, Leroy F, Teynie J, Hannequin J, Ayache RA, Bridoux F, Touchard G. Posterior reversible encephalopathy induced by intravenous immunoglobulin. Nephrol Dial Transplant. 2008 Jan;23(1):417-9. Epub 2007 Oct 30. PubMed PMID: 17971381.
• Doss-Esper CE, Singhal AB, Smith MS, Henderson GV. Reversible posterior leukoencephalopathy, cerebral vasoconstriction, and strokes after intravenous immune globulin therapy in guillain-barre syndrome. J Neuroimaging. 2005 Apr;15(2):188-92. PubMed PMID: 15746232.
• Lewis M, Maddison P. Intravenous immunoglobulin causing reversible posterior leukoencephalopathy syndrome? J Neurol Neurosurg Psychiatry. 2000 Nov;69(5):704. PubMed PMID: 11184238; PubMed Central PMCID: PMC1763438.

This possible side effect is now discussed in the revised manuscript and has been mentioned in Table 3. The above papers have all been included in the references.

6. Page 13: It is correct that nodal protein has been identified. However the frequency of nodal protein abs is much less compared to anti-ganglioside antibodies (around 4%). Please align and include the following references
• Ng JK, Malotka J, Kawakami N, Derfuss T, Khademi M, Olsson T, Linington C, Odaka M, Tackenberg B, Prüss H, Schwab JM, Harms L, Harms H, Sommer C, Rasband MN, Eshed-Eisenbach Y, Peles E, Hohlfeld R, Yuki N, Dornmair K, Meinl E. Neurofascin as a target for autoantibodies in peripheral neuropathies. Neurology. 2012 Dec 4;79(23):2241-8. doi: 10.1212/WNL.0b013e31827689ad. Epub 2012 Oct 24. PubMed PMID: 23100406; PubMed Central PMCID: PMC3542349.
• Prüss H, Schwab JM, Derst C, Görtzen A, Veh RW. Neurofascin as target of autoantibodies in Guillain-Barre syndrome. Brain. 2011 May;134(Pt 5):e173; author reply e174. doi: 10.1093/brain/awq372. Epub 2011 Jan 27. PubMed PMID: 21278083.

A new paragraph on antibodies against nodal proteins has been constructed. The suggested references have been included.

7. Page 14: I do not agree with the statement that the therapeutic action of IVIG in GBS is mainly attributed to the reduction of pathological autoantibodies through anti-idiotypes. Other mechanisms are considered of equal importance. References that need to be included here are:
• Mausberg AK, Dorok M, Stettner M, Müller M, Hartung HP, Dehmel T, Warnke C, Meyer Zu Hörste G, Kieseier BC. Recovery of the T-cell repertoire in CIDP by IV immunoglobulins. Neurology. 2013 Jan 15;80(3):296-303. doi: 10.1212/WNL.0b013e31827debad. Epub 2012 Dec 26. PubMed PMID: 23269592.
• Lehmann HC, Hartung HP. Plasma exchange and intravenous immunoglobulins: mechanism of action in immune-mediated neuropathies. J Neuroimmunol. 2011 Feb;231(1-2):61-9. doi: 10.1016/j.jneuroim.2010.09.015. Epub 2010 Nov 5. Review. PubMed PMID: 21056913.

The section on the therapeutic action of IVIg in GBS has been considerably modified along the Reviewer's observation, and the suggested references are now included in the manuscript.

8. Page 16: Again I do not agree that the effect is mainly mediated by anti-idiotypic antibodies. This is not substantiated by experimental studies since the targets for autoantibodies in CIDP are largely unknown. A more detailed paragraph about the MofA of IVIg in CIDP is needed:
• Regulation of Fc receptors: Tackenberg B, Jelcic I, Baerenwaldt A, Oertel WH, Sommer N, Nimmerjahn F, Lünemann JD. Impaired inhibitory Fcgamma receptor IIB expression on B cells in

chronic inflammatory demyelinating polyneuropathy. PNAS

The section on the therapeutic action of IVIg in CIDP has been considerably modified accordingly, including the effect on Fc receptors. The recommended references have been included.

Anti-cytokine antibodies (BAFF/APRIL):
• IVIG regulates BAFF expression in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Ritter C, Förster D, Albrecht P, Hartung HP, Kieseier BC, Lehmann HC. J Neuroimmunol. 2014 Sep 15;274(1-2):225-9. doi: 10.1016/j.jneuroim.2014.06.007.
• Intravenous immunoglobulin inhibits BAFF production in chronic inflammatory demyelinating polyneuropathy - a new mechanism of action Bick S, Tschernatsch M, Karg A, Fuehlhuber V, Trenczek TE, Faltermeier K, Hackstein H, Kaps M, Blaes F. J Neuroimmunol. 2013 Mar 15;256(1-2):84-90. doi: 10.1016/j.jneuroim.2013.01.001.
• Plasma exchange and intravenous immunoglobulins: mechanism of action in immune-mediated neuropathies. Lehmann HC, Hartung HP. J Neuroimmunol. 2011 Feb;231(1-2):61-9. Doi: 10

The part on the therapeutic action of IVIg in CIDP has been rewritten accordingly, including the effect on BAFF and other cytokines .The recommended references have been included.

Table 2: anti-cytokine abs have to be included

Anti-cytokine abs are now included in Table 2.

Reviewer 3
Specific comments:

1. The pharmacodynamic mechanism of action section needs to cite more recent references.

The section on pharmacodynamics and mechanism of action has been improved and new references have been added.

2. The recent advances in Intravenous immunoglobulin preparation needs to be discussed thoroughly.

The revised manuscript has been supplemented with a new paragraph on the advances in IVIg preparation.

3. Dosage regimen of Intravenous immunoglobulin for immune deficiency syndrome needs to be included.

The revised manuscript now includes the dose and therapeutic regimen of IVIg therapy for immunodeficiency syndrome.

4. Storage condition and safety consideration for handling of immunoglobulin preparation needs to be included.

Storage conditions and special considerations as regards the handling of IVIg preparations are now discussed in the revised manuscript.

5. The authors need to justify the use of IVIg over other Ig products.

The manuscript has been supplemented with a new paragraph discussing factors influencing the choice for the route of administration.

6. Pathophysiological mechanism of polyneuropathy needs to be explained in more detail.

The chapters discussing the pathophysiological mechanisms of polyneuropathies have been considerable modified and improved and is explained in more detail.

We are grateful to the Reviewers for their efforts put into our manuscript, which we feel has led to a considerable overall improvement.
We hope that the revised manuscript in its current form will be deemed suitable for publication.

Yours sincerely,

László Vécsei

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