



FcRn antagonists in ITP

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Abstract: Primary immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder. It is a diagnosis of exclusion and is associated with a persistent platelet count of $<100 \times 10^9/L$ without identifiable cause. In almost two thirds of patients, immunoglobulin G (IgG) autoantibodies directed against platelet receptors can be detected. They are associated with increased platelet clearance and destruction, inhibition of platelet production, and are also thought to impair platelet function. The clinical impact in many patients is an increased risk of bleeding and impaired quality of life. Current treatments have limited efficacy and significant side effects. Additionally, although current guidelines can educate treatment decisions, there is no real treatment paradigm which exists ('trial and error' approach), and optimal treatment decisions for each patient need to be individualised and remain a challenge in many cases, highlighting the current unmet needs. A novel approach to treatment is based on lowering levels of pathogenic IgG autoantibodies and is explored in this review. The neonatal Fc receptor (FcRn) is a major regulator in the homeostasis of IgG and albumin protecting them from degradation. FcRn-mediated extension of the half-life for IgG antibody responses is beneficial in the protection against pathogens, it will also prolong the serum half-life of IgG autoantibodies therefore promoting autoimmune diseases and their chronicity. It is postulated that targeted reduction of IgGs through FcRn blockade may either prevent or reduce the pathogenic actions of IgG autoantibodies and represents an exciting novel treatment modality in ITP. In this review article, we discuss the role of FcRn as the central regulator of IgG homeostasis, the therapeutic approaches involving IgG reduction, and the clinical trial results of two FcRn antagonists currently investigated in patients with ITP, efgartigimod and rozanolixizumab.

Keywords: FcRn antagonist; neonatal Fc receptor; IgG autoantibodies; immune thrombocytopenia

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Introduction

ITP is an acquired autoimmune bleeding disorder characterized by a low platelet count ($<100 \times 10^9/L$) in the absence of other causes or disorders associated with thrombocytopenia (1-3). Depending on the level of reduction in the platelet count there is an increased risk of bleeding, ranging from skin and mucosal bleeding, menorrhagia, gastrointestinal bleeding and in the most severe intracranial hemorrhage (1,4,5). It has also been recognised that there is

an increased incidence of depression and fatigue (6) as well as side effects of existing therapies, which all have an impact on quality of life (7-12). There are a number of different therapeutic approaches and, traditionally non-specific immunosuppression (e.g., steroids, rituximab and other immune suppressive therapies), and inhibition of platelet clearance [e.g., splenectomy, intravenous immunoglobulin (IVIg), anti-D immunoglobulin, and the recently FDA-approved Syk inhibitor fostamatinib (13)] have been the mainstay of treatment. Over the last decade stimulation of

platelet production [e.g., thrombopoietin receptor agonists (TPO-RA)] (4,14) has come increasingly to the fore and has been an important addition to the treatment options. Splenectomy remains the only treatment that provides sustained remission off therapy for a high proportion of patients (2,3) but has increasingly fallen out of favour as newer splenectomy sparing options have become available.

Although the pathogenesis of ITP is complex in nearly two-thirds of patient autoantibodies, predominantly of the IgG class can be detected. These mediate their pathogenic actions by targeting surface glycoproteins (GP) which are expressed on both platelets and megakaryocytes, the progenitor cells of platelets (15,16). Detected in approximately 60% of patients with ITP (17), they contribute to the platelet degradation, induction of platelet apoptosis, impairment of platelet production and platelet function (18-25). The importance of IgG autoantibodies in the development of ITP is supported by the observation of a low platelet count in infants born to mothers with ITP, due to placental transfer of autoantibodies (26,27). Older IgG-depleting treatment modalities, such as immunoadsorption and plasmapheresis, which lead to a reduction of platelet-associated autoantibodies (26) and an associated platelet count (28) increment support the central importance of autoantibodies.

The neonatal Fc Receptor (FcRn) is acknowledged as the central regulator of IgG homeostasis, protecting the IgG from lysosomal degradation and as a consequence increasing their half-life (29,30). FcRn also recycles albumin but binds at a site distinct from that of IgGs (31). The identification of FcRn as an integral component in the regulation of IgG homeostasis stimulated the development of FcRn antagonists. In healthy volunteers, FcRn antagonists, such as efgartigimod, a human IgG1 antibody Fc-fragment, or rozanolixizumab, an IgG4 monoclonal antibody (mAb), had no significant adverse events and were well tolerated. They induced a rapid reduction in total IgGs involving all IgG subtypes (32,33). The concept of targeted reduction of IgG autoantibodies through FcRn blockade to prevent their pathogenic actions has then been demonstrated in patients with ITP in Phase 2 clinical trials and is currently being evaluated in Phase 3 clinical trials.

In this review article, we discuss the role of FcRn as the central regulator of IgG homeostasis, the therapeutic approaches involving IgG reduction as well as the clinical trial results of two FcRn antagonists currently being investigated in Phase 3 clinical trials in patients with ITP, efgartigimod and rozanolixizumab.

FcRn is the central regulator of IgG homeostasis

FcRn roles

FcRn is a major histocompatibility complex (MHC) class I-related receptor, interacting with antibodies of the IgG class as a heterodimer of a heavy α -chain non-covalently associated with β 2-microglobulin, which binds to the constant or fragment crystallizable (Fc) region of the IgG subclasses (*Figure 1*) (34). Given that IgG is a homodimeric molecule and contains two Fc domains, FcRn-IgG interactions have been proposed to occur with a stoichiometry of two FcRn molecules per one IgG (2:1) (35). FcRn is a key player in regulating the dynamic behavior, including distribution, transport and persistence of IgG antibodies throughout the body, playing an important role in IgG homeostasis throughout life (36,37), FcRn may also have a role on antigen presentation, which could mean that its long-term blockade could affect autoimmune responses since the plasma cells producing the IgG autoantibodies would be deprived from survival signals linked to antigen presentation (38). The FcRn-mediated IgG recycling rate is estimated to be 42% greater than the IgG production rate, indicating that the recycling of IgG, not its production, is the dominant process for maintaining the IgG serum concentration in human (39). The serum concentration of IgGs is therefore controlled not only by antigen-driven production of IgGs, but by FcRn-mediated salvage of IgGs from degradation (39). The discovery of these activities extends the role of this Fc receptor well beyond its original identification as the transporter of IgGs from mother to developing fetus (hence the name n, for neonatal). Indeed, FcRn was originally isolated from the rat intestinal epithelial cell brush borders (40-43). During gestation in humans, FcRn mediates the transfer of IgGs from mother to fetus across the placenta, providing newborns with humoral immunity (35,44). FcRn is widely distributed in various mammalian organs, tissues and cells, it is most highly expressed in hematopoietic cells, intestinal epithelia, and in the vascular endothelium, particularly in skin and skeletal muscle (45-47).

FcRn as a regulator of the half-life of IgGs

FcRn binds to the Fc region of IgGs at a distinct site from the binding sites of the classical Fc receptors for IgGs (Fc γ Rs) or the C1q component of complement which binds near the upper CH2 domain and hinge region, which initiates the classical pathway of complement activation

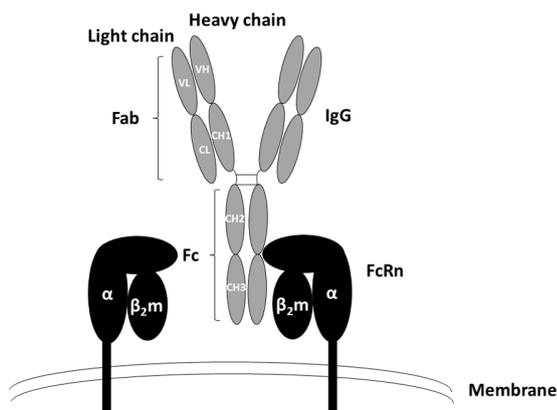


Figure 1 Schematic representation of the IgG-FcRn interaction. FcRn (depicted here in its transmembrane form) is a heterodimer structurally similar to the MHC-class I molecules, rather than the classical Fc γ R, consisting of a transmembrane glycosylated α -chain non-covalently coupled to β_2 -microglobulin. The α -chain has a large ectodomain comprising three subdomains, a transmembrane region, and a short cytoplasmic tail that encodes for a highly conserved signaling motif important for intracellular trafficking of FcRn. The gene encoding FcRn is located outside the MHC gene complex and, unlike the classical MHC class I proteins, the MHC peptide-binding groove is obstructed in FcRn. Given that IgG is a homodimeric molecule, and contains two Fc domains, FcRn-IgG interactions have been proposed to occur with a stoichiometry of two FcRn molecules per one IgG (2:1). The interaction site is distinct from the classical Fc γ R and complement binding sites. In contrast to glycan-dependent IgG binding for the classical Fc γ R, IgG binding to FcRn is independent of glycosylation. Four residues (Ile253, His310, His435 and Tyr436) located within the CH2-CH3 interface of the Fc region of IgG are highly conserved in mammals and play a central role in IgG binding to FcRn. FcRn, expressed in epithelial, endothelial, and hematopoietic cells, binds IgG at low pH, mediating the transfer of these antibodies from mother to young, and preserving it in the circulation throughout the life. β_2 m, β_2 -microglobulin; Fab, fragment antigen-binding; Fc, fragment crystallizable; FcRn, neonatal fragment crystallizable receptor; IgG, immunoglobulin G.

(Figure 1) (48,49), The IgG-FcRn interface is composed of three subsites, a hydrophobic core and two electrostatic sites. IgG residues that are critical for the binding of human IgGs to FcRn include isoleucine (Ile)253, histidine (His)310, His435, and tyrosine (Tyr)436. These are located on the exposed loops at the CH2-CH3 domain interface (30,49-51). In general, these amino acids show higher variability, such as residues 435 and 436, than Ile253 and

His310 across different IgG isotypes (52). The His residues of IgG interact with acidic residues of FcRn (49,53). The interaction of the protonated imidazole side chain of His (pKa ~6) with these acidic residues at pH ~6 confers the characteristic pH dependent binding (relatively high affinity at acidic pH, with very weak to negligible binding at pH 7.3–7.4) that is observed for the majority of IgGs (54,55). Therefore, FcRn binds to the Fc region of IgG in a strictly pH-dependent manner in contrast to Fc γ Rs and other Fc-binding proteins; at physiological pH 7.4, FcRn does not bind IgGs, but has a low micromolar to nanomolar affinity for the Fc region of IgGs at the acidic pH of the endosome (pH 6–6.5) (29). FcRn-IgG complexes are then internalized primarily by fluid phase pinocytosis (due to the very low affinity of FcRn for most IgG subclasses at extracellular, near neutral pH), sorted in early (sorting) endosomes away from lysosomal degradation and recycled back to the cell surface for exocytic release (Figure 2) (56-58). IgGs that do not bind FcRn, possibly due to saturation of FcRn interaction sites or IgG mutations that ablate FcRn binding, proceed through lysosomal degradation (59,60). FcRn recycling of IgGs results in the higher concentration and longer half-life of IgGs ($T_{1/2} \approx 21$ days) compared with other immunoglobulins, such as IgA ($T_{1/2} \approx 5.8$ days) and IgM ($T_{1/2} \approx 5.1$ days), which are not recycled by FcRn (42,61-63). As has been previously mentioned albumin is also recycled by FcRn, but it is known to bind at a site distinct from that of IgGs (64). This interaction is also pH-dependent (65).

Pathogenic properties of IgG autoantibodies in autoimmune diseases

Elevated levels of IgG autoantibodies are associated with many autoimmune diseases, including myasthenia gravis (MG), systemic lupus erythematosus, rheumatoid arthritis, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), pemphigus vulgaris (PV), and ITP (34,66-71). The position of FcRn as central regulator of IgG serum levels led to study of its manipulation in controlling the levels of IgG autoantibodies. While the mechanism by which IgG autoantibodies are initiated in ITP (72) is not entirely clear, they are central to the clinical impact of the disease by targeting surface GPs expressed on platelets and megakaryocytes (15-17). The IgG1 subclass of IgG immunoglobulin are the predominant form identified, while IgG2, IgG3, and IgG4 subclass autoantibodies may be present they are usually in association with IgG1 antibodies (73,74). Detected in approximately

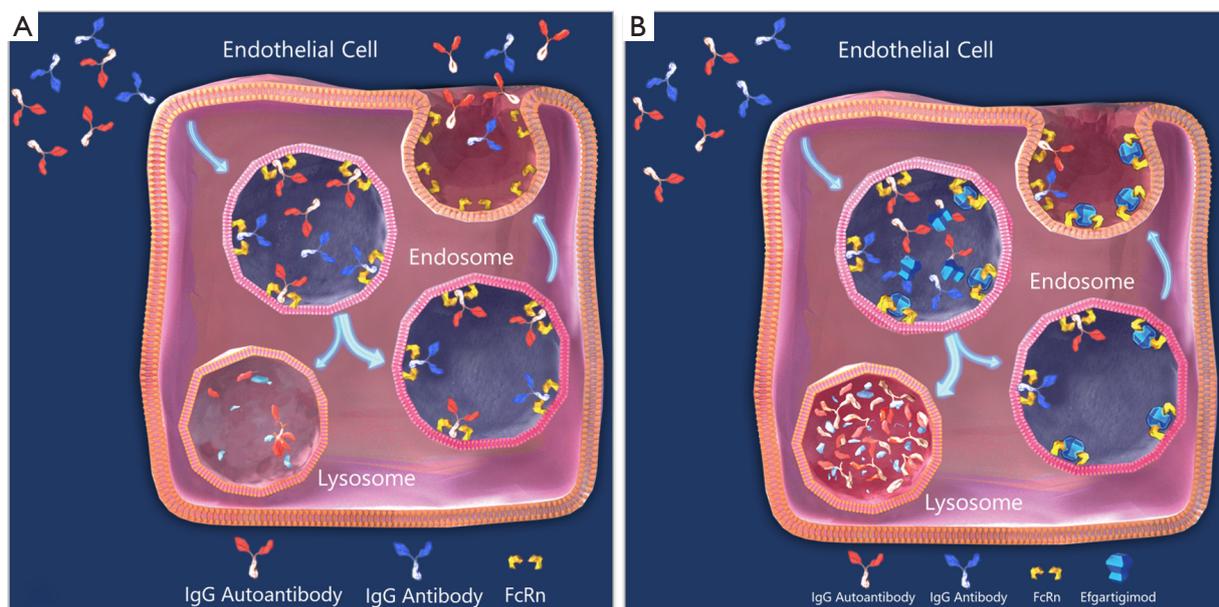


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Figure 2 FcRn is the central regulator of IgG homeostasis. (A) FcRn rescues IgGs from lysosomal degradation in a pH-independent manner (FcRn does not bind IgG at physiological pH 7.4 but does at the acidic pH of the endosome, pH 6–6.5), prolonging their half-life, and promoting their tissue penetration. (B) FcRn antagonists (efgartigimod, a human IgG1 antibody Fc-fragment depicted here) potentially block FcRn leading to IgG elimination. FcRn, neonatal fragment crystallizable receptor, IgG, immunoglobulin G. Permission for the reproduction of this figure here has been obtained from argenx US Inc.

60% of patients with ITP (17), IgG autoantibodies will, in general, opsonize platelets, resulting in clearance by splenic macrophages, inducing platelet apoptosis (18), complement-dependent lysis (19) or desialylation of platelets leading to Fc-independent liver clearance (*Figure 3A,B*) (20). A more recent finding is their ability to inhibit megakaryocyte proliferation and differentiation resulting in reduced platelet production (*Figure 3C*) (21–23). Some of the anti-GP antibodies also interfere with platelet function, leading to an inhibition of platelet aggregation (24) and therefore blood clot formation (*Figure 3D*) (25). The majority of anti-GP autoantibodies is directed against GPIIb/IIIa (~70%) and/or GPIb-IX-V complex (~25%) (75,76), but antibodies against GPIa-IIa or GPVI are also detected in sporadic cases (~5%) (17),

Established therapies reducing IgG autoantibodies

Therapeutic plasma exchange

Plasma exchange is a procedure that separates and

removes the patient's plasma allowing to get rid of the IgG autoantibodies. The plasma that is removed from the patient must be replaced to maintain volume and replenish other essential components. Commonly replacement fluids will contain some proportion of another protein solution, such as 5% human albumin. The standard dose is one plasma volume exchange once per day for one to eight days (77). Reduction in IgG levels correlates with improvement in ITP manifestations (29–80% response rate) (77), providing proof-of-concept that reduction of IgG levels through FcRn antagonism is a viable therapeutic option. Plasma exchange is frequently associated with a mix of side effects including fatigue, nausea, dizziness, feeling cold and tingling in the fingers and around the mouth. Allergic reaction and lowered blood pressure can be a particular problem (28,78,79).

Protein A immunoadsorption

Evidence of efficacy has been shown for extracorporeal immunoadsorption of plasma as a therapy for adults with treatment-resistant ITP to remove IgGs and circulating immune complexes. An average of six treatments (0.25 to

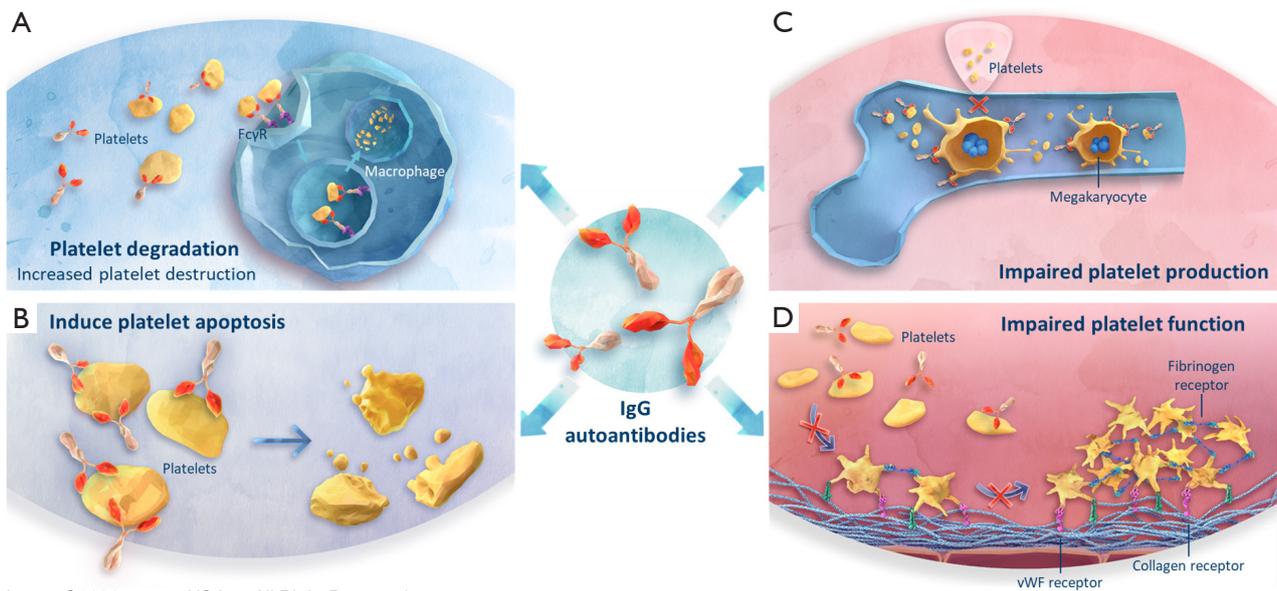


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Figure 3 IgG autoantibodies are key mediators of primary ITP pathophysiology. Autoantibodies in ITP, which are predominantly of the IgG class, mediate pathogenic actions by targeting surface glycoproteins expressed on platelets and megakaryocytes, the progenitor cells of platelets. Detectable in most patients, (A) they can opsonize platelets, resulting in clearance by splenic macrophages, (B) induce platelet apoptosis, complement-dependent lysis or desialylation of platelets leading to Fc-independent liver clearance. (C) Moreover, they can inhibit megakaryocyte proliferation and differentiation resulting in diminished platelet production. (D) Recently, it has been reported that some anti-glycoprotein antibodies interfere with platelet functionality, inhibiting platelet aggregation and blood clot formation. Permission for the reproduction of this figure here has been obtained from argenx US Inc.

2.0 L plasma per treatment) is generally given over two to three weeks (77). Clinical responses were associated with 21% response rate and significant decreases in specific serum platelet autoantibodies (including anti-GP IIb/IIIa), platelet-associated immunoglobulin, and circulating immune complexes (77). However, hypersensitivity reactions, pain, nausea/vomiting, and cardiopulmonary complications have been associated to this therapy (26,27).

High-dose intravenous immunoglobulin

IVIg products are prepared from the pooled plasma of healthy donors. It consists of over 95% IgGs with a subclass distribution corresponding to that in normal human serum (80). The use of high-dose IVIg for the treatment of ITP in both children and adults was shown more than four decades ago (81,82). The dose regimens used are variable but were initially given as 0.4 g/kg daily for 5 days. More recently it has been accepted that 1 g/kg IVIg is effective in the majority of recipients with two-thirds normalising their platelet count with fewer than 10% failing to elicit

any response. This is seen even those not responding to corticosteroids (83). Overall, response rates are similar to those of corticosteroids, but with a shorter time to response. This may last up to a week but is frequently as short as 24-48 hours (84). IVIg treatment has a significant cost and is associated with frequent side effects, the most common being headache, which may occur in up to 30%, and skin rashes. More rarely but of greater severity are renal failure and thrombosis although these are less common with the newer formulations, which have low sucrose content (83). Due to the cost and short response duration, IVIg is considered more as a rescue option in ITP than routine first-line treatment and is often used as a bridge until other treatments have had an effect (2,3). Therefore its use is reserved for patients with severe bleeding as part of combination therapy, as preparation for an urgent invasive procedure or as bridging to more definitive second-line treatment in a unresponsive patient population. There are several theories as to the mechanism of IVIg action and it is likely that it acts multiple mechanisms. The most likely early mechanism of response is by inhibition of

Fc γ R-mediated platelet destruction but it is also known to have immunomodulatory effects including anti-idiotypic neutralization of antiplatelet antibodies and stimulation of Fc γ RIIB expression (85). There is also a suggestion that it may also work through competitive inhibition of FcRn and IVIg-induced acceleration of antiplatelet antibody elimination (86).

IgG autoantibodies reduction through FcRn blocking

As indicated previously, FcRn is the predominant regulator of IgG levels, recycling IgGs at a faster rate than IgG production (39). Given the pathogenic roles of IgG autoantibodies in ITP and the proven efficacy of existing treatments capable of reducing IgG levels (e.g., therapeutic plasma exchange, protein A immunoadsorption, and IVIg), blocking the recycling of IgGs by FcRn represents a rational and promising approach for the treatment of patients with ITP. An understanding of the biochemistry of FcRn and on its interaction with IgGs stimulated further study, which was aided by the generation of FcRn knock-out and human FcRn transgenic mice. Recombinant soluble human FcRn can be produced in bacteria in high amounts, with the recombinant receptor reproducing the characteristic pH-dependent reversible binding to IgGs at pH 6.0, with almost undetectable binding at neutral pH (87). However, experimental evidence demonstrating its transfer into intracellular acidic compartments of endosomes where IgG binding to FcRn should occur, is lacking, indicating that it could not be used as a therapeutic approach. It was therefore considered that inhibition of the IgG-FcRn interaction was probably best achieved by using FcRn-specific blocking agents (*Figure 2B*) (88). There are a range of FcRn inhibitors from peptide/small protein to antibody-based blockers which have been generated, and many are in various stages of clinical development following preclinical analyses in animal models (*Table 1*).

FcRn antagonists in clinical development

Antibody fragments directed against FcRn

One class of FcRn antagonists involves the use of Fc engineering to generate competitive IgG molecules with substantially increased affinity for FcRn at both near neutral and acidic pH (89), such as efgartigimod, a human IgG1 antibody Fc-fragment (*Table 1*) (32). Unlike mAbs, efgartigimod does not have a Fab region. Instead,

efgartigimod binds to FcRn via its Fc region, which is the same way that endogenous IgGs binds to FcRn (34,90). This molecule is a natural ligand of FcRn that has been engineered with ABDEGTM (for AntiBodies that enhance IgG DEGradation) mutations [methionine (Met)252 to Tyr, serine (Ser)254 to threonine (Thr), Thr256 to glutamic acid (Glu), His433 to lysine (Lys), and asparagine (Asn)434 to phenylalanine (Phe)], which are located in the CH2 and CH3 domain of the Fc region. The impact of these mutations is to increase affinity for FcRn. Due to its superior 100-fold increased affinity for FcRn at pH 6.0 (K_D efgartigimod =15.5 nM *vs.* K_D wild-type human IgG1 =370 nM) and the retained significant binding activity at pH 7.2 (*vs.* no binding detected for wild-type human IgG1), efgartigimod therefore outcompetes IgGs for binding to FcRn (89). The impact of this results in accelerated degradation of endogenous IgGs (*Figure 2B*) (29,89,91). By contrast, mAbs that bind through their variable domains typically involve distinct sets of interacting residues and do not have this property (90). Due to the pH-dependent binding and especially the relative poor affinity at neutral pH, efgartigimod is able to dissociate from the complex with FcRn leading to a serum half-life that has been reported to be longer than for the FcRn targeting mAbs (i.e., approximately 85.1 to 104 hours over 2.0 to 50 mg/kg) (32).

Monoclonal antibodies directed against FcRn

The other class of FcRn antagonists consists of fully human and humanized mAbs, which have been engineered such that their Fab portions binds FcRn with high affinity and prevent the binding of wild type IgG Fc regions with FcRn. These mAbs ultimately outcompete binding of IgG autoantibodies and force their degradation, such as rozanolixizumab (*Table 1*).

Clinical Trial Results of Efgartigimod, a Novel FcRn Antibody Fragment Antagonist

Phase 1 study

A first-in-human, randomized, double-blind, placebo-controlled, dose-escalating study was conducted in 62 healthy volunteers to explore single and multiple ascending intravenous (IV) doses of efgartigimod (NCT03457649) (32). The study objectives were to assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity. Importantly

Table 1 FcRn antagonists in clinical development

Drug	Company	Molecule (Molecular Weight)	Clinical Development (Route of Administration and NCT number)
Efgartigimod (ARGX-113)	Argenx	Humanized IgG1 Fc fragment ABDEG TM (50 kDa)	<ul style="list-style-type: none"> • Phase 3: <ul style="list-style-type: none"> ○ MG (IV infusion, NCT03669588) ○ ITP (IV infusion, NCT04188379) • Phase 2: <ul style="list-style-type: none"> ○ CIDP (SC injection, NCT04281472) ○ Pemphigus (IV infusion, NCT03334058)
Rozanolixizumab (UCB7665)	UCB	Humanized IgG4 mAb (150 kDa)	<ul style="list-style-type: none"> • Phase 3: <ul style="list-style-type: none"> ○ MG (SC infusion, NCT03971422) ○ ITP (SC infusion, NCT04200456 and NCT04224688) • Phase 2: CIDP (SC infusion, NCT03861481)
Nipocalimab (M281)	Momenta Pharmaceuticals	Fc dead IgG1 mAb (150 kDa)	<ul style="list-style-type: none"> • Phase 3: WAIHA (IV infusion, NCT04119050) • Phase 2: <ul style="list-style-type: none"> ○ HDFN (IV infusion, NCT03842189) ○ MG (IV infusion, NCT03772587)
Orilanolimab (ALXN1830/SYNT001)	Alexion Pharmaceuticals/Syntimmune	Humanized IgG4 mAb (150 kDa)	<ul style="list-style-type: none"> • Phase 2: WAIHA (IV infusion, withdrawn, NCT04256148)
Batoclimab (IMVT1401/RVT1401/HBM9161)	Immunovant/HanAll Biopharma/Harbour BioMed	Fc dead IgG1 mAb (150 kDa)	<ul style="list-style-type: none"> • Phase 2: <ul style="list-style-type: none"> ○ MG (SC injection, NCT03863080) ○ Graves' Ophthalmopathy (SC injection, Phase 2a: NCT03922321 and Phase 2b: NCT03938545)

FcRn antagonists have been engineered to interrupt FcRn-IgG interactions resulting in reduction of all subclasses of IgG. As such, these agents may have therapeutic effects across all patients with ITP presenting IgG autoantibodies. Two FcRn antagonists are currently investigated in primary ITP Phase 3 clinical trials, efgartigimod and rozanolixizumab. CIDP, chronic inflammatory demyelinating polyneuropathy; HDFN, hemolytic disease of fetus and newborn; IV, intravenous; mAb, monoclonal antibody; MG, myasthenia gravis; PV, Pemphigus Vulgaris; SC, subcutaneous; WAIHA, warm autoimmune hemolytic anemia.

efgartigimod did not alter the homeostasis of either albumin or Igs other than IgGs, and no serious adverse events related to efgartigimod infusion were observed. One serious adverse event of hyperventilation was reported but was considered unlikely to be related to efgartigimod treatment. Single administration of efgartigimod (0.2, 2, 10, 25 or 50 mg/kg) reduced baseline IgG levels by approximately 50%, while multiple dosing (10 mg/kg q4d, 10 mg/kg q7d or 25 mg/kg q7d) further lowered IgG levels by an average of 75% from baseline levels, with 10 mg/kg q7d chosen as the ideal dose. IgG levels were observed to return to baseline approximately eight weeks after cessation of administration. This sustained PD effect contrasts with

the PK profile of efgartigimod, which demonstrated a rapid reduction in serum concentrations of the compound following the last dosing. These findings suggest that most of the administered efgartigimod is rapidly bound to FcRn, antagonizing its function for a prolonged period.

Phase 2 study

In a randomized, double-blind, placebo-controlled Phase 2 study (NCT03102593), 38 patients were randomized 1:1:1 to receive 4 weekly intravenous infusions of either placebo (N=12) or efgartigimod at a dose of 5 mg/kg (N=13) or 10 mg/kg (N=13) (92). Patients who were predominantly

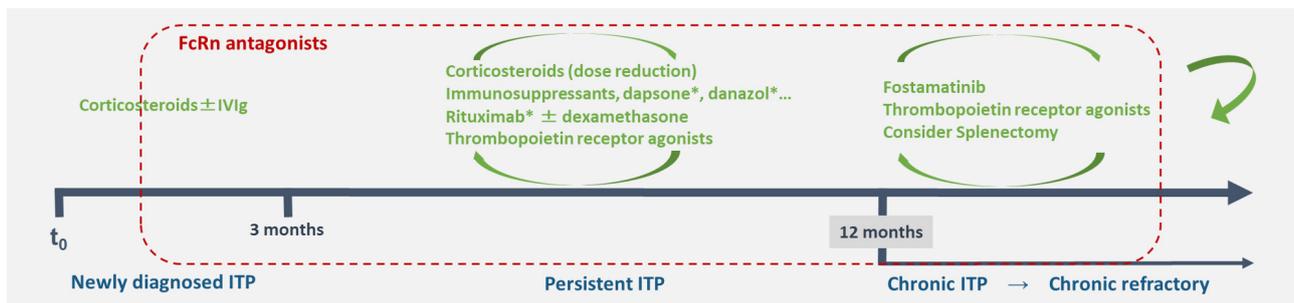


Figure 4 Window of opportunity for FcRn antagonists. Currently, patients cycle through therapies until they achieve their treatment goals.

refractory, or who had relapsed following previous lines of therapy were included in the study. This short treatment cycle of efgartigimod in patients with ITP, was designed to look at tolerability and to confirm the favourable safety profile seen in the Phase 1 studies. Following infusion of efgartigimod there was a rapid reduction of total IgG levels (up to 63.7% mean change from baseline), which was associated with clinically relevant increases in platelet counts (46% patients on efgartigimod *vs.* 25% on placebo achieved a platelet count of $\geq 50 \times 10^9/L$ on at least two occasions and 38% *vs.* 0% achieved $\geq 50 \times 10^9/L$ for at least 10 cumulative days). Although patients with severe bleeding were not entered into the randomised study there was also a reduced proportion of patients with minor bleeding episodes. There was also a parallel reduction in platelet-associated autoantibody (GPIIb/IIIa, GPIb/IX, and GPIa/IIa) levels.

Phase 3 study

A Phase 3, multicenter, randomized, double-blinded, placebo-controlled trial (NCT04188379), evaluates the efficacy and safety of efgartigimod in adults with persistent or chronic primary ITP. Trial participants will be eligible for continuation into a long-term open-label extension trial (NCT04225156).

Other indications

After positive results obtained in a Phase 2 proof-of-concept trial investigating the use of efgartigimod in patients with MG (NCT02965573) (93), positive topline Phase 3 results have been announced (NCT03669588). Phase 2 clinical trials investigating the use of efgartigimod in patients with CIDP (NCT04281472) and pemphigus (NCT03334058) are ongoing.

Clinical trial results of rozanolixizumab, a novel FcRn antagonist

Phase 1 study

A first-in-human, randomized, double-blind, placebo-controlled, dose-escalating study of IV or subcutaneous (SC) rozanolixizumab was conducted in healthy subjects (NCT02220153). The primary objective was to evaluate safety and tolerability with the secondary objectives of assessing the PK and PD, and the impact on IgG levels. Forty-nine subjects were randomized into 6 cohorts to receive rozanolixizumab ($n=36$) or placebo ($n=13$). Rozanolixizumab was given to 3 cohorts as an IV preparation, and the final 3 subcutaneously. The SC doses given were 1, 4, or 7 mg/kg ($n=6$ for each cohort; plus $n=7$ or 6 for placebo, respectively). The most frequent treatment-emergent adverse event [TEAE]; headache, 14 of 36 (38.9%) subjects]. This was dose-dependent and was more prominent after IV administration. Severe TEAEs occurred in four subjects, all in the highest-dose IV group [headache ($n=3$) and back pain ($n=1$)]. The safety profile of IV doses of 7 mg/kg precluded the use of higher doses in this study of healthy individuals. There were sustained dose-dependent reductions in serum IgG concentrations (IV and SC rozanolixizumab). IgG concentrations in the serum were reduced by up to 50% in this study, which is similar to the 50% to 60% reductions observed after plasma exchange (94,95). Rozanolixizumab PK demonstrated nonlinear increases with dose.

Phase 2 study

The Phase 2 study to assess the safety, tolerability and efficacy of rozanolixizumab was designed to explore a multiple dose regimen in order to inform the dosing

strategy for further development in ITP (NCT02718716). Sixty-six patients received either a single dose (1×15 mg/kg or 1×20 mg/kg) or multiple doses (5×4 mg/kg, 3×7 mg/kg, 2×10 mg/kg weekly) of SC rozanolixizumab. The total weekly dose was similar in all treatment groups, ranging from 15 to 21 mg/kg. The target platelet count was $\geq 50 \times 10^9/L$ and was seen across all groups in > 50% of patients and this coincided with the lowest mean IgG levels. There was a higher response rate (55–67% in 1×15 mg/kg and 1×20 mg/kg dose groups *vs.* 36–45% in 5×4, 3×7 and 2×10 mg/kg dose groups) and shorter time to response achieved by the 1×15 and 1×20 mg/kg rozanolixizumab dose groups (96). Results confirm that rozanolixizumab was well tolerated across all dose groups (96), consistent with previous rozanolixizumab studies. There is no specific description of the effect on autoantibody levels but the assumption is that that these paralleled the fall in IgG. The most commonly reported adverse event was headache, with mild-to-moderate headaches seen at higher doses; other reported adverse events included diarrhea and vomiting. These events were usually of short duration and the majority of events resolved without treatment. No patient discontinued the study due to side effects (96).

Phase 3 study and other indications

Phase 3 clinical trials investigating the use of rozanolixizumab in patients with primary ITP (NCT04200456 and NCT04224688) and MG (NCT03971422) are ongoing, as well as a Phase 2 in patients with CIDP (NCT03861481).

Comparison of different FcRn antagonists

The clinical trials results described above have shown that FcRn antagonists effectively reduce IgG levels with no impacts on levels of other immunoglobulins (32). This is in contrast to other common ITP treatments, such as steroids and non-steroidal immunosuppressants, which cause a wide-ranging depression of the immune system (97), and therapeutic plasma exchange, which removes normal and pathogenic IgGs, but depletes the blood of other Ig isotypes (such as IgM and IgA), coagulation factors, complement proteins, and albumin-bound medications (98).

Reduction in albumin levels were reported for nipocalimab (99), rozanolixizumab (33), and batoclimab (100) whereas this finding was not observed for the efgartigimod and orilanolimab (*Table 1*). Albumin is also recycled via FcRn, but binds to a different epitope,

suggesting that IgG and albumin can bind simultaneously to FcRn (101). The full-length mAbs have picomolar affinities, with no difference between pH 6.0 and pH 7.4 in contrast to efgartigimod, for example, which has a pH-dependent affinity in the nanomolar range (89). Interestingly, previous studies have shown that when there is crosslinking of FcRn by multivalent immune complexes, such as full-length mAbs, there is an increase in lysosomal trafficking of FcRn-ligand complexes and immune activation (102,103).

To date, the various FcRn antagonists in clinical development display a favourable safety profile with the majority of TEAEs being mild. Interestingly, SC administration of rozanolixizumab was better tolerated than IV administration in healthy volunteers with occurrence of dose-dependent headaches and back pain, including four severe TEAEs in the latter group (33). Dose-dependent vomiting, nausea, and pyrexia were also seen more frequently with the IV formulation compared to placebo and were less frequent with the SC formulation. As a result of these findings, subsequent clinical development was continued using SC administration only to avoid high C_{max} levels of the mAb. The improved tolerability profile of the SC administration was confirmed in patients with ITP, but when higher FcRn saturating doses were used the headaches were observed again (33,96). A similar TEAE profile was reported for orilanolimab (104), which is a humanized IgG4 like rozanolixizumab. Interestingly, neither nipocalimab (99) nor batoclimab (105), both humanized IgG1 mAbs (Fc engineered to take away effector functions), have reported this issue. These side effects may therefore be caused by FcγR-mediated effects. IgG4 antibodies differ functionally from the other IgG subclasses in their anti-inflammatory activity, making them the preferred subclass for applications where recruitment of immune effector functions is unnecessary. Nevertheless, it has been shown that the CD28 agonistic IgG4 mAb, TGN1412, via residual interactions with high affinity FcγR induced T-cell proliferation leading to the cytokine storm (106). Efgartigimod due to its ABDEGTM mutations has diminished affinity for FcγRs (107), which may explain that headaches and gastrointestinal problems were not observed with this drug.

Conclusions

Primary ITP is an acquired autoimmune bleeding disorder, characterized by a low platelet count ($< 100 \times 10^9/L$). In up to two-thirds of patients, IgG autoantibodies directed against platelet receptors can be detected. Their primary impact

is to enhance platelet clearance and destruction. They are also known to have a significant inhibitory effect on platelet production, and may also impair platelet function. The overall impact is that as the platelet count falls there is an increased incidence of spontaneous bruising and an increased risk of excessive, and occasionally life-threatening, bleeding. More recently it has been recognized that there is also an associated increase in fatigue and tiredness with an impact on quality of life. FcRn is the central regulator of IgG homeostasis, rescuing IgGs from lysosomal degradation, prolonging their half-life, and promoting tissue distribution of IgGs. While FcRn-mediated half-life extension is beneficial for IgG responses against pathogens, it also prolongs the serum half-life of IgG autoantibodies promoting therefore autoimmune diseases and their chronicity. Drugs that block FcRn-mediated recycling of IgGs could reduce all IgG subtypes without impacting concentrations of other immunoglobulin isotypes, allowing these therapies to potentially treat a broad patient population with reduced side effects (*Figure 4*). This form of targeted therapy by specifically reducing only IgG has a potential advantage over broader immunosuppressive treatments which may lead to bone marrow suppression, in addition to a more non-specific immune suppression with a more general infection risk.

One antibody fragment and four fully human/humanized mAbs are currently in various phases of clinical development. Collectively, the clinical data obtained from these FcRn antagonists suggest that targeted IgG reduction is a potential new treatment modality in primary ITP, and warrants further evaluation of longer-term treatment in larger Phase 3 studies to fully demonstrate the potential of this strategy by providing a safe and effective treatment for patients with ITP.

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