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10% liquid human immunoglobulin (KIOVIG®) for immunomodulation in autoimmune disorders

Intravenous immunoglobulins have been used to treat autoimmune disorders (ADs) for over 50 years. The etiologies of various ADs are not fully understood and although intravenous immunoglobulin treatment has proved its immunomodulatory properties, the roles of proposed mechanisms of action also remain a matter of speculation. A systemic search of the literature regarding KIOVIG® (Baxalta US, Inc., MA, USA) use in clinical trials on patients with ADs and a detailed review of retrieved articles revealed eight relevant publications. These articles reported KIOVIG use in multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, idiopathic thrombocytopenic purpura, Kawasaki disease, Guillain-Barré syndrome and other autoimmune and neurologic disorders and showed that KIOVIG is an effective, safe and well-tolerated treatment in the studied populations. Nevertheless, further studies on larger patient cohorts are needed.

First draft submitted: 17 March 2016;; Accepted for publication: 12 April 2016;
Published online: 29 April 2016

Keywords: autoimmune diseases • GAMMAGARD Liquid • intravenous immunoglobulin • KIOVIG®

Brief overview of autoimmune disorders

Autoimmune disorders (ADs) encompass a wide range of diseases and syndromes with complex immunopathology and diverse clinical manifestations, with neurologic disorders representing about half of the diseases with autoimmune pathogenesis [1]. The auto-inflammatory response is characterized by a derailment of humoral and cellular immunity, and may affect one or more organs or tissue types including joints, blood vessels, skin, nerve or muscle cells. Many ADs are relatively rare, such as idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, chronic inflammatory demyelinating polyneuropathy (CIDP) or Guillain-Barré syndrome (GBS), ranging from annual incidence rates of 1.1–1.8/100,000/year (GBS) to 67.3/100,000/year (Kawasaki disease, age group: children <5 years) [2–5].

Although the etiology of ADs is not completely understood, it is likely to involve a complex interaction of multiple environmental and genetic risk factors [6,7]. Over the past decades, intravenous immunoglobulin (IVIg) has been used as an immunomodulatory agent in an increasing number of immune and inflammatory disorders and has become a first-line treatment option in several autoimmune conditions. Today, all approximately 20 commercially available IVIg preparations are predominantly composed of IgG (>95%), but in fact each product is a unique formulation of IgG and excipients, with varying characteristics regarding pH, osmolality, sugar and salt content, as well as IgA and IgM concentration, all influencing product safety and tolerability [8,9].

The purpose of this manuscript is to review the published literature and discuss the use of KIOVIG® (human normal immu-

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noglobulin 10% liquid, manufactured by Baxalta US, Inc., licensed as GAMMAGARD LIQUID® in the USA and KIOVIG elsewhere, hereafter referred to as KIOVIG) in clinical trials involving patients with autoimmune diseases.

Overview of the history of using purified immunoglobulins for the treatment of autoimmune disorders

Immunoglobulin replacement was first introduced by Bruton in the 1950s for the treatment of congenital primary immunodeficiency disorders [10,11]. IVIG has been predominantly used in clinical practice since the 1980s, replacing administration via subcutaneous or intramuscular immunoglobulin route and thereby overcoming volume limitations of both [10,12]. In addition to its use as IgG replacement therapy, the immunomodulatory properties of IVIG became apparent in the early 1980s, when IVIG was shown to be efficacious in ITP: a landmark clinical trial conducted by Imbach *et al.* revealed that children with acute and chronic ITP had achieved rapid normalization of platelet counts following IVIG treatment [13]. These findings were confirmed in adult ITP patients [14], and since then numerous studies have been conducted to examine the effect of IVIG in other autoimmune diseases. In the 1990s, the administration of IVIG as immunomodulatory therapy started to expand and by the end of the 20th century, IVIG had become a commonly accepted therapy in the treatment of inflammatory and ADs [15–17]. Today, IVIG therapy is considered an efficacious and well-established treatment option in diverse disorders ranging from neurologic diseases to blistering skin diseases as well as numerous other inflammatory and autoimmune conditions [18–20].

In order to unfold the anti-inflammatory potential of IVIG, the doses used for the treatment of autoimmune and inflammatory diseases are considerably higher when compared with IVIG in immunodeficiency disorders, whereas patients with antibody deficiencies receive IVIG replacement therapy with 400–800 mg/kg bodyweight at approximately 3–4 week intervals to maintain adequate antibody levels; high-dose IVIG is administered at doses of up to 2.0 g/kg/month as an immunomodulatory agent for a variety of systemic inflammatory disorders as well as acute and chronic autoimmune diseases [21–23]. Patients with acute autoimmune conditions like ITP, Kawasaki disease or GBS normally receive IVIG during one treatment course, whereas chronic ADs such as CIDP, myasthenia gravis, multifocal motor neuropathy (MMN) or dermatomyositis require maintenance therapy whenever needed to alleviate symptoms [20,24–27]. In all instances, the overall treatment goal for patients with

acute as well as chronic ADs is to reduce symptoms and to control the autoimmune process.

Potential mechanisms of action of IVIG when used for immune modulation

Despite the broad efficacy of IVIG therapy, its mechanisms of action when used to treat and suppress autoimmune diseases are poorly understood. Notably, IVIG can exert anti-inflammatory as well as proinflammatory properties, depending on the dose administered, whereas anti-inflammatory effects are more generally observed with high-dose IVIG administration, proinflammatory activities including complement activation or antibody binding to the Fc γ receptors (Fc γ R) on innate immune cells tend to be seen with low IVIG doses [23].

IVIG preparations contain polyclonal IgG pooled from the plasma of thousands of donors, involving an extensive specificity repertoire of antibodies that recognize pathogens as well as a plethora of foreign and self-antigens. The IgG antibodies do not only confer immunity to patients with immunodeficiency disorders, but also protect the host from autoreactive IgG molecules directed against numerous self-antigens and immunomodulatory components. Many pathways in innate and adaptive immune responses may be potential targets of IVIG and various mechanisms of action mediated by either the antigen-binding Fab domain or the Fc domain of IgG have been proposed (Figure 1) [28–30]. It has been suggested that the Fab region of IgG may be of crucial importance for the therapeutic benefits of IVIG through binding to a variety of proteins, such as cytokines, CD95 (Fas), CD95 ligand (FasL) and CD4, the variable domains of other IgG antibodies, T-cell-expressed antigens, a number of integrins, as well as components of the complement system [19,28,31–35]. For example, anti-idiotypic antibodies contained in IVIG can neutralize circulating autoantibodies and target B lymphocytes that express these idiotypes in patients with autoimmune diseases, thereby downregulating or eliminating autoreactive clones [23]. Regarding its interaction with complement, it has been reported that the Fab region scavenges anaphylatoxins C3a and C5a, thereby neutralizing their proinflammatory effects [35]. Also, it has been shown that IVIG specifically binds to the surface of Schwann cells either via their Fab regions specific for surface epitopes or via their Fc domain to respective receptors, and a rat Schwann cell culture model revealed that IVIG (KIOVIG was used in this study) can positively influence the differentiation process of these myelinating glial cells. So, IVIG may enhance the regenerative potential of central components of repair in many peripheral neuropathies [36].

Figure 1. Potential mechanisms of intravenous immunoglobulin activity in the treatment of autoimmune diseases. Mechanisms of action may be exerted via the Fab and/or Fc portion of IgG as well as by other soluble proteins contained in IVIG (e.g., cytokines or chemokines). Fab-dependent mechanisms include the neutralization of cytokines, chemokines and autoantibodies by anti-idiotypic antibodies, as well as the inhibition of cell–cell interactions mediated by surface receptors (e.g., modulation of apoptosis by targeting CD95 [Fas]/Fas ligand interaction) and interactions with complement components (e.g., neutralization of anaphylatoxins C3a and C5a). Potential Fc-dependent modes of action involve interaction with the complement system (binding to early complement activation products C3b and C4b) as well as with FcγRs, such as binding and saturation of high-affinity FcγRs, immune complex formation and competitive blockade of immune-complex access to FcγRs, modulation of activating and inhibitory FcγR expression on immune effector cells, as well as saturation of the FcRn and thereby influencing the half-life of pathological autoantibodies. A further anti-inflammatory effect may be the binding of sialylated IgG Fc to the C-type lectin DC-SIGN on dendritic cells, thus upregulating the inhibitory FcγR on effector macrophages.

FcγRs: Fcγ receptors; IVIG: Intravenous immunoglobulin.

However, despite the anti-inflammatory and immunomodulatory properties potentially mediated by the Fab region, the importance of the IgG Fc domain for the benefits of IVIG in autoimmune diseases seems to be greater and it has been shown that the Fc region may even be sufficient for IVIG's therapeutic activity [37]. The potential mechanisms of action of the

Fc fragment may be explained by its interaction with the complement system as well as the activating and inhibitory FcγRs.

Notably, monomeric IgG molecules constitute >95% of IVIG and may not only bind and saturate the high-affinity IgG receptor FcγRI in their monomeric form but also recognize their respective antigen if pres-

ent, form high levels of immune complexes and compete with proinflammatory antigen–antibody immune complexes for activating FcγRs. Also, the binding of IVIG to receptors expressed on macrophages may slow the clearance of antibody-coated cells in the mononuclear phagocyte system in patients with autoimmune cytopenias [14,28].

The inhibitory receptor FcγRIIB, which negatively regulates immune cell activation, may also be closely linked to IVIG's anti-inflammatory properties, as mice lacking receptor expression were observed to lack protection against ITP or rheumatoid arthritis by IVIG [23,38,39]. It has been suggested that IVIG upregulates FcγRIIB on effector macrophages and B cells or that the number of myeloid cells expressing this receptor is increased, which may lead to enhanced competition with activating FcγRs for antigen–antibody complex binding and an increased threshold for effector cell activation [19,23,38,39]. Upregulation of FcγRIIB may be the crucial mechanism in CIDP and GBS, since B cells of CIDP patients were shown to have a reduced FcγRIIB expression pattern, which can be restored by IVIG treatment [19,40].

Also, a potential role of the neonatal Fc receptor (FcRn), which is expressed in many tissues, has been discussed. FcRn is responsible for the long IgG serum half-life of 3 weeks by acting as a protective receptor attenuating IgG catabolism and a loss of FcRn has been shown to substantially reduce the half-life of IgG [23,28,41,42]. The increase of IgG plasma concentrations through IVIG infusion leads to a competition for and saturation of FcRn receptors, resulting in a decreased half-life of the recipient's pathological IgG autoantibodies, which may result in a reduction of autoantibody-mediated tissue inflammation [29,43,44].

Concerning its interaction with the complement system, it has been shown that the Fc region binds larger fragments of the early complement activation products C3b and C4b [45,46]. Thus, high doses of IVIG modify or inhibit the deposition of these complement components on target cells, thereby preventing the formation of the cytolytic membrane attack complex C5b-9, which would otherwise provoke target cell destruction and increased inflammation [45,46]. These data show that scavenging potentially harmful complement fragments and thereby attenuating complement-mediated tissue damage may also contribute to the anti-inflammatory effect of high-dose IVIG.

Finally, the sugar domain attached to the IgG Fc-fragment is essential for optimal binding to FcγRs and has been identified as a potential molecular trigger to either block or enhance the inflammatory effector functions of antibody molecules [47]. It has been reported that antibody-dependent cellular toxicity is

reduced when the Fc glycans terminate in sialic acid residues [48,49]. This anti-inflammatory effect has been reported to be due to an upregulation of FcγRIIB, but it has also been shown that IgG Fc sialylation impaired the induction of complement-mediated toxicity [50]. Indeed, altered patterns of serum IgG glycosylation seem to be associated with active autoimmune disease in rheumatoid arthritis, systemic lupus erythematosus (SLE) and Crohn's disease and IVIG infusions have been demonstrated to prolong treatment responses due to the induction of sialylated IgG glycovariants in patients with Kawasaki disease [51]. Furthermore, it has been reported that induction of IgG Fc sialylation in sera of CIDP patients was associated with disease remission [50], and sialylated IVIG also seemed to be necessary for its activity in two ITP models, in inflammatory arthritis and in epidermolysis bullosa acquisita, but not in other model systems or in other experimental environments [47].

However, despite all available data on potential mechanisms of action, it can at present only be speculated about the relevance and specific role of these different pathways for the immunomodulatory and anti-inflammatory properties of IVIG.

KIOVIG: a 10% liquid human immunoglobulin preparation

Although all commercially available IVIG preparations are primarily composed of IgG (>95%), each product is a unique formulation of IgG and excipients, with varying characteristics regarding pH, osmolality, sugar and salt content, as well as IgA concentration, all influencing product tolerability [8,9]. Human normal immunoglobulin 10% liquid (Baxalta US, Inc.) is a highly purified ready-to-use liquid preparation containing 10% immunoglobulin, with at least 98% IgG and low IgA content (maximum concentration 140 µg/ml) and only trace amounts of IgM [8,52,53]. As a 10% liquid preparation, KIOVIG provides the advantage of easier use by healthcare professionals and allows for a smaller volume of the product to be administered [54].

As for all IVIG products, ensuring pathogen safety during production is of high priority among manufacturers as well as health authorities. Transmission of blood-borne pathogens including new or re-emerging infectious agents is a concern whenever blood derivatives are prepared from large numbers of donors [28,54]. Following initial screening of plasma donations for antibodies to viral pathogens and PCR testing for viral genomes in pooled plasma, the manufacturing process of KIOVIG further involves three effective and robust clearance steps to ensure high margins of safety with respect to transmission of known blood-borne pathogens, such as viruses and prions.

These dedicated pathogen inactivation steps comprise solvent/detergent treatment, 35-nm nanofiltration and low pH/elevated temperature incubation [55,56]. It has been shown that lipid-enveloped viruses were completely inactivated/removed by each of the three inactivation steps, and HIV-1 as well as pseudorabies virus also by the upstream cold ethanol fractionation. Critical nonenveloped viruses such as hepatitis A virus and parvovirus B19 were effectively removed by nanofiltration and cold ethanol fractionation, and additionally partial inactivation of non-enveloped viruses was achieved by low pH incubation. Also, prions were completely removed during the cold ethanol precipitation process [57].

Literature review on KIOVIG use in autoimmune diseases

A systematic literature search of the following databases was performed on 21 August 2015 to identify clinical trials using KIOVIG in patients with autoimmune diseases: Ovid Journals (up to 21 August 2015), BIOSIS Previews (January 1993–21 August 2015), Embase (January 1974–21 August 2015), International Pharmaceutical Abstracts (January 1970–21 August 2015) and Ovid MEDLINE® In-Process & other nonindexed citations and Ovid MEDLINE® (January 1946–21 August 2015). The following keywords and search strategy were used: (KIOVIG or GAMMAGARD liquid) or Baxter or Baxalta and ('10%' and 'liquid' and [IVIG or IGIV or IVGG or intravenous or iv or immunoglobuline or immunoglobulines or immunoglobulins or immunoglobulin]); and (CIPD or polyneuropath* or polyradiculoneuropath* or neuropath* or neuritis or polyradiculoneuritis or Guillain Barre or ITP or thrombocytopenia or autoimmune thrombocytopenic or immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura or Kawasaki syndrome or Kawasaki disease or myasthenia gravis or GBS or MMN or multifocal motoneuropathy or multifocal motor neuropathy or multiple sclerosis or SLE or systemic lupus or polymyositis or dermatomyositis or rheumatoid arthritis or autoimmune skin blistering or pemphigoid or pemphigus or epidermolysis bullosa or autoimmune disease or autoimmune diseases). Duplicate abstracts, case reports, methodologies, clinical study reviews and pharmacoeconomic studies were excluded from the final list, as were nonhuman studies and non-English language publications.

The above described search terms and strategy resulted in the identification of 153 articles or congress abstracts. After a detailed review, eight publications were deemed suitable for inclusion, referring to clinical studies and retrospective reviews on the use of KIOVIG in autoimmune diseases (Table 1) [22,54,58–63].

Of these, two articles referred to patients with multifocal motor neuropathy (MMN) (an indication approved for KIOVIG in the USA and Europe), one article referred to patients with chronic ITP (an indication approved for KIOVIG in Europe), two publications involved patients with CIDP, one article referred to patients with acute ITP, Kawasaki disease and GBS (all indications approved for KIOVIG in Europe, and two articles reported about safety studies involving KIOVIG in multiple autoimmune or neurologic indications.

KIOVIG use in idiopathic thrombocytopenic purpura

ITP is an AD caused by the production of auto-antibodies against platelet surface membrane proteins, leading to the subsequent destruction of platelets by phagocytosis in the spleen and other parts of the reticuloendothelial system [64–66]. Acute and chronic forms can be distinguished, with acute ITP mainly manifesting in children after viral infections and chronic ITP being a long-lasting disorder in adults [67]. IVIG has initially been shown effective for the treatment of ITP in 1981 and has since then become a standard treatment for this disorder, along with corticosteroids, platelet transfusion and splenectomy [13,68].

The use of KIOVIG in ITP was investigated by Varga *et al.* in a prospective, open-label study in 23 adult patients with chronic ITP and platelet counts of $\leq 20 \times 10^9/l$ at screening [54]. A standard dose of 2 g/kg bodyweight was applied over 2–5 days. The majority of patients (71%) responded to treatment, achieving a platelet count of at least $50 \times 10^9/l$ by day 8 and maintaining the platelet response for a median of 25 days. Overall, 40 nonserious adverse reactions occurred (35 mild, 3 moderate and 2 severe), with headache and pyrexia being most common. The authors concluded that KIOVIG is an effective and safe treatment for adult subjects with chronic ITP.

Both efficacy and safety of KIOVIG were also investigated in pediatric and adult patients with acute ITP. A recent article by Blažek *et al.* documented the efficacious and safe use of KIOVIG in patients with acute ITP ($n = 26$), GBS ($n = 14$) as well as Kawasaki disease ($n = 9$), all three being licensed indications in Europe [22]. For ITP, the median total dose of KIOVIG was 1.69 g/kg bodyweight, administered over 1 or 2 days in most subjects. A high response rate was noted as evidenced by a resolution of bleeding episodes as well as an increase in post-treatment platelet counts to $>30 \times 10^9/l$ in all subjects dosed (median baseline platelet count: $7 \times 10^9/l$). When compared with the results obtained in chronic ITP patients published by Varga *et al.*, a higher response rate to KIOVIG

Table 1. Clinical studies and retrospective reviews investigating KIOVIG treatment in patients with autoimmune diseases.

Study (year)	Study design	Participants	KIOVIG dosing schedule	Efficacy outcomes	Safety outcomes	Conclusion	Ref.
Idiopathic thrombocytopenic purpura							
Varga <i>et al.</i> (2006)	Prospective, open-label, multicenter, noncontrolled trial over 4 weeks	Adults with chronic ITP (n = 23 in total, n = 21 for the per-protocol analysis set [two subjects did not meet all selection criteria]) with platelet counts $\leq 20 \times 10^9/l$	IVIG 10% 2 g/kg BW infused over 2–5 days, with a maximum of two booster doses (400–1000 mg/kg) if platelet count dropped to $\leq 20 \times 10^9/l$	15 of 21 subjects responded to treatment (71.4%), achieving a platelet count of at least $50 \times 10^9/l$ by day 8 Fourteen of 15 responders reached this level by day 5 The median duration of platelet response was 25 days	After a total of 81 infusions administered, 40 nonserious AEs related to KIOVIG were reported, 35 of which were mild, three were moderate and two were severe The most frequent related AEs were headache (11 occurrences in eight subjects) and pyrexia (seven occurrences in seven subjects)	IVIG 10% liquid is effective in the treatment of adult patients with chronic ITP and is well tolerated	[54]
Multifocal motor neuropathy							
Cats <i>et al.</i> (2008)	Prospective, open-label, noncontrolled study over 12 months	Patients (n = 20) with either definite or probable MMN	Patients' regular maintenance dose of freeze-dried 5% IVIG (GAMMAGARD, Baxter BV) for 3 months, then IVIG 10% liquid for additional 9 months	Muscle strength was comparable between the period in which patients used 5% IVIG and the period with IVIG 10% liquid (Wilcoxon signed-rank test for two related samples, two-tailed, p = 0.126) Mean infusion time with IVIG 10% liquid was 2.5 h compared with 4.5 h with 5% IVIG	Eight out of 20 patients (40%) reported side effects with 5% IVIG; seven patients (35%) reported side effects with IVIG 10% liquid	10% IVIG liquid was well-tolerated in patients with MMN. Muscle strength and disability scores remained stable. Infusion times were substantially reduced in 85% of patients	[58]

[†]IgG = IgG level after treatment minus IgG level just before treatment.

AE: Adverse event; AR: Adverse reaction; BW: Bodyweight; CIDP: Chronic inflammatory demyelinating polyneuropathy; ITP: Idiopathic thrombocytopenic purpura; IVIG: Intravenous immunoglobulin; MMN: Multifocal motor neuropathy.

Table 1. Clinical studies and retrospective reviews investigating KIOVIG treatment in patients with autoimmune diseases (cont.).

Study (year)	Study design	Participants	KIOVIG dosing schedule	Efficacy outcomes	Safety outcomes	Conclusion	Ref.
Hahn <i>et al.</i> (2013)	Multicenter randomized controlled trial (1:1), with a crossover, double-blind 12-week treatment period (placebo or IVIG) sandwiched between 12-week open-label IVIG treatment periods at the start, middle and end of the double-blind treatment periods	44 adults with probable or definite MMN on a stable regimen of IVIG for ≥3 months at 0.4–2.0 g/kg BW every 2–5 weeks	10% liquid IgG or placebo (0.25% human albumin in normal saline)	Treatment with IVIG increased the maximal grip strength of the more affected hand by a mean of 3.75% compared with a significant decrease by 31.38% during placebo (p = 0.005). As determined by Guy's neurological disability scores, 15 of the 42 evaluable patients (35.7%) deteriorated during the placebo period but not during IVIG, while five patients (11.9%) worsened only while receiving IVIG (p = 0.021). Two patients (4.8%) deteriorated during both periods and the remaining 20 patients (47.6%) showed no change in disability scores. An accelerated switch to open-label IVIG occurred in 29 (69.0%) patients during placebo treatment. In contrast, only one patient (2.4%) switched to open-label treatment while receiving blinded IVIG (p < 0.001)	AR rates per infusion during the blinded study periods were similar for IVIG 10% and for placebo, ranging from 2.9 to 15.2% during IVIG 10% infusions and from 5.9 to 18.0% during placebo infusions. One serious AR occurred during the study with IVIG: pulmonary embolism in a 71-year-old subject (treated effectively)	10% IVIG liquid was effective, safe and well-tolerated in adults with MMN. The findings support the current recommendation of IVIG as a first-line therapy for MMN	[59]
Chronic inflammatory demyelinating polyneuropathy							
Kuitwaard <i>et al.</i> (2010)	Randomized controlled trial, multicenter, double-blind treatment period followed by open-label treatment period	Patients (n = 27) with active CIDP	Patients were randomized to either four blinded infusions of GAMMAGARD S/D (n = 13) or KIOVIG (n = 14). In the open-label period, all patients received five IVIG 10% infusions	No significant difference in efficacy between the treatments was seen as assessed by the overall disability sum score (difference 0.004 [GAMMAGARD minus IVIG 10%]; 95% CI: -0.4 to 0.4)	There were no significant differences between the two treatments in respect to the number of commonly reported AEs, except for the lower occurrence of cold shivers in patients randomized to 10% liquid IVIG	There are no significant clinical differences between these two IVIG brands in their efficacy to treat CIDP	[60]

*ΔIgG = IgG level after treatment minus IgG level just before treatment.
AE: Adverse event; AR: Adverse reaction; BW: Bodyweight; CIDP: Chronic inflammatory demyelinating polyneuropathy; ITP: Idiopathic thrombocytopenic purpura; IVIG: Intravenous immunoglobulin; MMN: Multifocal motor neuropathy.

Table 1. Clinical studies and retrospective reviews investigating KIOViG treatment in patients with autoimmune diseases (cont.).

Study (year)	Study design	Participants	KIOViG dosing schedule	Efficacy outcomes	Safety outcomes	Conclusion	Ref.
Chronic inflammatory demyelinating polyneuropathy							
Kuitwaard <i>et al.</i> (2013)	Randomized controlled trial, multicenter, double-blind treatment period followed by open-label treatment period	Patients (n = 25) with active but stable CIDP were included	Same as Kuitwaard <i>et al.</i> (2010)	IgG was measured, showing that the intrapatient variability of the pretreatment, post-treatment and increase in IgG concentration was low (CV: 3, 4 and 10%, respectively). The interpatient variability between patients treated with the same dose and interval was low in pretreatment, post-treatment and Δ IgG ⁺ level (mean CV: 13, 11 and 20%). The Δ IgG levels were associated with IVIG dosage using the Spearman ranked-order coefficient (correlation coefficient [rs]: 0.78, $p < 0.001$)	None assessed	Clinically stable CIDP patients show a steady serum IgG concentration after serial IVIG infusions. The low intra- and interpatient variability in IgG may indicate that constant levels are required to reach this stability	[61]
Multiple indications							
Markvardsen <i>et al.</i> (2014)	Prospective, open-label, 2-week duration	84 patients (34 <i>de novo</i> treated patients with post-polio syndrome and 50 maintenance therapy patients with CIDP and MMN)	PrIVIgen (CSL Behring AB, Marburg, Germany) 2 g/kg for <i>de novo</i> treated patients (0.4 g/kg/day for 5 days; n = 34); PrIVIgen (n = 28) or KIOViG (n = 22) at individualized doses for maintenance therapy	Not assessed	Laboratory tests performed prior to and 2 weeks after infusion: blood hemoglobin, plasma haptoglobin, blood reticulocytes, plasma lactate dehydrogenase, plasma bilirubin, direct agglutination test (indicates hemolysis)	There were no significant differences between PrIVIgen and IVIG in any of the laboratory parameters tested, except that patients who received PrIVIgen maintenance treatment had a higher mean plasma concentration of lactate dehydrogenase 2 weeks after infusion	[62]

[†] Δ IgG = IgG level after treatment minus IgG level just before treatment.

AE: Adverse event; AR: Adverse reaction; BW: Bodyweight; CIDP: Chronic inflammatory demyelinating polyneuropathy; ITP: Idiopathic thrombocytopenic purpura; IVIG: Intravenous immunoglobulin; MMN: Multifocal motor neuropathy.

Table 1. Clinical studies and retrospective reviews investigating KIOVIG treatment in patients with autoimmune diseases (cont.).

Study (year)	Study design	Participants	KIOVIG dosing schedule	Efficacy outcomes	Safety outcomes	Conclusion	Ref.
Blažek <i>et al.</i> (2015)	Postauthorization safety surveillance study, duration 6 ± 1 weeks to 12 ± 2 months depending on indication	Patients with ITP (n = 26), GBS (n = 14), Kawasaki disease (n = 9) or immunodeficiency (n = 39)	According to the prescribing information for the corresponding indication	Overall efficacy rated good or very good by the investigator in 73.1% of patients with ITP, 92.9% with GBS and 77.8% with Kawasaki disease Patients with ITP reached a platelet count of >50 × 10 ⁹ /l within a median of 3 days; 22/26 patients maintained this level throughout the study Following treatment, no patients with Kawasaki disease fulfilled ≥5 diagnostic criteria according to Ayusawa <i>et al.</i> [82], compared with seven of nine patients at baseline The majority (71.4%) of patients with GBS had a disability score of Grade 0 ('healthy') at the end of the 12-month follow-up period	ARs were reported in 30.6% of patients with autoimmune disorders (46.2% with ITP, 21.4% with GBS and none with Kawasaki disease); the most commonly reported ARs were headache, vomiting, pyrexia and chills, none of which were severe One AR (moderate urticaria) was categorized as serious due to brief hospitalization of a patient with immunodeficiency	IVIg 10% was shown to be efficacious, safe and well-tolerated for the treatment of ITP, Kawasaki disease and GBS in a real-world setting	[22]
Rigas <i>et al.</i> (2008)	Retrospective review of overall safety of high-dose IVIG administered to patients with neuroimmunologic disorders in a clinically defined, home-based therapeutic regimen	1085 KIOVIG infusion given to 70 patients	According to the prescribing information for the corresponding indication	Efficacy was not investigated	ARs were reported in 33% of patients, with an overall reporting rate of 4.7% (51 AEs in 1085 infusions) All AEs were nonserious, headache and rash were the most common AEs. No serious AEs were reported	The study revealed a favorable tolerability profile for KIOVIG, also in patients who had never been treated with IVIG before	[63]

^aΔIgG = IgG level after treatment minus IgG level just before treatment.

AE: Adverse event; AR: Adverse reaction; BW: Bodyweight; CIDP: Chronic inflammatory demyelinating polyneuropathy; ITP: Idiopathic thrombocytopenic purpura; IVIG: Intravenous immunoglobulin; MMN: Multifocal motor neuropathy.

was noted among subjects with acute ITP: all but a patient (96%) reached a platelet count of $>50 \times 10^9/l$ within a median of 3 days and 22 of 26 patients maintained this level throughout the study. Adverse reactions to KIOVIG were reported in 46.2% of subjects (all of them transient and of mild or moderate severity) [22], which was within the range seen in previous studies on the use of various IVIG formulations in ITP patients [69–72]. The authors concluded that the therapeutic profile of KIOVIG with respect to safety, tolerability and efficacy was confirmed.

KIOVIG use in chronic inflammatory demyelinating polyneuropathy

Being one of the most common immune-mediated chronic disorders of the peripheral nervous system, CIDP is suggested to be provoked by an abnormal immune response involving autoantibodies, autoreactive T cells and activated macrophages, leading to a progressive loss of immunologic tolerance to peripheral nerve components such as myelin, Schwann cell axon, as well as motor and ganglionic neurons [73,74]. IVIG is considered as a first-line treatment option for CIDP, along with steroids and plasmapheresis.

A study by Kuitwaard *et al.* compared the clinical efficacy of four infusions of KIOVIG with four infusions of GAMMAGARD S/D to maintain the condition in 27 patients with active but stable CIDP [60]. The trial consisted of ten infusions in three phases: following an initial single open-label infusion of standard GAMMAGARD S/D, the patients were randomized at an equivalent allocation ratio to receive four double-blinded infusions with either GAMMAGARD S/D or KIOVIG. In a third phase, all patients received five open-label KIOVIG infusions. All infusions were administered at the same doses and intervals used for maintenance treatment prior to study begin. Efficacy outcome was determined by measurement of disability by the overall disability sum score and muscle weakness by the Medical Research Council (MRC) sum score and Vigorimeter. As a result, no significant differences between KIOVIG and GAMMAGARD S/D were found in any of the outcome measures and the number of adverse events reported in both treatment groups was similar. The authors proposed that since there were no clinical differences between these two IVIG brands, it may be assumed that this may also be true for the treatment of ADs other than CIDP with KIOVIG and GAMMAGARD S/D.

Pharmacokinetic data obtained from the study by Kuitwaard *et al.* were collected and published in a later article that examined the potential influence of interpatient variation in serum IgG levels on the required dose and frequency of administration of IVIG for maintenance

treatment of CIDP [61]. As a matter of fact, CIDP patients differ in their requirements regarding dosage and frequency of IVIG administration, presumably due to individual differences in IVIG metabolism, and a minimum serum IgG level may be necessary to maintain a stable clinical condition. Pharmacological data obtained from this study revealed a low interpatient variability in serum IgG levels measured immediately prior to and 5 min after KIOVIG infusion, as well as in the peak increase in serum IgG after infusion; mean CVs were 13, 11 and 20%, respectively. Inpatient variability was even lower (mean CVs: 3, 4 and 10%, respectively), indicating that a steady state in serum IgG levels had been reached after several IVIG infusions. However, additional studies will be needed to gain deeper insight into the diverging requirements regarding IVIG dosage and frequency to guarantee successful maintenance therapy for CIDP.

KIOVIG use in Guillain–Barré syndrome & Kawasaki disease

GBS is a rare immune-mediated peripheral demyelinating neuropathy consisting of at least four subtypes and leading to progressive bilateral weakness of the limbs with or without involvement of the respiratory muscles [75,76]. Being considered a postinfectious disorder, GBS has been reported after *Campylobacter jejuni*, Cytomegalovirus or Epstein–Barr virus infections as well as after vaccinations or operations [75,76]. Most recently there are reports of relating infections with Zika virus to increased incidence of GBS [77]. Causality and pathophysiology are still under debate, but there is evidence that GBS is provoked by an infection-induced aberrant immune response involving antiganglioside autoantibodies that cause damage to peripheral nerves [75,76].

Kawasaki disease is an acute multisystem autoimmune condition of unknown cause found predominantly in children under the age of 5 years. It is described as an acute inflammation of the vasculature bed characterized by symptoms such as persistent fever, erythema of the oral mucosa and rash, with up to 25% of cases potentially developing cardiac sequelae like coronary artery aneurysms, myocardial infarction or heart failure. Notably, IVIG has been shown to inhibit the production of the proinflammatory cytokines IL-1, TNF- α and IL-6 as well as endothelial cell proliferation and the expression of chemokines and growth factors such as GM-CSF, thereby modifying inflammatory responses in patients with Kawasaki disease [78,79]. For both conditions, GBS as well as Kawasaki disease, IVIG is a first-line agent for treatment. Whereas GBS patients usually receive a standard IVIG dose of 0.4 g/kg bodyweight over 5 consecutive days, a single

large dose of IVIG was shown to be most effective in patients with Kawasaki disease [80,81]. Blazek *et al.* investigated the efficacy and safety of KIOVIG in a small cohort of patients with Kawasaki disease and GBS (9 and 14 patients, respectively) [22]. The median KIOVIG dose administered to treat Kawasaki disease was 1.93 g/kg bodyweight over 1–2 days and for GBS 1.94 g/kg bodyweight administered over 1–5 days. The patients were followed up for an observational period of 4 ± 1 weeks or until they were discharged from hospital, with an additional follow-up visit of 12 ± 2 months after enrollment. The overall efficacy of KIOVIG was assessed as good or very good in 77.8% of patients with Kawasaki disease. Efficacy outcome measures confirmed these results, with none of the patients fulfilling ≥ 5 diagnostic criteria by the end of the observational period compared with seven of nine patients at baseline [82]. Also, all but a patient was afebrile following treatment. Notably, no adverse reactions were observed in the nine patients treated.

Similarly, in 92.9% of subjects with GBS, the overall efficacy was also considered good or very good. The patients showed an improvement in physical functioning by the 4 ± 1 weeks assessment with evidence of further recovery at 12 ± 2 months as demonstrated by the number of patients with disability scores [83] of at least Grade 2 (14 patients at study start, 7 after 4 weeks and 2 patients after 12 months, respectively). The majority (71.4%) of patients with GBS were considered healthy with a disability score of Grade 0 at the 12-month follow-up visit. Mild adverse reactions to KIOVIG occurred in two patients and a patient experienced at least one moderate adverse reaction. Overall, the results obtained for this relatively low number of subjects showed that KIOVIG was efficacious and well tolerated in patients with GBS as well as Kawasaki disease.

KIOVIG use in multifocal motor neuropathy

MMN is a rare immune-mediated demyelinating neuropathy with progressive, asymmetric, predominantly distal weakness of the limbs, for which IVIG has become the first-line therapy, attenuating muscle weakness and delaying damage to the nerves [84–86]. In contrast to CIDP and GBS, MMN only responds to IVIG treatment and not to steroids and plasmapheresis [20]. The efficacy of IVIG has been demonstrated in several studies but since its beneficial effects only last a few weeks, maintenance therapy is crucial [87–89].

Cats *et al.* investigated the safety, efficacy and tolerability of KIOVIG in 20 patients with MMN who had been treated with freeze-dried 5% IVIG for at least one year prior to enrollment [58]. After enrollment, patients received GAMMAGARD S/D for 3

months during a first treatment period followed by 9 months with KIOVIG at an equivalent dose as a second treatment period. Efficacy was evaluated using the modified MRC scale to assess muscle strength and the Guy's Neurological Disability and Self Evaluation Scales to determine functional impairment. The two treatment periods were compared and it was shown that muscle strength and disability remained stable during KIOVIG administration; MRC sum scores were unchanged ($p = 0.126$) and scores for functional impairment were comparable except for a single patient who reported a minor reduction in leg impairment. The mean infusion time was substantially reduced from 4.5 h with GAMMAGARD S/D to 2.5 h with KIOVIG. Overall, KIOVIG was well-tolerated and muscle strength as well as disability scores remained stable.

A double-blinded crossover study conducted by Hahn *et al.* confirmed the efficacy and safety of KIOVIG use in MMN, revealing improved disability scores and enhanced muscle strength. A total of 44 patients were randomized with an allocation ratio of 1:1 to receive either double-blind treatment with KIOVIG followed by placebo for 12 weeks each, or the reverse. At the beginning and end of the study as well as between the two double-blinded treatment periods, open-label KIOVIG was administered for 12 weeks to ensure clinical stabilization and prevent carryover effects. Notably, efficacy was compared only for the double-blinded treatment periods and it was shown that mean maximal grip strength of the more affected hand increased slightly during KIOVIG treatment (3.75%), but deteriorated by 31.4% during placebo administration ($p = 0.005$). Similarly, Guy's Neurological Disability scores worsened in 35.7% of patients during placebo but not during KIOVIG treatment, whereas the converse was observed in only 11.9% of patients ($p = 0.021$). A premature transition to open-label KIOVIG without breaking the blind was permitted if deterioration occurred during a double-blinded study period; this was implemented in the majority of patients during placebo administration (69.0%), but in only 2.4% during KIOVIG treatment ($p < 0.001$). Overall, KIOVIG proved to be an effective, safe and well-tolerated treatment for patients with MMN, which is superior to placebo.

Data obtained in these two studies support the use of IVIG as a standard therapy for MMN.

Safety studies on KIOVIG in patients with autoimmune disorders

IVIG is generally considered a safe treatment option, but each IVIG product has a unique and specific safety profile, which is influenced by various factors, such as

diluent composition, impurity levels or the manufacturing process [12,90]. With respect to adverse reactions, <10% of patients experience side effects, usually minor in nature, with the most commonly reported events being headache, fever and chills [20]. Some of the rare, more severe adverse events are thromboembolic complications occurring during or after IVIG administration, which was discussed to be due to increased serum viscosity in patients with predisposing risk factors such as hypertension, previous vascular disease or dyslipidemia, with the majority of events occurring within 24 h post IVIG infusion [91,92]. However, there is evidence that the consensus that IVIG administration increases the risk for thromboembolic events (TEE) may be unwarranted. A literature review published by Basta *et al.* did not find any indication that IVIG infusion causes TEE, but on the contrary even hypothesized about a potential neuroprotective effect of IVIG treatment [93]. The authors reported that IVIG administration to patients with primary immunodeficiencies was associated with a four-times lower overall stroke prevalence when compared with the general population, and elderly patients (>65 years) seemed to benefit the most [93]. These findings were further supported by animal models mimicking thrombogenic conditions, such as arteriosclerosis or sickle cell anemia, in which IVIG therapy reduced arteriosclerotic plaque by up to 50% and improved blood flow, respectively [93–96].

A 5-year retrospective claims-based cohort study with the aim to identify the rate of same-day TEE in association with IVIG treatment revealed an elevated but nonsignificant increase of the TEE rate for lyophilized IVIG products when compared with the liquid reference brand KIOVIG [97,98]. However, when comparing the number of TEEs following treatment with either lyophilized GAMMAGARD S/D or liquid KIOVIG, Baxalta could not find a significant difference in TEE risk between these two product formulations [98].

Gelmont *et al.* conducted a placebo-controlled, double-blind, multicenter study in 383 subjects between 50 and 89 years of age with mild to moderate Alzheimer's disease (mini mental state examination score: 16–26) [99]. Subjects were randomized 1:1:1 to receive biweekly infusions of 400 mg/kg KIOVIG, 200 mg/kg KIOVIG or 0.25% human albumin over 18 months. The proportion of subjects with thromboembolic events was lower in the IVIG treatment groups compared with the placebo group (1.5 vs 5% of control subjects), a finding that would be in accordance with the hypothesis of a protective effect exerted by IVIG therapy against the occurrence of TEE.

Another rare severe adverse reaction is hemolytic anemia, with risk factors such as high-dose IVIG treatment

and non-0 blood group, as well as the product-related risk factor of varying isohemagglutinin contents [100,101]. However, the role of these risk factors as well as the pathomechanisms behind IVIG-linked hemolysis, is still a matter of controversy. A retrospective review of Baxalta's pharmacovigilance database on hemolytic events spontaneously reported from 2006 to 2013 after the administration of GAMMAGARD S/D or KIOVIG revealed 26 hemolytic events among a total of 1552 spontaneous AE reports received for KIOVIG from the USA alone, corresponding to a low reporting rate of 0.27 cases per 10^6 g of product distributed [12].

Markvardsen *et al.* investigated the extent of anemia and hemolysis in patients receiving IVIG for the treatment of chronic neurological disorders such as CIDP, MMN, myasthenia gravis or post-polio syndrome. This included a subset of patients treated with KIOVIG for the indications of CIDP and MMN [62]. Hemolytic anemia is a known adverse reaction to IVIG and has been observed in various indications including ADs [62,102–104]. Patients received maintenance treatment at an individualized dose with either KIOVIG (mean dose: 1.7 g/kg; $n = 22$) or PrIVIGen (CSL Behring AB, mean dose: 1.53 g/kg; $n = 28$), or *de novo* treatment with 2.0 g/kg bodyweight of PrIVIGen ($n = 34$). Assessment of hemolytic parameters of the complete treatment group before and 2 weeks after infusion showed a significant decrease in hemoglobin of 0.54 ± 0.94 mM ($p < 0.001$) as well as a significant decline in haptoglobin of 0.32 ± 0.41 μ M ($p < 0.001$), paralleled by a significant increase in reticulocytes (37 ± 69 billion/l, $p < 0.0001$) and lactate dehydrogenase (33 ± 65 U/l, $p < 0.0001$), indicating a rise in hemolytic parameters. Changes in hemoglobin by AB0 blood group were not analyzed separately for each treatment group; however, a clear correlation was evident for all patients combined; 40/48 patients with blood groups A, B or AB showed a decline in hemoglobin (mean $\pm$ SD: 1.0 ± 1.0 mM) compared with 2/17 patients with blood group 0 (mean $\pm$ SD: 0.3 ± 0.4 mM), revealing that hemolysis following high-dose IVIG treatment occurred predominantly in blood types A, B and AB. As the authors concluded, there was no statistical difference demonstrated in the degree of anemia between the PrIVIGen and KIOVIG preparations [62].

A retrospective analysis on the safety of high-dose KIOVIG infusions in 70 patients with neurologic immunologic disorders was conducted by Rigas *et al.*, with the majority of patients having received treatment for CIDP ($n = 44$) [63]. A total of 1085 infusions were given to these patients, reaching a mean monthly KIOVIG dose of 1.6 g/kg bodyweight per patient. In total, 51 nonserious AEs occurred in 23 of 70 patients, corresponding to an overall reporting rate of 4.7%

when considering the number of infusions. Headache and rash were the most frequent nonserious AEs and there were no serious AEs reported. This study revealed a favorable tolerability profile for KIOVIG in these neuroimmunologic patients, even in those who had never received IVIG treatment before.

Conclusion

Although IVIG has been used as a mainstay treatment option for decades, with rising demands, its mechanisms of action are still a matter of debate. This review aimed to summarize the clinical experience gained so far with KIOVIG in the treatment of various ADs. A detailed review of eight relevant publications, referring to KIOVIG use in MMN, CIDP, ITP, Kawasaki disease, GBS and other autoimmune conditions, revealed that the therapeutic as well as safety profiles of KIOVIG were confirmed in all studies and for all indications. However, additional studies with larger patient numbers would be beneficial to further foster these data. In general, the growing demand for IVIG over the past decades prompts research for alternative treatment approaches, which are not yet fully developed to be applied in routine clinical practice.

Future perspective

During the past decades, the clinical success of IVIG therapy has led to a slow increase in the number of registered indications as well as a more rapid growth of off-label uses. Being considered an efficacious and safe treatment option for immunodeficiencies and autoimmune conditions, the growing demand for IVIG has led to shortages and elevated costs in recent years [20]. As these costs are partially due to the need of intravenous access and hospitalizations and given that some patients may have difficult venous access or prefer a home care setting, subcutaneous immunoglobulin has recently been made available as an alternative treatment option. Its use in practice is currently extended to autoimmune diseases, and it has already been proved beneficial and safe in patients with inflammatory myopathies [105].

The problems coming along with the rising demand for IVIG have also prompted research for alternative treatment molecules with similar efficacy spectra, but the inherent polyclonality of IVIG represents a considerable challenge for the design of next-generation biologics. Nevertheless, attempts to capture the full immunoglobulin repertoire and express it as a recombinant IVIG formulation are presently ongoing, however, the approach to replace IVIG preparations in some indications by recombinant alternatives is currently far from becoming a mainstream treatment option. Whereas some effector functions of IVIG are

mediated by the Fab regions of IgG, many anti-inflammatory properties, such as to block immune complex binding to activating FcγRs, are thought to be exerted by the Fc portion, with antigen-specificity being of secondary importance. Hence, current molecular strategies are directed toward appropriately formulated Fc fragments instead of full-length IgG [106]. Promising preclinical data have shown that molecules generated by controlled multimerization of Fc fragments might not only be able to mimic one or more effector functions of IVIG, but also show efficacy at lower doses when compared with complete IgG as well as provide the advantage of a reproducible, homogeneous product [106]. Different approaches to achieve Fc multimerization are presently under investigation, such as fusing the IgG1 Fc to the IgG2 hinge region, which allows a polymerization of Fc fragments into higher-order multimers, or a fusion to the IgM tail-piece, leading to a hexamerization of IgG [106–109]. Other strategies involve antagonistic or agonistic monoclonal antibodies against FcγRs and against the FcRn; mutated Fc fragments that lead to increased binding and blockade of FcRn, thereby reducing the half-life of autoantibodies; or a soluble FcγRIIB molecule that serves as a bait for IgG, thereby inhibiting IgG–FcγR interactions [88,106,110,111]. Some of these new strategies are already under investigation in clinical trials, for example, a soluble recombinant version of FcγRIIB (SM101) has already demonstrated promising results in Phase II clinical trials in ITP as well as SLE patients [112,113]. If the promising preclinical data of the other approaches are also confirmed in human use, these newly generated molecules may become an alternative treatment option for ADs.

Also, IVIG composed of highly sialylated IgG may be a possible approach to replace conventional IVIG in the treatment of autoimmune conditions [27]. Notably, sialylated IVIG shows elevated anti-inflammatory potency when applied in the form of a subfraction that can be derived from commercially available IVIG via affinity purification, targeting specific antigens/antibodies associated with a specific AD [114]. Moreover, recombinant highly sialylated IgG may be of interest for the development of therapeutic antibodies exerting anti-inflammatory properties to be applied as an alternative to IVIG [49].

By all means, with all present and future developments, safety considerations will have to be of pivotal importance.

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Acknowledgements

The **Figure 1** illustration was developed by N Preiswerk (content) and G Codoni (graphics) from Medicalwriters.com (Zurich, Switzerland).

Financial & competing interests disclosure

N Nikolov is an employee and shareholder of Baxalta GmbH. HP Schwarz is an employee and shareholder of Baxalta Inno-

vations GmbH, and J Reisinger was an employee of Baxalta Innovations GmbH at the time this manuscript was written. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Intravenous immunoglobulin has been used in clinical practice for decades to treat autoimmune disorders and its immunomodulatory properties have been confirmed for many different indications.
- Despite its widespread use as an anti-inflammatory agent, its exact mechanisms of action are still not clearly understood.
- The constant rise in intravenous immunoglobulin demand over the years has prompted research for alternative treatment molecules to target specific pathophysiological pathways.
- This review article summarizes the experience gained with KIOVIG use in clinical trials involving patients with autoimmune disorders.
- For this purpose, a systemic search of the scientific literature was conducted and eight relevant publications were selected for detailed review.
- These articles confirmed the favorable efficacy and safety profiles of the product in the subject populations studied.
- To further substantiate these findings, additional studies with larger patient numbers would be beneficial.

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