The humoral immune response provides specific, long-lived protection against invading pathogens, via immunoglobulin production and other memory functions. IgG, the most abundant immunoglobulin isotype, has the longest half-life and protects against bacterial and viral infections. The neonatal Fc receptor (FcRn) transports IgG across barriers, for example, the placenta, enhancing fetal humoral immunity to levels similar to their mothers'. Importantly, FcRn, by protecting IgG from intracellular degradation, results in an approximately 21-day circulating IgG half-life and high plasma levels; similarly, FcRn recycles albumin and is the portal of entry for enteric cytopathic human orphan (echo) virus infection. Dysregulated immune responses may lead to antibodies against self-antigens (autoantibodies), resulting in organ-specific or systemic autoimmune diseases. Autoantibody-mediated diseases have been treated by nonspecific immunoglobulin-lowering/modulating therapies, including immunoabsorption, plasma exchange, and high-dose intravenous immunoglobulin. However, targeting FcRn with specific inhibitors results in reduction in only IgG levels. The effectiveness of FcRn inhibitors in autoimmune diseases, including myasthenia gravis and immune thrombocytopenia, provides further evidence that IgG is a primary driver in these autoantibody-mediated diseases. We describe the role of FcRn in human biology, including insights that clinical testing of FcRn inhibitors have provided into FcRn biology and autoimmune disease mechanisms, allowing fact-based speculation on their therapeutic potential. (J Allergy Clin Immunol 2020;146:467-78.)

**Key words:** Immunoglobulin, IgG, IgG lowering, autoimmune disease, FcRn inhibitors, plasma exchange, echovirus, half-life, IVIg

The humoral (antibody) immune response offers a targeted, specific, long-lived protection against many invading pathogens. It is an adaptive response wherein high-affinity antibodies are generated to pathogenic antigens. Antibodies (also termed physicochemically as immunoglobulins) provide protection in 3 ways: neutralization (binding pathogens and preventing their entry into cells), opsonization (facilitating pathogen uptake by phagocytic cells), and complement activation (facilitating opsonization and direct pathogen killing or lysis through activation of complement proteins).1

Immunoglobulins exist in 5 isotypes, IgM, IgD, IgG, IgA, and IgE, which vary in structure and function. IgG is the most abundant circulating immunoglobulin isotype, has the longest serum half-life, and is fundamental for systemic immunity and protection against infection. IgG provides a link between innate immune effector mechanisms and specific humoral recognition of antigen.2 IgG itself can be subdivided into 4 subclasses, IgG1, IgG2, IgG3, and IgG4, which are observed in decreasing abundance and have subtle but significant differences in structure and function (reviewed by Vidarsson et al3).

The neonatal fragment crystallizable (Fc) receptor (FcRn) is a multifunctional atypical Fc-gamma receptor (FcγR). FcRn was initially identified as responsible for IgG transport from maternal to fetal circulation across the placenta, and later for IgG recycling.4 Subsequently, additional roles of FcRn have been defined, including albumin recycling, bidirectional transport of IgG and albumin across a range of polarized cellular barriers, potentiating efficient responses to IgG-immune complexes (IgG-ICs), and as a receptor for enteric cytopathic human orphan (echo) viruses.3,4

This overview provides insights from basic and clinical research into FcRn biology. Subsequently, therapeutic benefits of IgG lowering in patients with IgG autoantibody-mediated disease are discussed followed by existing treatment options and accomplishment of IgG lowering via development of novel therapeutics targeting FcRn. Finally, wider clinical implications of FcRn inhibitors are explored.

**IDENTIFICATION AND CHARACTERIZATION OF FcRn**

IgG and albumin are the most abundant proteins in circulation, perhaps a result of their uniquely long half-lives of more than 3
weeks. The first hypothesis explaining the long half-life of IgG was made in the 1960s by F.W. Rogers Brambell who recognized a link between transmission of passive immunity from mother to offspring and protection against catabolism of IgG. Brambell proposed that a receptor system was responsible for transporting IgG. It took 20 years before the receptor mediating this transfer was identified and characterized as an atypical FcγR, named FcRn. Structural characterization has classified FcRn as a relative of the MHC class I receptor family, composed of a heavy chain (consisting of 3 extracellular alpha domains and a transmembrane domain) that noncovalently associates with beta2-microglobulin (β2-m) (Fig 1).9

Although FcRn was first identified as a receptor transporting IgG, it has been shown to bind albumin and play a fundamental role in its homeostatic regulation.11,12 IgG and albumin bind to FcRn via distinct, noncooperative binding sites (Fig 1).13 The stoichiometry of binding differs: IgG interacts with FcRn in a 2:1 ratio, whereas the albumin:FcRn stoichiometry is 1:1.13,14,17 Within the immunoglobulin class, FcRn is specific for IgG and does not interact with other immunoglobulin isotypes.

THE PROTEAN FUNCTION OF FcRn IN HEALTH Protection of IgG from degradation

IgG is salvaged from intracellular degradation by FcRn via a pH-dependent cellular recycling mechanism (Fig 2, A).18 Unlike conventional FcγRs and other Fc-binding proteins, such as complement protein C1q, FcRn binds IgG only at mildly acidic pH 5.0 to 6.5 (KD [dissociation constant], 73-98 nM at pH 6.0),16,21 the pH in endosomal compartments, not at physiological pH of 7.4. This pH dependence is mediated by histidine residues (in particular His310 and His435) in the Cγ2-Cγ3 hinge region of IgG and their interaction with acidic residues on the surface of FcRn.22-24 Therefore, although FcRn is expressed on the endothelial cell surface, it does not bind IgG there.

Considering the process of FcRn recycling, IgG, albumin, and other plasma proteins are ingested via pinocytosis (Fig 2, A). Following internalization and acidification of the endosome, FcRn binds IgG (and albumin), retaining it within the endosome, whereas other molecules are shunted to lysosomes for degradation.25,26 FcRn-bound IgG is then transported back to the plasma membrane, where the vesicle content is exocytosed, the pH thus returns to pH 7.4, and IgG is released into circulation. In IgG-mediated autoimmune diseases, it is believed that both normal and pathogenic IgG antibodies are recycled without preference in the same manner.

Two recent studies have proposed a potential further role for FcRn.27,28 In vitro, FcRn recycling of IgG3, alone is comparable with that of other IgG subclasses. However, when assessed in the presence of other IgG subclasses, IgG3 recycling is inhibited because of structural disadvantages in the intracellular competition for FcRn-mediated recycling, leading to the shorter half-life observed for Arg435 IgG3 molecules.29,30

Ethnic variances in the prevalence of His435 versus Arg435 in IgG3 antibodies (for greater detail, see Peter et al in this issue) may influence transplacental transfer of IgG3, and may have implications for the use of FcRn inhibitors.

Transcytosis of IgG across barriers

FcRn is evolutionarily conserved and facilitates delivery of IgG to locations where it supports immunity.31 FcRn is expressed in diverse tissues throughout the body, including epithelia, endothelia, and cells of hematopoietic origin, and facilitates transcytosis of IgG across polarized cell barriers, including the placenta, intestines, lungs, central nervous system, and kidney (Fig 3). The direction of transport is highly cell- and organ-specific, the biomechanical details of which are beyond the scope of this review.

Placenta. Intrapartum transfer of IgG across the placenta from mother to fetus affords immune protection to the newborn,
to compensate for having a naive and immature immune system (Fig 3, A). IgG transfer increases throughout gestation as the fetus and placenta mature and grow.\(^4^0\) In vitro cellular and human placenta transport studies show that IgG transfer is dependent on FcRn expression in apically located vesicles within syncytiotrophoblasts, which are the placental interface to maternal circulation.\(^4^1^-^4^3\) At birth, the mother provides a full complement of IgG to the neonate’s IgG concentration comparable to if not slightly higher than the mother’s. Although the fetus and neonate have been shown to be capable of making specific IgM and IgG antibody if challenged, slow production of IgG results in neonatal IgG levels reaching a nadir at age 3 to 4 months before gradually increasing.\(^4^4^-^4^5\)

**Intestine.** Bidirectional transcytosis of IgG occurs within the intestine, both into and out of the circulation. FcRn mediates the transport of IgG into the lumen, and IgG or IgG-ICs are delivered back into the lamina propria, allowing delivery of these complexes to mucosal dendritic cells that regulate immune response. In line with this, FcRn is expressed at intestinal mucosal surfaces of the small and large intestine, including villous and crypt enterocytes, goblet cells, and subpopulations of enteroendocrine cells.\(^3^,^3^4^-^3^6,^4^6\) IgA, the most important mucosal immunoglobulin, uses a different system of transcytosis.\(^7\)

**Lung.** FcRn is expressed in bronchial epithelial cells\(^3^7,^4^6\) and can transcytose IgG across the mucosal surface of the respiratory epithelium from lumen to serosa.\(^7\) Therefore, IgG and/or IgG-ICs are reabsorbed across mucosal surfaces to function in immune surveillance and host defense.

**Central nervous system.** Unlike other organ systems, FcRn removes IgG from the central nervous system, putting it into the circulation by reverse transcytosis across the blood-brain barrier (see Fig E1 in this article’s Online Repository at www.jacionline.org).\(^4^8^-^5^0\) FcRn is expressed in brain microvascular endothelium and choroid plexus epithelium.\(^4^6,^5^1\) Via FcRn, IgG is transported out of the perivascular space and interstitial fluid into the blood,\(^3^8\) a process that may limit central nervous system inflammation in pathological situations such as bacteremia.\(^4^7^-^4^8\)

**Kidney.** FcRn functions at 2 sites in the kidney (Fig 3, B). When expressed in podocytes of glomeruli, FcRn transcytoses IgG from the filtration membrane for delivery to the urinary space.\(^3^9^-^5^2\) IgG and IgG-ICs are too large to pass through the size-selective filtration of the kidney glomerulus into the urinary space. Extensive studies in animal models such as that of Heymann nephritis, a model of membranous nephropathy, have shown that ICs (both circulating and those formed \textit{in situ}) are deposited in the glomerular capillary wall.\(^5^3\) FcRn plays an active clearance role at the filtration membrane, preventing the accumulation of IgG and IgG-ICs and avoiding organ damage due to blockade of kidney filtration. FcRn also provides protective IgG to the urinary tract.\(^5^4,^5^5\) Given the protective role of FcRn in avoiding the accumulation of IgG and IgG-ICs in the kidney (as in the central nervous system described above), inhibiting FcRn could be potentially harmful in certain disease situations, such as lupus nephritis and cryoglobulinemic glomerulonephritis. However, FcRn inhibition may be beneficial in diseases such as membranous nephropathy, whereby a study has shown that global reduction in IgG concentration prevents the deposition of ICs in the glomerular basement membrane.\(^5^6\) Downstream of the glomerulus, albumin and IgG are reabsorbed by FcRn in the proximal tubule and returned to the systemic circulation.\(^5^5,^5^6\)

**Antigen presentation**

FcRn is expressed in antigen-presenting cells (APCs; eg, dendritic cells and macrophages).\(^5^7^-^5^8\) which is potentially important for generation of targeted, T-cell–mediated immunity.\(^7^9\) In contrast to FcRn-mediated recycling of monomeric IgG to the cell surface, pinocytosed IgG-ICs bind to and cross-link FcRn within APCs, leading to the trafficking of the antigen-bearing IgG-ICs into endolysosomal compartments.\(^7^9\) Antigen is then processed into immunostimulatory antigenic epitopes, which are loaded onto both MHC class I and II molecules, in turn enabling
A

**FIG 3.** FcRn mode of action: transcytosis of IgG across barriers, (A) placenta and (B) kidney. A, Transcytosis of IgG across the placenta. FcRn is expressed in the fetal endothelium and apically localized vesicles within syncytiotrophoblasts. FcRn can bind IgG in the acidic endosome; bound IgG is retained and released by exocytosis into the fetal circulation. B, Transcytosis of IgG and IgG-ICs in the kidney. FcRn is expressed at 2 locations in the nephron; in podocytes of the glomerular capsule and in renal proximal tubular epithelial cells. Transcytosis occurs from the glomerular capillary to the urinary filtrate, and then later from the urinary filtrate back into the blood. FcRn can bind IgG in the acidic endosome; bound IgG is retained and released by exocytosis into the urinary filtrate or blood.
activation of both CD4$^+$ and CD8$^+$ T-cell responses.$^{59}$ This process may “bridge the gap” between the humoral and cellular branches of the adaptive immune response.$^{59}$ Recent studies demonstrating the formation of intracellular and extracellular ternary complexes of FcRn, IgG-ICs, and FcγR (CD32a) highlight the potential role of FcRn in enhanced immune responses.$^{21,28}$

**FcRn AS A CAUSE OF DISEASE**

**Familial hypercatabolic hypoproteinemia**

There is genetic evidence of a role for FcRn function on levels of IgG and albumin. A mutation in the $\beta_2$-m gene, leading to compromised interaction with the signal recognition protein (a cytoplasmic ribonuclear protein complex that directs newly synthesized proteins from the ribosome to the endoplasmic reticulum) and abnormal insertion into the endoplasmic reticulum membrane, resulted in very low (<1% of normal) serum concentrations of soluble $\beta_2$-m affecting not only FcRn activity but also other $\beta_2$-m functions, such as surface expression of MHC class I proteins.$^{60}$ Two siblings with this mutation had markedly reduced serum IgG (1.3 and 3.1 mg/mL) and albumin (19 and 21 mg/mL) concentrations due to an abnormally short half-life in these proteins, rather than disordered rates of synthesis,$^{61}$ suggesting that FcRn activity was impaired.

Genetic variations in FCGRT, the gene encoding FcRn, have been described and studied, with the primary focus being on variable number tandem repeats (VNTRs) in the gene promoter. A full review of this literature is beyond the scope of this article; to date, no associations have been reported between the VNTRs and the risk of disease. Genome-wide association studies, which assessed common FCGRT polymorphisms (but would not capture the VNTRs), have not reported any disease associations.

**FcRn as an echovirus receptor**

Echoviruses are common causes of aseptic meningitis worldwide, and also of severe hepatitis, neurological disease, and death in neonates and infants.$^{70,71}$ Echovirus particles attach to the host cell surface by directly binding FcRn (Fig 4), a receptor both necessary and sufficient for echovirus infection.$^{4,72}$ FcRn is expressed in sites often affected by echovirus infection, such as the placenta, intestinal enterocytes, liver hepatocytes, and endothelial cells that line the blood-brain barrier.$^{4}$ In vitro studies demonstrated that resistance to infection by echoviruses occurs when FcRn or $\beta_2$-m is either not expressed or obstructed by a blocking antibody, suggesting that FcRn inhibitors could potentially be treatment or prophylaxis for echovirus.$^{7}$ Because echovirus virions bind both extracellularly and intracellularly, FcRn inhibitors that bind at both neutral and acidic pH may more effectively prevent echovirus infection than those that bind only at acidic pH (like normal IgG).

**THE ROLE OF FcRn AND IgG IN AUTOIMMUNE DISEASE**

**Autoimmune disease**

Many autoimmune diseases result from dysregulated humoral immune response leading to autoantibody production. Elkon and Casali$^{73}$ classified autoimmune diseases as either organ-specific, with autoantibodies binding directly to the target organ and activating FcγRs, or as systemic, in which autoantibodies react with free molecules and cell surface or nucleoprotein antigen to form pathogenic ICs. In systemic autoimmune diseases, autoantibodies injure tissues and organs through IC binding to FcγR with activation of complement as well as internalization and activation of Toll-like receptors.$^{74}$ Examples of organ-specific autoimmune diseases are myasthenia gravis (MG),$^{75}$ immune thrombocytopenia (ITP),$^{76}$ Goodpasture’s syndrome,$^{77}$ and autoimmune hemolytic anemia,$^{78}$ whereas examples of systemic autoimmune diseases include rheumatoid arthritis,$^{79}$ systemic lupus erythematosus,$^{79}$ and cryoglobulinemic vasculitis (Table E1).$^{80}$

Characterization of autoimmune diseases has shown involvement of a range of immunoglobulin isotopes, from low-affinity IgM autoantibodies to high-affinity IgA, IgE, or IgG autoantibodies (Table E1). Given its abundance, IgG is associated with many autoimmune diseases. IgG$\_1$ and IgG$\_3$ have long been thought to be primarily responsible for IgG-mediated autoimmune diseases perhaps in part because they fix complement better than IgG$\_2$ and IgG$\_4$. However, in recent decades, IgG$\_4$ (the least prevalent IgG subclass) has been identified as the pathogenic driver in several autoimmune diseases, including pemphigus vulgaris (PV), pemphigus foliaceus (PF), and muscle-specific kinase MG.$^{81,82}$ The role of IgG$\_4$, whether pathogenic or protective, in other autoimmune diseases such as IgG$\_4$-related disease and bullous pemphigoid remains unknown.$^{83}$ The contributions and pathogenicity of different immunoglobulin classes and IgG subclasses to various diseases and their relationship to disease severity are not well understood.

**Lowering IgG—current therapies**

Removal or lowering of IgG, in particular pathogenic IgG antibodies, has been explored as treatment for IgG-mediated disease by several different modalities.

**Plasma exchange.** Plasma exchange (PLEX, therapeutic plasma exchange) is a nonspecific method to remove immunoglobulins, including autoantibodies, from the circulation, and is a first- or second-line treatment for many immune neurological,
PLEX involves removal of 1 to 1.5 plasma volumes daily over several days. The plasma from a patient is passed through a medical device to separate plasma from other blood components. Because PLEX is nonspecific, all large plasma proteins including albumin, beneficial antibodies, IgA and IgM, and clotting factors are also removed with IgG autoantibodies when plasma is removed. The removed plasma is replaced with a substitute solution returned to the patient, either crystalloid, colloid solution (albumin and/or plasma), a combination of crystalloid and colloid solution, or normal plasma. Following PLEX in patients with MG, acetylcholine receptor autoantibody titers were lowered by a similar mean maximum reduction in IgA, IgM, and total IgG. PLEX is predominantly used in the acute setting to ameliorate disorders mediated by autoantibodies, such as MG, chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barre syndrome, ITP, systemic lupus erythematosus crisis (including catastrophic antiphospholipid syndrome), and pulmonary-renal syndrome. Short-term PLEX is less effective in chronic diseases, due to continued autoantibody synthesis and/or rapid IgG redistribution from the extravascular to the intravascular space.

Because IgM is 95% intravascular, a single PLEX is very effective for IgM-mediated autoimmune diseases. PLEX is required for a minimum of 2 to 3 days, because IgG is 60% extravascular. PLEX may be associated with a rebound overshoot of IgG production and accelerated recovery of pathologic autoantibodies and, as such, is often combined with an immunosuppressive agent to block the rebound synthesis.

**Intravenous immunoglobulin.** Intravenous immunoglobulin (IVIg) is pooled polyspecific human IgG from thousands of healthy donors. It was originally developed for IgG replacement in antibody deficiency and first used for treatment of autoimmune diseases (ITP) in 1981. IVIg has since been widely used for the treatment of CIDP, Kawasaki disease, toxic epidermal necrolysis, and dermatomyositis, as well as many others. For autoimmune-mediated diseases, IVIg is typically administered at high doses, for example, 1 to 2 g/kg delivered over 1 to 2 days. The many potential mechanisms of action for IVIg have not been resolved (see the Rostrum in this issue by Shock et al). In ITP, interfering with the destruction of antibody-coated platelets appears to be the dominant initial effect, with another accepted mechanism being shortening the half-life of pathogenic autoantibodies through competitive binding of the infused IgG to FcRn (1 g/kg of IVIg is roughly equivalent to the total IgG contained in the body). Other hypothesized mechanisms of IVIg function include neutralization of cytokines, inhibition of anti-idiotypic autoantibodies, and anti-inflammatory effects of infused IgG4 (through binding to inhibitory FcγRIIB).

The relative impact of these different mechanisms in autoimmune disease is unclear and may vary depending on the disease and the patient.

**Immunoadsorption.** Immunoadsorption (IA) is a more specific therapeutic filtration procedure to remove immunoglobulins from circulation. Plasma from the patient is passed through an adsorption column, and antibodies or other molecules are specifically removed by binding to selected ligands, for example, protein A, on the matrix surface of the column. The “cleaned” plasma is then recombined with the patient’s red cells and platelets and returned to the patient. For many reasons, IA is currently not widely used in autoimmune diseases.

In summary, several effective methods for treatment of autoantibody-mediated diseases involve lowering pathogenic IgG levels: PLEX, IA, and IVIg. These procedures involve significant treatment burden and have side effects, which impact patients’ quality of life (reviewed in this issue by Peter et al). Based on the hypothesis that blocking the function of FcRn will result in increased catabolism of IgG antibodies, specific inhibitors of FcRn have been developed (Fig 2, B). As part of this mechanism of IgG lowering, IgA and IgM levels would be unaffected and production of IgG antibodies would be normal, minimizing the risk of infection.

**Lowering IgG—the era of FcRn inhibitors.** Several FcRn inhibitors exhibiting different structures and biophysical properties are currently in clinical development (Fig 5). mAbs under development include rozanolizumab (105,106), nipocalimab (M281), IMVT-1401/RVT-1401, orilanolimab (SYNT001(ALXN1830), and a bivalent antibody mimetic (ABY-039). Fc fragments include efgartigimod (ARGX-113) and CSL730/M323. These FcRn inhibitors all bind pH-independently to FcRn, displaying a high affinity at pH 7.4 (Fig 5). As discussed above, the primary biologic effects of FcRn inhibitors are IgG lowering and blockade of IgG transfer across barriers. FcRn inhibitors have no known effect on FcRn expression, turnover, or production of pathogenic IgG autoantibodies; thus, maintenance therapy is anticipated. Reduction of serum IgG concentration, following administration of FcRn inhibitors, is seen across multiple species: mice, primates, and humans. In humans, FcRn inhibitors have consistently and specifically led to decreases in circulating IgG by up to 85% in a dose-dependent manner. These levels are at least as low as PLEX, without appreciable effects on other antibody isotypes. When tested, all 4 IgG subclasses have thus far been equally lowered, albeit 1 study showed more lowering of IgG3 compared with other subclasses. Although immunologic rebound as postulated with PLEX is hypothetically possible, there has been no evidence of this phenomenon in animal or human studies. Importantly, clinically active FcRn inhibitors that increase IgG catabolism have shown no clinically relevant effect on circulating albumin levels.

Clinical trials of these molecules are focused on prototypical IgG-mediated autoimmune diseases such as MG, ITP, CIDP, PV, or PF, and warm autoimmune hemolytic anemia, as well as in hemolytic disease of the fetus and newborn. FcRn inhibitors are at a relatively early stage of clinical development, and further phase III studies, with repeated infusions, are required to fully inform the role of this class of treatment in different diseases. Given continued normal IgG production, the specific action for this modality, only reducing the IgG isotype, and the likely preservation of cell-mediated immunity, would suggest that clinical complications would hopefully be minimal.

**Preclinical evidence for FcRn inhibitors in autoimmune disease.** The ability of FcRn inhibitors to block IgG transfer across the placenta has been demonstrated in a human placental lobule model, following work in preclinical animal models. In addition to IgG lowering and blockade of IgG transfer, FcRn inhibitors may have further benefits for treatment of autoimmune diseases. For example, orilanolimab reduced patients’ quality of life (reviewed in this issue by Peter et al). Based on the hypothesis that blocking the function of FcRn will result in increased catabolism of IgG antibodies, specific inhibitors of FcRn have been developed (Fig 2, B). As part of this mechanism of IgG lowering, IgA and IgM levels would be unaffected and production of IgG antibodies would be normal, minimizing the risk of infection.
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**FIG 5.** Summary of FcRn inhibitors in clinical development. 

**HDFN,** Hemolytic disease of fetus and newborn; **KD,** dissociation constant; **WAIHA,** warm autoimmune hemolytic anemia.
circulating ICs and inhibited antigen-presenting cell cytokine release in healthy volunteers.109

FcRn inhibitors, given their specificity of lowering only IgG levels, will primarily impact IgG autoantibody-driven diseases. Preclinical studies in animal models of autoimmune diseases have shown efficacy of FcRn inhibitors in ITP.110 MG,112,113 epidermolysis bullosa acquisita,114 experimental autoimmune encephalomyelitis,111 and inflammatory arthritis.118

Therapeutic efficacy of PLEX, IVIg, and IA, all of which can reduce IgG autoantibodies (and have other effects), suggests which autoimmune diseases are most likely to be responsive to FcRn inhibitors. However, the pleiotropic effects of the former modalities neither guarantee FcRn inhibitor efficacy nor categorically indicate that those diseases are driven by IgG autoantibody. Review of publications presents numerous diseases reportedly associated with IgG, IgA, IgM, or IgE autoantibodies in Table E1. Although some of the diseases detailed are highly characterized and the immunoglobulin isotype responsible for mediating disease is generally accepted, there remain many diseases in which the immunoglobulin isotype driving the disease and whether critical pathophysiology is in fact antibody-driven are less well understood. On the basis of above, we postulate that efficacy of FcRn inhibitors in a given autoimmune disease would provide evidence to characterize it as being driven by the IgG isotype.

Clinical trials of FcRn inhibitors in ITP. Phase II clinical trials of efgartigimod and rozanolixizumab in patients with primary ITP demonstrated clinical efficacy and confirmed the potential of FcRn inhibitors as treatment options for ITP.

For efgartigimod, 38 adults with primary ITP were randomized into 3 groups (placebo [n = 12], efgartigimod 5 mg/kg [n = 13], or efgartigimod 10 mg/kg [n = 13]) receiving 4 once-weekly intravenous infusions.106 Patients could receive multiple concurrently occurring ITP treatments, including in some cases thrombopoietin receptor agonists. Platelet counts greater than or equal to 100 × 10^9/L were achieved by 46% and 39% of patients in the efgartigimod 5 mg/kg and 10 mg/kg groups, respectively, and 8% in the placebo group.106 Forty percent of patients in each efgartigimod group maintained a platelet count greater than or equal to 50 × 10^9/L for more than 10 cumulative days (compared with no patients in the placebo group).106 Time to achievement of a platelet count greater than or equal to 50 × 10^9/L was inconsistent, ranging from 8 to 43 days.106 Rapid reductions in total IgG were observed for both efgartigimod-treated groups, 3 days after the fourth infusion, up to a maximum mean change of 60% (efgartigimod 5 mg/kg) and 64% (efgartigimod 10 mg/kg), respectively; IgG levels were unchanged in the placebo group.106 All 4 IgG subtypes were reduced; no clinically relevant changes in IgA, IgD, IgE, IgM, and albumin were observed.106

Rozanolixizumab was evaluated in 66 adults with primary ITP who received single (15 or 20 mg/kg) or multiple (5 × 4 mg/kg, 3 × 7 mg/kg, or 2 × 10 mg/kg) subcutaneous (SC) infusions, with each group receiving an overall total dose ranging from 15 to 21 mg/kg.103 Concomitant medications were restricted; for example, no thrombopoietic agents were allowed. A platelet count of greater than or equal to 50 × 10^9/L was more frequently achieved in patients receiving single (15 or 20 mg/kg) SC rozanolixizumab infusions (67% and 55%, respectively) compared with those receiving multiple SC infusions (36%, 36%, and 46% in the 4, 7, and 10 mg/kg groups, respectively).103 Early responses, classified as those patients who achieved a platelet count of more than 50 × 10^9/L by day 8, were dose-dependent, with 58% and 55% of patients in the 15 and 20 mg/kg single infusion groups, respectively; responding by day 8, compared with 7%, 14%, and 27% in the 4, 7, and 10 mg/kg groups, respectively (although there were a few more responders in all dose groups after day 8). Mean serum IgG concentrations also decreased in a dose-dependent manner by day 8; the 20 mg/kg single infusion group achieved IgG nadir on day 8 (60% reduction from baseline), compared with day 29 for the 5 × 4 mg/kg infusion group (44% reduction from baseline).103

Further investigations of efgartigimod and rozanolixizumab in patients with ITP are ongoing, with phase III clinical trials underway (NCT04274452, NCT04225156, NCT04188379, and NCT04224688, NCT04200456, respectively; Fig 5).

Clinical trials of FcRn inhibitors in MG. FcRn inhibitors have also demonstrated efficacy in patients with MG; data from phase II studies for efgartigimod and rozanolixizumab are presented below.

A randomized, placebo-controlled study of efgartigimod was conducted in 24 adults with generalized MG, who received 4 doses of intravenous efgartigimod (10 mg/kg; n = 12) or placebo (n = 12) combined with ongoing standard-of-care therapy.105 Efgartigimod treatment led to rapid, sustained improvement in all 4 clinically relevant scales (MG activities of daily living, quantitative MG, MG composite, and MG quality of life 15-item), with initial effects seen from 7 days after first infusion and reduction of almost 50% in all scales.105 Efgartigimod treatment resulted in reduction of serum IgG as in the ITP studies, in addition with an approximately 40% reduction in anti–acetylcholine receptor autoantibodies.105

In a 2-period study of rozanolixizumab, 43 adults with moderate to severe generalized MG were randomized to receive 3 once-weekly SC infusions of rozanolixizumab (7 mg/kg; n = 21) or placebo (n = 22) in period 1 (days 1-29); on day 29, patients were rerandomized to receive rozanolixizumab 7 mg/kg or rozanolixizumab 4 mg/kg (3 once-weekly SC infusions) (period 2, day 29–43).104 At the end of period 1, a least squares mean difference of −0.7 (P = .221), −1.8 (P = .089), and −1.4 (P = .036) between rozanolixizumab and placebo was observed for quantitative MG, MG composite, and MG activities of daily living, respectively.104 In period 2, patients rerandomized from placebo to rozanolixizumab saw clinical improvements and those patients who continued receiving rozanolixizumab 7 mg/kg showed improvement in efficacy scores.104 Rapid reductions were seen in total IgG and anti–acetylcholine receptor autoantibody levels, with mean reductions of approximately 68% in patients continuing rozanolixizumab 7 mg/kg.104

Two further FcRn inhibitors, nipocalimab and IMVT-1401, are currently undergoing phase II clinical evaluation for treatment of MG (NCT03772587 and NCT03863080, respectively; Fig 5). Investigations of efgartigimod and rozanolixizumab in patients with MG continue, with phase III trials underway (NCT03770403, NCT03669588, and NCT04124965, NCT03971422, respectively; Fig 5).

Clinical trials of FcRn inhibitors in other IgG-mediated diseases

FcRn inhibitors are also being evaluated for the treatment of pemphigus (PV and PF); a phase Ib/II study of orilanolimab was...
terminated early, citing that study objectives had been achieved. Interim results are available, and the full study data have been submitted to clinicaltrials.gov.99,111 This open-label study of 24 patients receiving orilanolimab was conducted in PV or PF, with patients receiving 5 once-weekly intravenous doses of orilanolimab (≤45 mg/kg). Interim data showed that orilanolimab was well tolerated. Proof-of-concept was demonstrated with decreases in IgG, circulating ICs, and IgG autoantibodies (desmoglein 1 and desmoglein 3) observed.111 Clinical effect was also demonstrated with numerical reductions in pemphigus disease area index scores for patients with PV and PF, compared with baseline; a greater reduction was observed in patients with PV compared with PF.111

The efficacy of FcRn inhibitors is also being evaluated in other autoimmune diseases including warm autoimmune hemolytic anemia (nicoalimab and orilanolimab), CIDP (rozanolizumab), and Graves’ ophthalmopathy (IMVT-1401), and also in blocking maternal-fetal IgG transfer in Rhesus disease (hemolytic disease of the fetus and newborn, nicoalimab) (Fig 5).100

We have reviewed the efficacy and pharmacokinetic findings for FcRn inhibitors under development in a range of autoimmune diseases. The safety and susceptibility to infections accompanying the use of these molecules is reviewed at length in another article in this issue (see Peter et al11). Considering the totality of data reviewed, the FcRn inhibitors described here have all consistently demonstrated the ability to reduce circulating IgG levels in both healthy volunteers and patients. However, it should be noted that all studies have evaluated a relatively small sample of patients/healthy volunteers and investigated short treatment times, characteristic for phase II stage clinical development. Results from ongoing phase III studies with repeated dosing are eagerly anticipated to provide greater insights into the true utility of this treatment approach for IgG-mediated autoimmune diseases.

CONCLUSIONS

This review of IgG lowering describes the effects of IVIg, PLEX, IA, and especially FcRn inhibitors. Although pathogenic IgG is lowered by all 4, the evidence that reducing serum IgG autoantibody concentration is the primary mechanism of that modality is the strongest (most specific) for PLEX and FcRn inhibitors. The mechanism(s) of action for IVIg beyond FcRn inhibition and FcγR blockade remains uncertain, as it has for more than 30 years. Given their relatively specific mechanism of action, the results with FcRn inhibitors summarized here confirm that the dominant factor behind a number of autoimmune diseases is pathogenic IgG autoantibodies. Current therapies such as PLEX are associated with an IgG reduction of 60% to 70% from baseline,119 a short-lived reduction due to re-equilibration of extravascular IgG. Based on currently available data, FcRn inhibitors may be expected to provide comparable reduction of IgG (60%-70% from baseline)105,106; however, greater longevity of IgG reduction is expected (2-4 weeks following a single injection) compared with currently available treatments, which will be furthered by repeated infusions. Because of their substantial reductions in IgG levels, shorter infusion times, and apparent minimal toxicity, FcRn inhibitors may afford patients improved quality of life.

What do we know?

- FcRn binds IgG and albumin in a strictly pH-dependent manner, with pinocytosis responsible for ingesting the IgG to the intracellular space so that it can access FcRn in phagolysosomes at an acidic pH.
- Key functions of FcRn are (1) to extend the half-life of IgG and albumin by salvaging them from degradation, (2) to facilitate transcytosis across cell layers (eg, transcytosis of maternal IgG to the fetus), (3) to potentially mediate presentation of antigens by APCs, thereby activating T cells, and (4) possibly to contribute to the immune response by synergizing with FcRIIa.
- Because pathogenic IgG autoantibodies to specific cellular and tissue components play a key role in many autoimmune diseases, reduction of serum IgG may be an effective treatment.
- PLEX and IVIg lower pathogenic IgG levels, but also have more pleiotropic effects on the immune system.
- FcRn inhibitors in clinical trials are relatively specific for lowering IgG and do not substantially alter IgA, IgM, or albumin metabolism.
- Several FcRn inhibitors are currently undergoing clinical evaluation in healthy individuals and in patients with auto (and allo) immune disease and have shown efficacy in diseases also treated by PLEX and/or IVIg including MG, ITP, and pemphigus.
- Clinical response to FcRn inhibitors may provide a means to identify and categorize IgG autoantibody-driven diseases.

What is still unknown?

- Additional mechanism(s) of action for IVIg leading to clinical efficacy in autoimmunity.
- The importance of FcRn function in antigen presentation, T-cell activation, and induction of thrombosis.
- Whether CIDP, successfully treated with both PLEX and IVIg, is predominantly IgG autoantibody-driven, and which of many other diseases are IgG autoantibody-driven.
- Long-term effects of IgG lowering by FcRn inhibition on patient health.

Key concepts and therapeutic implications

- Unlike IVIg and PLEX, which have numerous mechanisms of action (some of which are unknown), the comparable efficacy observed for FcRn inhibitors in patients with various autoimmune diseases provides confirmation that reduction in IgG autoantibody levels is a specific and effective treatment strategy.
- Although FcRn inhibitors appear to work primarily via lowering IgG, additional effects such as blocking prothrombotic effects of IgG-ICs and inhibiting T-cell sensitization may also be important in certain diseases.
- The use of FcRn inhibitors in pregnancy would block IgG transport to the fetus and potentially be very effective in fetal diseases caused by maternal IgG antibodies, for example, hemolytic disease of the fetus and newborn, fetal and neonatal alloimmune thrombocytopenia, and anti-Ro causing fetal heart block.

REFERENCES

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