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Review Article

IgG regulation through FcRn blocking: A novel mechanism for the treatment of myasthenia gravis

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ABSTRACT

The neonatal Fc receptor (FcRn) is an MHC class I–like molecule that is widely distributed in mammalian organs, tissues, and cells. FcRn is critical to maintaining immunoglobulin G (IgG) and albumin levels through rescuing these molecules from lysosomal degradation. IgG autoantibodies are associated with many autoimmune diseases, including myasthenia gravis (MG), a rare neuromuscular autoimmune disease that causes debilitating and, in its generalized form (gMG), potentially life-threatening muscle weakness. IgG autoantibodies are directly pathogenic in MG and target neuromuscular junction proteins, causing neuromuscular transmission failure. Treatment approaches that reduce autoantibody levels, such as therapeutic plasma exchange and intravenous immunoglobulin, have been shown to be effective for gMG patients but are not indicated as ongoing maintenance therapies and can be associated with burdensome side effects. Agents that block FcRn-mediated recycling of IgG represent a rational and promising approach for the treatment of gMG. Blocking FcRn allows targeted reduction of all IgG subtypes without decreasing concentrations of other Ig isotypes; therefore, FcRn blocking could be a safe and effective treatment strategy for a broad population of gMG patients. Several FcRn-blocking antibodies and one antibody Fc fragment have been developed and are currently in various stages of clinical development. This article describes the mechanism of FcRn blockade as a novel approach for IgG-mediated disease therapy and reviews promising clinical data using such FcRn blockers for the treatment of gMG.

1. History and physiology of the neonatal Fc receptor

1.1. Neonatal Fc receptor structure and function

The neonatal Fc receptor (FcRn) is an MHC class I–like molecule that is a heterodimer of an alpha chain non-covalently bound to β_2-microglobulin [1–3]. FcRn was originally isolated from the epithelial cells of neonatal rats, where it mediates the transport of immunoglobulin G (IgG) from mother's milk to suckling neonates [4,5]. During gestation in humans, FcRn transfers IgG from mother to fetus across the placenta, providing newborns with humoral immunity [2,6,7]. Although FcRn was initially isolated from neonatal intestinal tissue, it plays an important role in the homeostasis of IgG throughout life [8,9]. It is widely distributed in various mammalian organs, tissues, and cells, where it regulates IgG transport within and across cells [10–13]. FcRn is most highly expressed in hematopoietic cells, intestinal epithelia, and in the vascular endothelium, with the expression per gram of tissue greatest in the spleen, lymph nodes, liver, and lung [8,10–15].

1.2. Regulation of IgG and albumin levels by FcRn

FcRn has a critical role in maintaining both IgG and albumin levels through rescuing these molecules from lysosomal degradation within cells [16–18]. The interaction of FcRn with IgG is highly pH-dependent, with binding at acidic pH that becomes negligible as near-neutral pH is approached [4,5,19]. Consequently, for most cell types, uptake of IgG

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occurs through fluid phase, rather than receptor-mediated, processes (Fig. 1A) [20,21]. Following cellular uptake, FcRn binds IgG in the acidic environment (pH <6.5) of the early (or sorting) endosome. Bound IgG is then rescued from lysosomal degradation by endosomal sorting into the recycling pathway [16,20,21]. FcRn can also transport IgG across polarized cells, such as epithelial barriers in a process called transcytosis [22,23]. Following recycling (or transcytosis), IgG molecules are released from FcRn and returned to the extracellular space [24,25]. This recycling of IgG by FcRn results in longer half-life of IgG ($t_{1/2} \approx 23$ days) compared with other immunoglobulins, such as IgA ($t_{1/2} \approx 5.8$ days) and IgM ($t_{1/2} \approx 5.1$ days) [26,27]. Studies have also shown that FcRn expression in hematopoietic cells protects circulating immune complexes comprising IgG and antigen from being eliminated from the blood and promotes the transport of immune complexes into the intracellular compartments involved in antigen presentation to CD4+ and CD8+ T cells [28,29].

Following cellular uptake, some IgG molecules may not bind to FcRn, possibly due to the saturation of FcRn interaction sites, or IgG mutations/post-translational modifications (e.g. methionine oxidation, which is associated with antibody aging) that ablate FcRn binding [30–33]. These unbound IgG molecules, as well as other unbound plasma proteins, undergo degradation in the lysosome [16,20,21,31]. Albumin is also salvaged from lysosomal degradation by FcRn via a pH-dependent interaction, albeit through interacting with a distinct binding site on FcRn. Importantly, these two ligands bind FcRn non-competitively and this can occur concurrently [18,34–38].

1.3. Pathogenic properties of IgG in autoimmune diseases

Many autoimmune diseases are mediated by IgG autoantibodies, including myasthenia gravis (MG), subtypes of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), pemphigus, and primary immune thrombocytopenia [39–42]. Specifically, the pathogenic actions of IgG autoantibodies in MG are very well-described, causing failure of neuromuscular signal transduction by targeting receptors and proteins of the neuromuscular junction [43,44].

The most common autoantibody target in generalized MG (gMG) is the skeletal muscle nicotinic acetylcholine receptor (AChR), with antibodies to this receptor found in ~85% of patients [43]. Autoantibodies against other targets have been identified, including muscle-specific tyrosine kinase (MuSK, found in ~5% of patients) and low-density lipoprotein related protein-4 (LRP4, found in ~1% of patients) [43].

Anti-AChR autoantibodies, which are almost exclusively of the IgG1 and IgG3 subtypes, impair neurotransmission through three mechanisms (Fig. 2) [43,44]. Autoantibody binding to the acetylcholine interaction site of the AChR creates a functional blockade of the AChR [44]. Anti-AChR autoantibodies also cross-link the AChR molecules, accelerating their endocytosis and degradation [45]. Finally, anti-AChR autoantibodies may activate complement, resulting in damage to the neuromuscular membrane [46]. These actions ultimately reduce the function and number of AChRs and diminish the structural integrity of the neuromuscular junction, leading to failure of neuronal transmission [44].

Anti-MuSK autoantibodies are mostly of the IgG4 subtype and do not activate complement [44]. Instead, these autoantibodies block the LRP4-MuSK interaction, a mechanism that disrupts the structure of the synapse, compromising synaptic transmission [47]. Antibodies against LRP4 are of the IgG1 and IgG2 subtypes and similarly disrupt the protein complex regulating AChR clustering, resulting in disorganization of AChR at the neuromuscular junction [48].

In some patients, IgG autoantibodies cannot be identified; in these cases, it is possible that the disease is not antibody mediated or that they recognize epitopes not detected by the assay or bind unknown targets [49]. Additionally, antibodies may be present in low concentrations in plasma that are below the detection limits of the assay; however, they may be enriched at their biologic binding site. Notably, a recent study showed similar response rates to treatment with therapeutic plasma exchange (TPE) in gMG patients with and without detectable

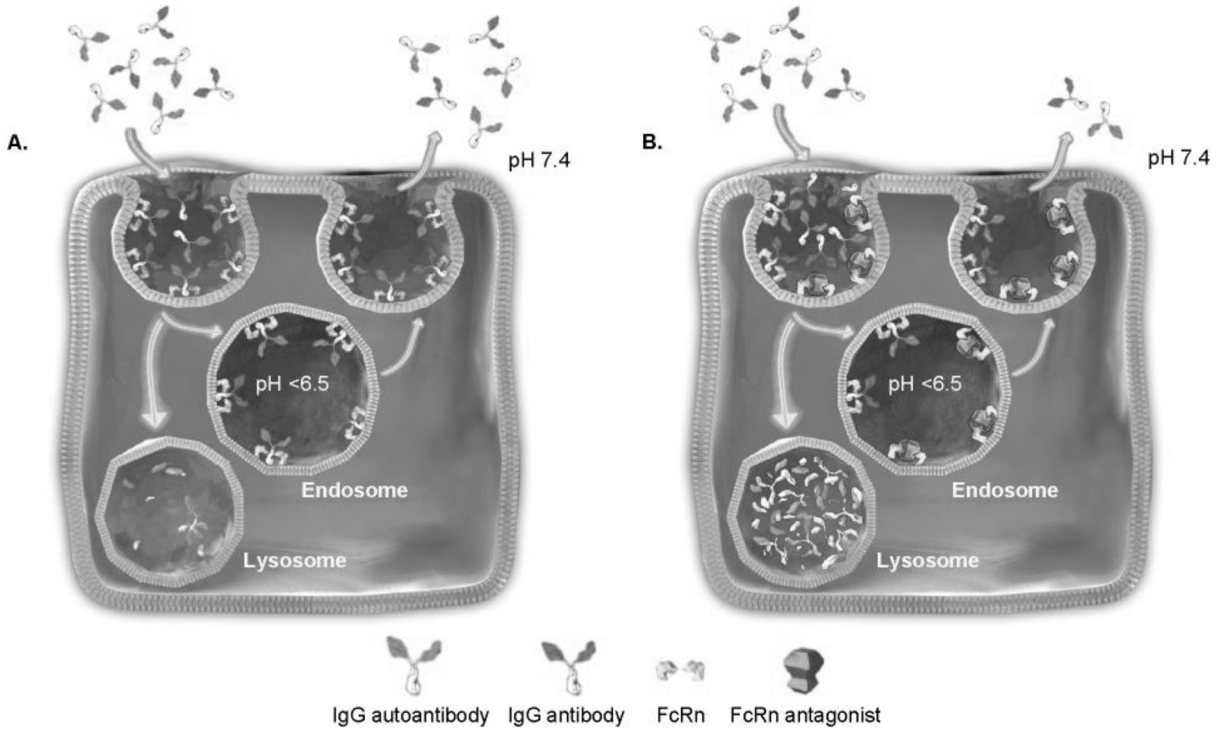

Fig. 1. IgG Recycling by FcRn Under Normal Conditions[a] (A) and With an FcRn Antagonist[b] (B) [114].
[a]Under steady state, IgG is taken up by pinocytosis, bound by FcRn in acidic vesicles, and recycled. Only a fraction is not recycled and degraded in lysosomes.
[b]Catabolism of IgG in enhanced in the presence of FcRn-blocking molecules.

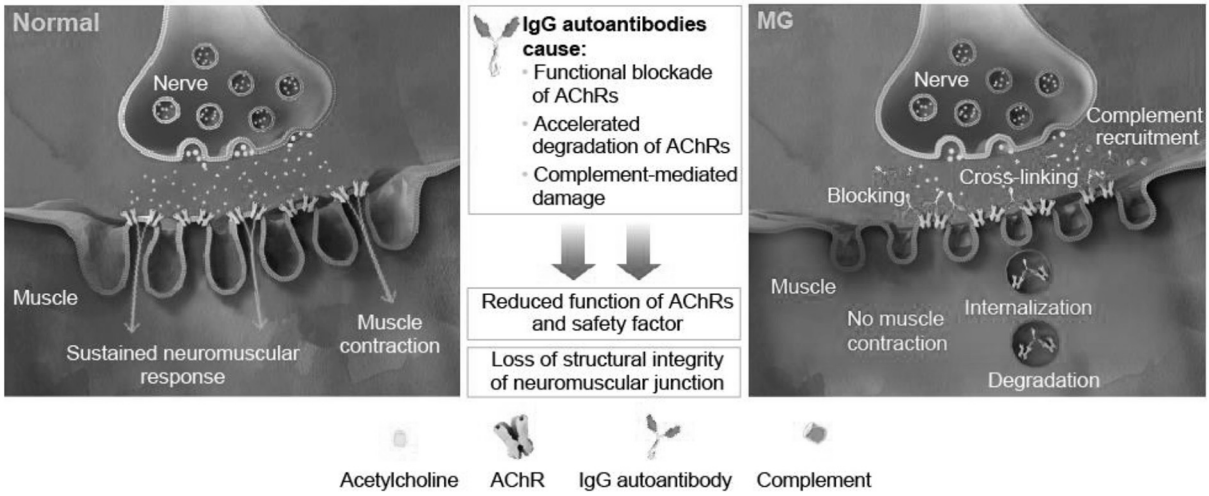

Fig. 2. Inhibition of Neuromuscular Junction Activity by Anti-AChR Autoantibodies in gMG [49].

autoantibodies [50]. These results suggest that all gMG may be autoantibody-mediated, even when IgG autoantibodies cannot be identified [50]. Additionally, up to one-third of infants born to mothers with MG develop transient symptoms, further supporting the pathogenic role of IgG autoantibodies in MG, as no other Ig isotypes (such as IgM and IgA) or immune cells are transferred from mother to fetus [51].

2. Established therapeutic approaches that reduce pathogenic IgG

Many first-line treatments for gMG, including corticosteroids, acetylcholinesterase inhibitors, and non-steroidal immunosuppressive drugs, target inhibition of acetylcholine breakdown or T-cell function [52]. The treatments are non-specific and are associated with side effects such as glucose intolerance, weight gain, osteoporosis, gastrointestinal issues, bradycardia, hepatotoxicity, and renal dysfunction [52].

Considering the direct pathogenicity of IgG in gMG, therapies that reduce concentrations of pathogenic IgG, such as TPE and intravenous immunoglobulin (IVIG), are accepted, guideline-recommended practices [53]. TPE provides proof of concept that IgG reduction is a viable therapeutic option, as gMG patients receiving TPE experience improvement in symptoms that correlates with reductions in the concentrations of all IgG subtypes [52,53] Additionally, the depletion of non-IgG components, such as complement proteins, may also help to relieve gMG symptoms [54]. Despite the beneficial effects of TPE, the removal of other non-IgG components can cause unwanted side effects, such as coagulation abnormalities and infection of indwelling catheters, which can lead to sepsis [54,55]. Immunoadsorption (IA) is a special type of TPE that can more selectively remove IgG while preserving other plasma proteins [56]. Although IA reduces some unwanted side effects of TPE associated with the removal of non-IgG components in plasma, IA is also associated with catheter line sepsis, is invasive and burdensome for the patient, and is not available in all clinical settings due to the specialized instrumentation and monitoring required [57,58].

IgG therapies involve administering a large volume of exogeneous IgG to a patient, either intravenously (IVIG) or subcutaneously (SCIG) [58]. The proposed mechanism of action of IV/SC IG involves interference of autoantibody binding to the AChR [59,60]. The large quantity of IgG is also reported to competitively saturate the FcRn recycling pathway, leading to the degradation of endogenous IgG, and ultimately shortening the serum half-life of IgG (including IgG autoantibodies), thereby improving gMG symptoms [59,60]. However, these therapies require a mixed pool of hundreds to thousands of individual donors, making this a supply-sensitive, precarious, and expensive treatment option that requires rigorous quality control to ensure the absence of viral and other contaminents [52].

3. FcRn blocking as a potential treatment for gMG

FcRn blocking reduces IgG concentrations, targeting the core of MG pathophysiology [39]. More specifically, reduction in IgG leads to diminution in anti-AChR autoantibodies, which limits interference with AChR activation, prevents AChR downmodulation, and averts downstream complement activation [39,61]. Thus, by acting early in the pathogenic pathway compared to complement inhibitors such as eculizumab, FcRn blockade could potentially inhibit all 3 mechanisms associated with anti-AChR pathogenicity, a characteristic that has prompted investigation of FcRn blockade as a promising therapeutic strategy for patients with gMG [39,62].

Blocking FcRn also allows targeted reduction of all IgG subtypes, including pathogenic autoantibodies. This reduction of all IgG subtypes could potentially allow for application to a broad population of gMG patients, including patients with IgG1 and IgG3 AChR autoantibodies, IgG4 MuSK autoantibodies, IgG1 and IgG2 LRP4 autoantibodies, and any other IgG autoantibodies with currently unidentified antigens [43]. Studies have also shown that FcRn blocking effectively reduces IgG levels without decreasing concentrations of other Ig's, which may contribute to sustained and general protection against infectious diseases [28,63,64]. Additionally, ~20–30% of normal IgG levels are maintained during treatment, and IgG concentrations return to baseline when treatment ceases due to IgG production not being impaired by blocking FcRn [63]. Therefore, it is anticipated that patients can still mount an immune response while receiving agents that block FcRn. Indeed, studies in cynomolgus monkeys confirmed that treatment with a FcRn blocker does not interfere with IgM responses to foreign antigens, although IgG titers are lowered [65]. Moreover, studies in mice lacking β2-microglobulin or FcRn α-chain genes resulted in immune responses with normal numbers of antibody-secreting plasma cells, whilst IgG hypercatabolism led to reduced levels of (antigen-specific) IgG [66,67]. Importantly, in β2-microglobulin-deficient mice, the IgG levels were sufficient to protect against vaccinia virus infection [68]. Similarly, although β2-microglobulin deficient humans have lower IgG levels, with IgA and IgM levels in the normal range, immune responses against rubella, tetanus toxoid and other vaccines are still observed [69,70].

The maintenance of antibody production during FcRn blockade is expected to result in a much less severe and lower infection risk with FcRn inhibitor treatment compared to conditions that lead to a deficiency in antibody production such as B cell depletion. In addition, the

targeted mode of action of FcRn inhibition is less likely to pose an increased infection risk compared to other immunomodulators such as general immunosuppressants. Importantly, preliminary studies using FcRn blockers have demonstrated that these treatments are generally well-tolerated with no evidence of increased infection risk being observed to date; however, given the short timeframes of these studies and the role of IgG in host defense, the risk of infection should be investigated in long-term studies [28,63,71,72].

4. Therapies in clinical development for IgG reduction through FcRn blocking

4.1. Monoclonal antibodies directed against FcRn

Proof-of-concept studies for the use of monoclonal antibodies that bind FcRn through their Fab arms to prevent the binding of wild type IgG were first described in rodent models [73,74]. These antibodies bind with high affinity to FcRn in a pH-independent fashion [39]. Following several successful studies in rodents, human and humanized antibodies have been developed for therapeutic use in patients with gMG (Table 1) [28,65,75–77].

4.2. Engineering the Fc fragment to target FcRn

The binding site for FcRn on the Fc fragment of IgG can be engineered to bind FcRn with increased affinity [75]. The only engineered Fc fragment currently in development, efgartigimod, is a human IgG1-derived Fc fragment [63]. Efgartigimod retains the pH-dependent binding (i.e. higher affinity at pH 6.0 than at near-neutral pH) that is observed for its parent, wild-type Fc, but has substantially increased affinity for FcRn at both physiological and acidic pH, thereby acting as a competitive inhibitor of wild type IgG-FcRn interactions (Fig. 1B) [63]. The pH-dependent binding displayed by efgartigimod allows it to dissociate from FcRn during the recycling process, leading to a serum half-life of 4.89 days when dosed at 10 mg/kg [78]. This is a relatively long half-life compared with that of full-length monoclonal antibodies targeting FcRn, which have half-lives $\leq$1 day [28,64,65]. Given that FcRn mediated transcytosis bears similarities to recycling, the lower affinity of efgartigmod for FcRn at neutral pH also potentially allows for more efficient transport into the tissues. This would provide the potential to locally inhibit FcRn which could add to its therapeutic efficacy [37,79] (Table 1).

4.3. Peptide or affibody-based inhibitors directed against FcRn

Several peptides have been identified that act as ligands for FcRn and inhibit the FcRn-IgG interaction. These peptides are limited by exceedingly short half-lives in the circulation [80]. Recent studies have investigated coupling an affibody (6–7 kDa) with FcRn binding activity to an albumin binding domain to increase in vivo half-life, but no such agents are currently in development [81].

5. Monoclonal antibodies against FcRn

5.1. Nipocalimab

Nipocalimab is a fully human, aglycosylated monoclonal IgG1 FcRn antibody with no effector function that inhibits FcRn-mediated IgG recycling [64]. Nipocalimab binds with picomolar affinity to FcRn at both endosomal pH 6.0 and extracellular pH 7.3 to 7.4, occupying FcRn throughout the recycling pathway [64]. A first-in-human, two-part, ascending-dose Phase 1 study of nipocalimab in 50 healthy volunteers investigated single ascending IV doses up to 60 mg/kg and multiple weekly doses of 15 or 30 mg/kg [64]. This study demonstrated that four weekly doses of 15 or 30 mg/kg administered as an IV infusion achieved mean IgG reductions of approximately 85% from baseline and maintained IgG reductions of $\geq$75% for up to 24 days [64]. Decreases in serum concentrations were consistent across IgG subclasses, and no effect was observed on of other Ig's levels [64]. During this study, the incidence of treatment-emergent adverse events (TEAEs) related to the study drug was similar in the nipocalimab and placebo groups (66.7% vs 75.0%, respectively), and most TEAEs were mild [64]. Transient reductions in total protein and albumin (up to 22%) were observed in participants receiving a single dose of 60 mg/kg or multiple doses of 15 and 30 mg/kg [64].

A subsequent Phase 2 clinical trial evaluated the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of nipocalimab in adults with gMG [82]. This study included 68 participants, and consisted of an 8-week treatment period with four active arms (5 mg/kg IV every 4 weeks [Q4W], 30 mg/kg IV Q4W, 60 mg/kg IV every 2 weeks [Q2W], and a 60 mg/kg IV single dose) and a placebo arm [82]. Topline data from this study revealed that 52% of patients who received nipocalimab had at least a 2-point reduction from baseline in MG activities of daily living (MG-ADL) scores for at least 4 consecutive weeks across all four dosing arms, versus 15% of placebo-treated patients ($p = 0.017$). There was a significant relationship between IgG reduction and clinical benefit [82]. No severe or serious adverse events related to nipocalimab were reported, and most adverse events were characterized as mild [82]. Reported reductions in albumin levels were observed, with the largest reductions seen in patients receiving 60 mg/kg Q2W, including one patient in this group who had an asymptomatic Grade 2 hypoalbuminemia [83]. As FcRn inhibitors are expected to inhibit transport of IgG across the placenta [84,85], nipocalimab is also being evaluated in pregnant women at high risk for early onset severe hemolytic disease of the fetus/newborn (Phase 2 trial actively recruiting) and for the treatment of warm autoimmune hemolytic anemia (Phase 2/3 trial recruiting) [86,87]. Although this approach has the potential to be effective, it may also subject neonates to infectious diseases due to the expected lowered maternal IgG levels at birth. This is particularly relevant during pregnancy, as neonates do not acquire IgA and IgM through placental transfer, and IgA is the primary isotype that is acquired through mothers' milk. A possible solution could be treatment of the neonates with IVIg [88,89].

5.2. Rozanolixizumab

Rozanolixizumab is a humanized, high-affinity, anti-human FcRn IgG4P-monoclonal antibody (S241P mutation to prevent Fab-arm exchange), which is an IgG isotype with very low, if any, binding to Fcγ receptors [72,90]. Rozanolixizumab is administered via SC infusion and is currently being evaluated for the treatment of gMG [71,72]. A Phase 1 study with 49 participants investigated rozanolixizumab administered IV (1, 4, or 7 mg/kg) and SC (1, 4, or 7 mg/kg) [72]. This study showed that rozanolixizumab reduced IgG concentrations by up to 50% compared with baseline, with maximal reductions achieved 7 to 10 days after administration; Serum (or plasma) IgG levels gradually returned to baseline by Day 57 [72]. The maximal reductions in IgG concentrations were similar with either IV or SC administration [72]. Rozanolixizumab selectively reduced IgG concentrations with no significant effect on the levels of other Ig's, complement, or other immune-related biomarkers [72]. There was a modest decrease in mean albumin concentration over time after both IV and SC administration (at Day 10, −0.5 g/L for the 7 mg/kg IV group and − 2.0 g/L for the 7 mg/kg SC group) [72]. Severe TEAEs of headache ($n = 3$) and back pain ($n = 1$) were reported by participants in the 7 mg/kg IV group but did not lead to discontinuation [72]. Participants in the SC group had fewer and less severe adverse events compared to those in the IV group, and future trials focused on pump infusion SC administration [72].

A Phase 2 proof-of-concept study of SC-infused rozanolixizumab (7 mg/kg or placebo in the first period, then rerandomized to 4 mg/kg or 7 mg/kg in the second period) in patients with gMG showed that treatment resulted in clinically meaningful improvement in multiple disease-

Table 1
FcRn blockers under investigation for the treatment of gMG.

Compound	Manufacturer	Type	Admin. Route	Clinical Development Phase	Tested dosing	Efficacy in gMG	Adverse events	Other indications
Nipocalimab	Momenta Pharma	Fully human, monoclonal IgG1 anti-FcRn antibody [64]	IV	Phase 3 (recruiting) [82]	• Phase 2: ◦ 5 mg/kg every 4 weeks for 8 weeks [82] ◦ 30 mg/kg every 4 weeks for 8 weeks [82] ◦ 60 mg/kg every 2 weeks for 8 weeks [82] ◦ 60 mg/kg single dose [82]	• Phase 2 topline data: • 52% had ≥2-point reduction in MG-ADL for ≥4 consecutive weeks with nipocalimab vs 15% with placebo ($p = 0.017$) [82]	• Phase 2 topline data: ◦ No serious adverse events [82] ◦ Non-clinically relevant reductions in albumin observed [83]	• Early onset severe hemolytic disease of the fetus and newborn [86] • Warm autoimmune hemolytic anemia [87]
Rozanolixizumab	UCB	Humanized, anti-human FcRn IgG4P monoclonal antibody [72]	IV or SC	Phase 3 (recruiting) [112]	• Phase 2: ◦ First treatment period: 3 weekly, SC-infusions of 7 mg/kg or placebo [71] ◦ Second treatment period: 3, weekly, SC-infusions of 7 mg/kg or 4 mg/kg [71]	• Phase 2: ◦ Statistically significant improvement in in MG-ADL [71] ◦ ~68% mean reduction of total IgG and anti-AChR antibody titers [71]	• Phase 2: ◦ Headache was more frequent with rozanolixizumab (57.1%) vs placebo (13.6%) (Period-1) [71]	• Chronic primary immune thrombocytopenia • Chronic inflammatory demyelinating polyradiculoneuropathy [93]
IMVT-1401 (RVT-1401)	Immunovant	Fully human IgG1 monoclonal antibody [95]	IV or SC	Phase 2 [113]	• Phase 2: ◦ Weekly SC doses of IMVT-1401 (340 or 680 mg) or placebo for 6 weeks [96]	• Phase 2: ◦ IMVT-1401 at 340 mg or 680 mg resulted in mean IgG reductions of 59% and 76%, respectively, at Day 42 [96] ◦ Statistically significant improvements in MG-ADL and MGC [96]	• Phase 2: ◦ No SAEs were reported [96]	• Graves' ophthalmopathy [97] • Warm autoimmune hemolytic anemia [98]
Orilanolimab (ALXN1830)	Alexion Pharmaceuticals	Humanized, affinity-matured, deimmunized IgG4 monoclonal antibody [28]	IV	Phase 2 [28]	• In Phase 2: ◦ Single IV dose of 1, 3, 10, or 30 mg/kg [28]	• In Phase 2: ◦ Median decreases observed were − 68.3% for IgG3, −51.6% for IgG1, −36.9% for IgG2, and–42.9% for IgG4 [28]	• In Phase 2: ◦ The most common TEAE was headache [28]	• Warm autoimmune hemolytic anemia [101]
Efgartigimod	argenx	Human IgG1 antibody Fc-fragment [75]	IV	Phase 3 (ongoing) [102]	• Phase 3: ◦ Four weekly IV (10 mg/kg) infusions over 4 weeks [102,103] ◦ Subsequent treatment cycles administered according to clinical evaluation [102,103]	• Phase 3 topline data: ◦ Met the primary endpoint: 67.7% achieved ≥2-point MG-ADL improvement for ≥4 consecutive weeks with efgartigimod vs 29.7% with placebo ($p < 0.0001$) [102,103]	• Phase 3 topline data: ◦ Efgartigimod was well-tolerated [102] ◦ Headache was the most common TEAE in the Phase 2 trial (28.6% with efgartigimod and 27.7% with placebo) [78,103]	• Immune thrombocytopenia [104] • Pemphigus [105] • Chronic inflammatory demyelinating polyneuropathy [106]

related endpoints with statistical significance for the MG-ADL scores [71]. Additionally, rozanolixizumab resulted in an approximately 68% mean reduction of total IgG and anti-AChR antibody titers [71]. The incidence of headache was greater in the rozanolixizumab group compared with placebo (57.1% vs 13.6%, respectively) and three patients were withdrawn due to headache [71]. Rozanolixizumab is also being evaluated in patients with CIDP (ongoing Phase 2 trial) and chronic primary immune thrombocytopenia (Phase 3 trial actively recruiting) [91–93]. Despite the ongoing phase 2 trial, rozanolixizumab will not be further evaluated in a phase 3 trial for CIDP after its completion as development is being focused on autoantibody mediated neuro-inflammation [94].

5.3. IMVT-1401 (RVT-1401)

IMVT-1401 is a fully human aglycosylated IgG1 monoclonal antibody that is being investigated for the treatment of gMG [95]. Studies in healthy participants have demonstrated that a single SC dose of 765 mg of IMVT-1401 resulted in average IgG reduction of 47% from baseline, with weekly SC injections affording maximum reductions >75% [95]. Dose-dependent and reversible albumin reductions of up to 31% from baseline were observed in the single and multiple ascending dose cohorts [95]. A Phase 2 trial assessing the efficacy and safety of IMVT-1401 in patients with gMG was recently completed [96]. This study contained 15 patients who were randomized to placebo, 340 mg IMVT-1401 SC, or 680 mg IMVT-1401 SC weekly for 6 weeks [96]. Topline data from this trial showed that weekly dosing of IMVT-1401 at 340 mg or 680 mg resulted in mean IgG reductions from baseline of 59% and 76%, respectively, at Day 42 [96]. IMVT-1401 also resulted in statistically significant and clinically meaningful improvements in MG-ADL and MGC [96]. The mean albumin reduction from baseline was 16% and 26% in the 340 mg and 680 mg dose groups, respectively [96]. No SAEs were reported [96]. IMVT-1401 is also being assessed for the treatment of Graves' ophthalmopathy (Phase 2 trial actively recruiting) and warm autoimmune hemolytic anemia (Phase 2 trial not yet recruiting) [97,98]. Clinical dosing of IMVT-1401 was voluntarily paused in February 2021 due to elevated total and low density lipoprotein (LDL) cholesterol levels, that appear to be driven by reductions in albumin [99]. Clinical development is planned to resume in late 2021 or early 2022 [99].

5.4. Orilanolimab (ALXN1830)

Orilanolimab is a humanized, affinity-matured, deimmunized IgG4 monoclonal antibody containing a S241P mutation that binds FcRn at neutral and acidic pH and has been investigated for the treatment of gMG [28]. A single-center, double-blind, randomized, single ascending dose, first-in-human study assessed the safety, pharmacokinetic, and pharmacodynamic effects of IV-administered orilanolimab in 31 healthy participants [28]. This study showed no evidence of dose-limiting adverse reactions with orilanolimab up to a maximum dose of 30 mg/kg [28]. Reductions across all four IgG subtypes were observed in response to orilanolimab, with the 30 mg/kg dose group displaying the lowest levels [28]. The greatest median decreases were observed for IgG3, with lesser reductions of IgG1, IgG2, and IgG4 [28]. Serum (or plasma) IgG levels returned to within 25% of baseline by Day 28 in all dose groups [28]. No significant changes were observed in the levels of albumin, IgA, and IgM [28]. Orilanolimab also resulted in a dose-dependent decrease in IgG circulating immune complexes, with the greatest reductions observed in the 30 mg/kg dose group [28]. The most common TEAE observed in this study was headache, which was most frequent in the 30 mg/kg dose group ($n = 5$, 100%). While most headaches were mild, one individual in the 10 mg/kg dose group reported a moderate severity headache [28]. No significant changes in albumin levels were observed [100]. Orilanolimab is also being investigated for the treatment of warm autoimmune hemolytic anemia (Phase 2 trial temporarily paused) [101].

6. Antibody Fc Fragment Against FcRn

6.1. Efgartigimod

A Phase 1, randomized, double-blind, placebo-controlled, first-in-human study of efgartigimod was conducted in 62 healthy volunteers to explore single and multiple ascending IV doses (up to 50 mg/kg) [63]. Results from this study revealed that a single administration of efgartigimod reduced baseline IgG levels by approximately 50% from baseline, whereas multiple (i.e. 4 weekly) administrations further lowered circulating IgG levels by an average of 75%, with 10 mg/kg identified as the ideal dose [63]. Efgartigimod did not alter the homeostasis of albumin, other Ig's, and no serious adverse events related to efgartigimod infusion were observed [63].

A randomized, double-blind, placebo-controlled, multicenter Phase 2 study evaluated the safety and efficacy of four weekly 10 mg/kg IV-administered doses of efgartigimod in 24 patients with AChR antibody-positive gMG [78]. Eligible participants were required to be on a stable dose of an existing gMG therapy prior to randomization and were not required to have previously received or failed pre-specified gMG treatments [78]. Patients receiving efgartigimod demonstrated a maximum mean total IgG reduction of 71% (Fig. 3A) and a significant reduction of anti-AChR antibody levels [78]. Clinical improvement, assessed through MG-ADL score, was noted as early as 7 days after the first infusion, with a maximal reduction of 4.4 points (55% reduction) occurring within 2 weeks of the last infusion (Fig. 3B) [78]. Treatment with efgartigimod also resulted in clinically meaningful and sustained improvements in clinical symptoms, which were consistent across 4 MG scales [78]. Specifically, 75% of efgartigimod-treated patients had a sustained, clinically meaningful improvement in MG-ADL score for a period of at least 6 consecutive weeks versus 25% of patients who received placebo ($p = 0.039$) [78]. Although serum IgG levels approached baseline by the end of the study (8 weeks after the last dose), patients continued to show sustained improvements 78 days after the first infusion in MG-ADL, quantitative myasthenia gravis (QMG), and myasthenia gravis composite (MGC) scores [78]. The most common TEAE was headache, which occurred in 33.3% of patients in the efgartigimod group compared with 25.0% in the placebo group; headaches were all mild in severity, except for one patient in the placebo group who experienced a moderate headache [78]. Efgartigimod did not reduce IgM, IgA, or albumin concentrations [78].

A randomized, double-blind, placebo-controlled, multicenter Phase 3 trial (ADAPT) evaluated efgartigimod in 167 patients with AChR antibody-positive or AChR antibody-seronegative gMG [102]. Patients were not required to have received or failed pre-specified gMG treatments to be eligible for this trial, and participants continued existing gMG therapy during the study [102]. Participants were treated with 4 IV infusions of 10 mg/kg efgartigimod at weekly intervals, with subsequent treatment cycles administered according to clinical response, based on MG-ADL score [102]. Topline data from the ADAPT trial showed that more efgartigimod treated patients met the primary endpoint of the trial, defined as the percentage of participants achieving ≥2-point improvement on the MG-ADL score for ≥4 consecutive weeks, than placebo treated patients [103]. Efgartigimod was demonstrated to be safe overall, with a profile of TEAEs and discontinuations due to TEAEs similar to placebo, including a similar rate of headaches among patients in both treatment groups [103]. No reductions in albumin levels, nor increases in total or LDL cholesterol levels were observed during the trial [103].

In addition to the trials investigating efgartigimod for the treatment of gMG, a Phase 3 trial in patients with immune thrombocytopenia is actively recruiting [104]. Two Phase 2 clinical trials investigating the use of efgartigimod in patients with pemphigus and chronic inflammatory demyelinating polyneuropathy are also ongoing [105,106].

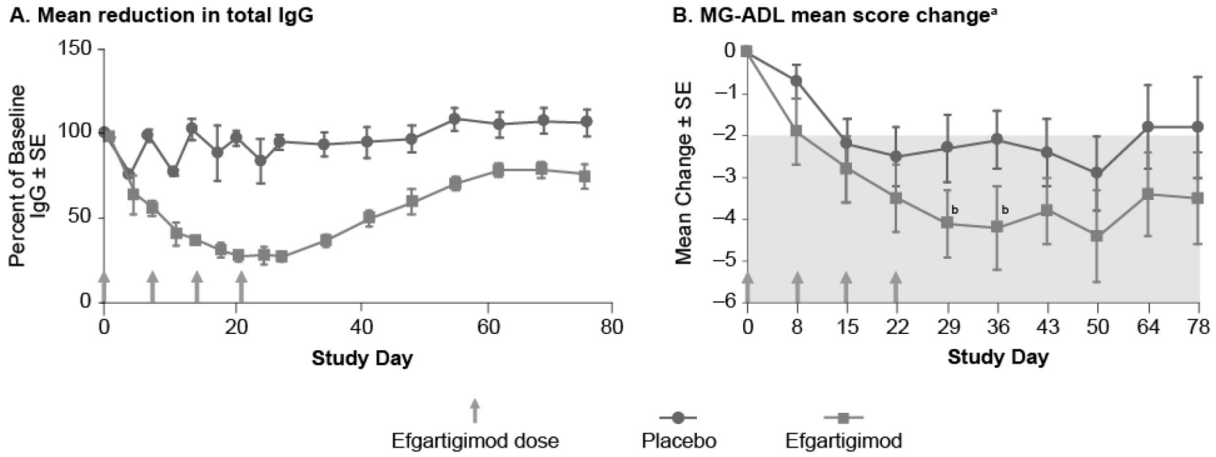

Fig. 3. Change in IgG (A) and MG-ADL Score (B) From a Phase 2 Trial of Efgartigimod in gMG [78].
SE, standard error.
[a]Shaded portion of graph represents clinically meaningful improvement in MG-ADL (reduction ≥2).
[b]$p \leq 0.05$ (mixed repeated measures model).

7. Conclusion

FcRn plays a critical role for IgG and albumin homeostasis by rescuing these molecules from lysosomal degradation. Because IgG autoantibodies are associated with many autoimmune diseases, including gMG, reducing serum IgG levels is an attractive treatment strategy for these diseases. However, current treatment options for reducing pathogenic IgG concentration are accompanied by serious side effects and limitations, creating a significant unmet need in this therapeutic area [52].

Agents that selectively block FcRn-mediated recycling of IgG could reduce all IgG subtypes without decreasing concentrations of other Ig isotypes, allowing these therapies to potentially treat a broad patient population with reduced side effects. Several FcRn-blocking antibodies and one antibody Fc fragment are currently in various phases of clinical development. Further evaluation of these various approaches to blocking FcRn will be vital in determining the complete efficacy and safety profile of each therapy.

Clinical data and studies to date of FcRn-blocking agents have shown that these therapies are generally well-tolerated and have not been associated with an increased risk of infection. As impact on infection rate is potentially the primary area of risk for FcRn inhibitors, additional and longer term analyses continue to be necessary and of critical importance. Notably, these therapies have been demonstrated to specifically reduce IgG concentrations without affecting levels of other Ig isotypes [28,63,64,78,103]. Due to the selective reduction of IgG and lack of impairment of antibody production [107], FcRn inhibition is not currently expected to compromise the induction of immune responses against vaccines. Although lower IgG levels due to IgG hypercatabolism during treatment are expected, IgG levels return to normal following treatment with FcRn blockers [79,103,108,109]. Studies in FcRn or β2-microglobulin knockout mice demonstrated that protective responses can still be elicited against ocular herpes simplex virus type 1 and vaccinia virus, respectively [68,110]. However, given the dual functions of FcRn in maintaining IgG levels and in antigen presentation pathways involving immune complexes [28,29], the extent of protection under conditions of FcRn blockade is likely to depend on the pathways of immune-mediated clearance of specific pathogens. Consequently, additional data regarding vaccinations in patients being treated with FcRn inhibitors will be of critical importance as these therapies become more prevalent in clinical settings. The decrease in albumin concentrations associated with some of the FcRn-targeting monoclonal antibodies is of interest as these agents do not interact with the site of albumin binding on FcRn, perhaps suggesting an effect on FcRn-stoichiometry or levels that affect albumin recycling and requires further investigation. A signal for headache is more often observed with IgG4 monoclonal antibodies than with aglycosylated IgG1 monoclonal antibodies or Fc fragment. Since the latter lack affinity for Fcγ receptors due to the absence of the N-linked carbohydrate, and IgG4 has been shown to interact with Fcγ receptors (as was demonstrated to be the cause of the cytokine release syndrome for the superagonistic anti-CD28 antibody TGN1412), the headaches observed with IgG4 monoclonal antibodies can be hypothesized to be associated with immune effector functions [111]. In addition to this favorable safety profile, clinical data from studies of FcRn-blocking agents have also demonstrated the efficacy these therapies have for treating the clinical symptoms of gMG. Taken together, these data establish the promise of FcRn-blocking agents in the treatment of gMG and other IgG-mediated human diseases.

Authorship

All authors contributed to the conception, drafting, and revision of the article and approved the final version for submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Mamatha Pasnoor, MD	[5]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA	Assisted in the conception, drafting, and revision of the article and approved the final version for submission
Gestur Vidarsson, PhD	Sanquin Research, and Landsteiner Laboratory, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.	Assisted in the conception, drafting, and revision of the article and approved the final version for submission

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