REVIEW ARTICLE

Neonatal Fc Receptor — Biology and Therapeutics

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Autoimmune diseases represent a major health care problem, affecting more than 5% of the world's population and involving virtually every organ system.[1] A major pathogenic mechanism involves IgG autoantibodies that recognize self-antigens and induce pathologic effects by way of diverse pathways[2] (Table 1 and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). IgG is the most abundant antibody type in the bloodstream (with a concentration of 10 g per liter), second only to albumin (with a concentration of 40 g per liter); the high concentrations of IgG and albumin are due to their plasma half-life of 21 days, which exceeds that of any other circulating protein.[3,4]

There is substantial interest in the development of therapeutic approaches to treat IgG-mediated autoimmune diseases that target B cells and plasma cells and the IgG they produce. These strategies include biologic agents that deplete B cells by targeting cell-surface proteins such as CD19 or CD20. Long-lived IgG-producing plasma cells can be targeted by means of their expression of CD38. Alternatively, B cells can be deprived of the B-cell activating factor required for their survival, or activation can be prevented with the use of Bruton's tyrosine kinase inhibitors. Unlike glucocorticoid agents, which are broadly suppressive and modestly decrease the levels of IgG, the levels and activity of IgG are more directly altered by the use of intravenous immune globulin, plasmapheresis, or immunoadsorption, which are toxic, invasive, or of limited availability. Recently, a new class of therapeutics that disable the neonatal Fc receptor (FcRn), which protects IgG from degradation, has emerged to treat IgG-mediated autoimmune disease.[4,5] Here, we review how advances in our understanding of the biologic features of FcRn led to this new therapeutic approach.

History of FcRn Biology

Our understanding of FcRn derives from foundational studies in the late 19th century by Paul Ehrlich, who used rodent models to investigate the passive transport of immunity from mothers to their offspring through milk.[4] This concept was revived in the mid-20th century by various investigators (reviewed by Brambell[6]) who showed that transmission of immunity through mother's milk in rodents occurred in the small intestine and was restricted to neonatal life. Transmission was dependent on the Fc, but not the antigen-binding or the Fab region of IgG (Fig. 1A), and was a saturable process because, at higher IgG concentrations, antibodies were degraded and not transported. Brambell et al. proposed that a selective, receptor-mediated process internalizes and then carries luminal IgG across intestinal epithelial cells into tissues. This transport process (or transcytosis) in rodents involved fluid-phase (or pinocytic) uptake into apical intracellular vesicles, where the IgG bound cell membranes at acidic, but not neutral, pH.[7]

KEY POINTS

FCRN INTERACTIONS IN IGG-MEDIATED THERAPIES

- The neonatal Fc receptor (FcRn) is a developmentally regulated, major histocompatibility complex class I–related molecule that binds IgG and albumin in a pH-dependent manner.
- FcRn protects IgG and albumin from destruction and enables the long half-lives of these circulating proteins.
- FcRn transports IgG across polarized cells and is important for IgG movement across barrier surfaces such as the placenta.
- FcRn regulates IgG function in innate and adaptive immune activities associated with professional antigen-presenting cells; such regulation is involved in protection from infection and cancer and in the development of autoimmune diseases.
- Understanding the biologic features of FcRn has enabled the development of therapeutics that block FcRn–IgG interactions to disrupt placental transport of IgG, cause IgG degradation, and decrease activation of cellular immunity as a new avenue for IgG-mediated treatment of autoimmune and alloimmune diseases.
- Augmentation of IgG–FcRn interactions can be used to extend the half-life of IgG-based therapeutics or enable their transport across epithelia for vaccination or delivery of therapeutic drugs.

By the 1980s, the Fc-binding protein that served as a receptor on the cell membranes in epithelial brush borders (or FcRn) in neonatal rats was identified as a 41-to-50–kD heavy chain in noncovalent association with a 15-kD light chain. Its landmark cloning in 1989 showed that these chains represent a newly identified class I human leukocyte antigen (HLA)-related protein and β2-microglobulin, respectively.[8] Thus, FcRn of the neonatal rat and mouse — and of the human placenta,[9] where passive transfer of immunity in humans occurs[10] — was a class I HLA-related molecule. However, the gene encoding FcRn, Fc gamma receptor and transporter (*FCGRT*), resides on human chromosome 19q13.3[4] and not in the HLA superlocus on chromosome 6p21. Despite its gene name, FcRn is structurally distinct from the classical Fc gamma receptors (FcγRs).[11]

STRUCTURE AND LIGANDS OF FCRN

Although human FcRn resembles class I HLA proteins, it does not bind antigenic peptides from foreign agents such as pathogens to stimulate the immune system.[12] Instead, FcRn uses the HLA-like structure to specifically engage IgG–Fc in a pH-dependent manner.[13,14] IgG binds to FcRn at a stoichiometry of 2:1, wherein two FcRn heterodimers bind to one IgG with the Fab (antigen-binding) arms oriented toward the cell membrane (Fig. 1A).[13] Basic histidine residues within the constant heavy-chain (CH2, CH3) domain interface of an Fc region and acidic residues on the side of FcRn are critical for this interaction (Fig. 1A, 1B, and 1C), and account for the strict pH dependence of IgG binding to FcRn.[14]

Histidine uniquely exhibits a p*K*a that is approximately 6.0, depending on its local environment. Histidine is protonated at or below pH 6.0 and gradually loses this protonation as the environment reaches neutrality. This process allows formation of salt bridges with oppositely charged residues on FcRn at acidic pH but not at neutral pH. This cycle of protonation–deprotonation is critical for intracellular binding of IgG to FcRn and release of IgG on the cell surface. Mutation of specific hydrophobic amino acids in an IgG-Fc such as isoleucine-253 or basic amino acids such as histidine-310 and histidine-435 in an IgG-Fc eliminates binding to FcRn (Fig. 1B).[14] These contact sites are mostly shared in all four subtypes of human IgG (IgG1, IgG2, IgG3, and IgG4), so the binding of each to FcRn is similar.[12]

However, most human IgG3 allotypes (distinct alleles of IgG3) uniquely exhibit arginine, rather than histidine, at position 435. Thus, IgG3 does not undergo optimal deprotonation at pH 7.4, which leads to residual binding at neutral pH and decreased dissociation from FcRn.[15] Antibodies such as IgG3 that possess increased binding to FcRn at neutral pH exhibit decreased half-life.[16]

FcRn also binds albumin with similar affinity to IgG at acidic pH, owing to a critical histidine residue in FcRn, but at a stoichiometry of 1:1 and on the side that is opposite to IgG.[3,13,17] This

characteristic allows FcRn to bind albumin and IgG simultaneously (Fig. 1C).[3,13] Echoviruses in the enterovirus B family and human astroviruses that cause gastrointestinal, airway, and systemic infections also directly bind FcRn, but they do so in a pH-independent fashion and use the receptor for host invasion.[18,19]

EXPRESSION AND REGULATION OF FCRN

Originally considered a protein restricted to neonatal life,[8] FcRn is now understood to be expressed by many somatic cell types in adults, a finding that was based originally on the functional expression of FcRn in rat hepatocytes[20] and its presence in the human placenta.[9] FcRn is broadly expressed in adult human parenchymal cells of epithelial and endothelial origin and in hematopoietic cells.[4]

The coding region of the gene for FcRn is nonpolymorphic, unlike class I HLA; however, its promotor contains a variable number of terminal repeats (VNTRs) that consist of a 37–base pair motif that is repeated up to five times.[21] More than 90% of people are homozygous for three repeats (VNTR3/VNTR3) that are transcriptionally more active,[21] a trait that potentially results in higher IgG levels. This characteristic may also lead to a greater response to intravenous immune globulin for the treatment of autoimmune disease or immunodeficiency in this population than among persons who are heterozygous (i.e., those who have an allele with two repeats and an allele with three repeats [VNTR2/VNTR3]).[22,23] Biologic drug levels may also be higher in people with the VNTR3/VNTR3 genotype consistent with increased FcRn expression,[24] although the clinical significance of this characteristic is unknown.

Fcgrt transcription is repressed by glucocorticoids and thyroxine in neonatal rodents, which suggests that FcRn is under hormonal control.[25] In contrast, the level of tumor necrosis factor, which is elevated in many inflammatory and autoimmune disorders, increases *FCGRT* expression in humans.[4]

FUNCTIONS OF FCRN

There are three broad categories of FcRn function: a transporter of IgG across polarized cells such as epithelia, a protector of IgG and albumin from catabolism, and a regulator of cellular pathways of immunity associated with myeloid cells.[4,5] Each pathway may contribute to the pathogenesis of autoimmune diseases and thus influence the therapeutic effects of FcRn blockade.

FCRN AS A TRANSPORTER

FcRn is expressed in virtually all polarized human epithelial cell types that separate two tissue interfaces, and it is associated with IgG transport across the cell.[4,5] Foundational studies using human intestinal epithelial-cell monolayers showed that transcytosis mediates bidirectional transport of IgG.[4,26] Consistent with the mechanism envisioned by Brambell et al. for neonatal intestinal epithelial-cell transport,[27] this pathway involves fluid-phase endocytosis of IgG and internalization into acidified intracellular endosomes, where FcRn binds IgG. IgG bound to FcRn is subsequently shuttled by means of intracellular trafficking vesicles to the opposite cell surface and released at the point of neutral pH in the extracellular milieu.

Physiologically, these pathways enable the inside-out movement of IgG from the tissues to mucosal surfaces to protect against pathogens and the outside-in transfer of antigens bound to IgG from the lumen for immune surveillance by local dendritic cells (Fig. 2A).[4] Pathogens such as human immunodeficiency virus[28] and Zika virus[29] may co-opt these pathways for host entry by way of epithelial barriers. These pathways are being investigated as a means of delivering vaccine antigens or therapeutics by coupling the immunizing protein or drug to the Fc domain of IgG and applying it to the luminal surface of epithelia.[4] Expression of FcRn by endothelial cells, which also exhibit polarity at the blood–brain barrier, may regulate transport of IgG from the central nervous system to the bloodstream, with therapeutic potential to remove toxic proteins associated with neurodegenerative diseases.[30]

FcRn also plays a critical role in transporting IgG from mother to fetus by expression in the placenta during gestation. Passive acquisition of maternal IgG by the human fetus mainly occurs during the third trimester and is necessary for early-life immunity until the infant's IgG production can maintain adequate IgG levels.[10] Studies in human placental explants directly show the

Table 1. IgG-Mediated Autoimmune Diseases under Evaluation for Anti-FcRn Therapies.*

Category or Organ System and Disease	Representative Autoantigens	Major IgG Subclasses
Peripheral and central nervous system		
CIDP†	Myelin-associated antigens — contactin-1, contactin-associated protein 1, neurofascin-155	IgG1, IgG3, and IgG4
Myasthenia gravis‡	Acetylcholine receptor, muscle-specific kinase	IgG1, IgG3, and IgG4
Autoimmune encephalitis	N-methyl-D-aspartate receptor, leucine-rich glioma-inactivated 1, contactin-associated protein-like 2, γ-aminobutyric acid-B receptor	IgG1 and IgG3
Guillain–Barré syndrome	Gangliosides (GM1, GD1a, GT1a, GT1b, and GQ1b)	Various subclasses
Myelin oligodendrocyte glycoprotein antibody-associated disease and neuromyelitis optica spectrum disorder	Myelin oligodendrocyte glycoprotein, aquaporin-4	IgG1
Stiff-person syndrome	Glutamic acid decarboxylase, glycine receptor, amphiphysin, gephyrin, dipeptidyl peptidase-like protein 6	IgG1
Skin		
Pemphigus vulgaris	Desmoglein 1 and desmoglein 3	IgG1 and IgG4
Pemphigus foliaceus	Desmoglein 1	IgG1 and IgG4
Bullous systemic lupus erythematosus	Collagen VII	IgG2 and IgG3
Bullous pemphigoid	Type XVII collagen (BP180), bullous pemphigoid antigen (BP230)	IgG1 and IgG4, occasionally IgG2 and IgG3
Hematologic system		
Immune thrombocytopenic purpura§	Platelet glycoproteins (GPIIb/IIIa, GPIb/IX)	IgG1 and IgG3
Warm autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh complex, band 3, glycophorin A)	IgG1 and IgG3
Rheumatologic diseases		
Rheumatoid arthritis	Citrullinated proteins (vimentin, fibrinogen, enolase)	Various subclasses, particularly IgG1
Autoimmune inflammatory myopathies (dermatomyositis, polymyositis, necrotizing myopathy)	Nuclear helicase Mi-2, transcription intermediary factor 1-γ, melanoma differentiation-associated protein 5, nuclear matrix protein 2, aminoacyl-tRNA-synthetases (especially histidyl-tRNA synthetase), signal recognition particle, HMG-coA-reductase, and other myositis-specific autoantigens	IgG1 and IgG3
Sjögren's syndrome	Ro Sjögren's syndrome (SS)–related antigen A, lupus antigen (La) SS antigen B	IgG1 and IgG3
Systemic lupus erythematosus	Double-stranded DNA, Smith antigen (small nuclear ribonucleoproteins)	IgG1 and IgG3
Fetal and newborn conditions		
Fetal and neonatal alloimmune thrombocytopenia	Human platelet antigen	IgG1
HDFN	Fetal red-cell antigens (RhD, RhC, Kell)	Various subclasses, particularly IgG1 and IgG3
Renal diseases		
Lupus nephritis	DNA, RNA, histones, and other nuclear antigens	Various subclasses, often IgG1 and IgG3
Primary membranous nephropathy¶	Phospholipase A2 receptor, thrombospondin type-1 domain-containing protein 7A	IgG4

Table 1. (Continued.)

Category or Organ System and Disease	Representative Autoantigens	Major IgG Subclasses
Organ transplantation — antibody-mediated rejection	Donor-specific human leukocyte antigen	Various subclasses
Gastrointestinal diseases — autoimmune pancreatitis¶	Lactoferrin, carbonic anhydrase II	IgG4
Infectious disease-induced autoimmunity — Covid-19–mediated postural orthostatic tachycardia syndrome	Autoantigens not yet fully characterized	Not strongly linked to a specific immunoglobulin subtype
Endocrine disorders		
Graves' disease	Thyroid-stimulating hormone receptor	IgG1
Thyroid eye disease	Thyroid-stimulating hormone receptor, type 1 insulin-like growth factor receptor	IgG1
Idiopathic diseases — fibromyalgia	Autoantigens not clearly defined	No specific immunoglobulin subtype associated

* Details and references regarding individual diseases are provided in the Supplementary Appendix. CIDP denotes chronic inflammatory demyelinating polyneuropathy, Covid-19 coronavirus disease 2019, and HDFN hemolytic disease of the fetus and newborn.
† Efgartigimod is approved for treatment in the United States.
‡ Efgartigimod and rozanolixizumab are approved for treatment in the United States.
§ Efgartigimod is approved for treatment in Japan.
¶ This disease is IgG4 related.

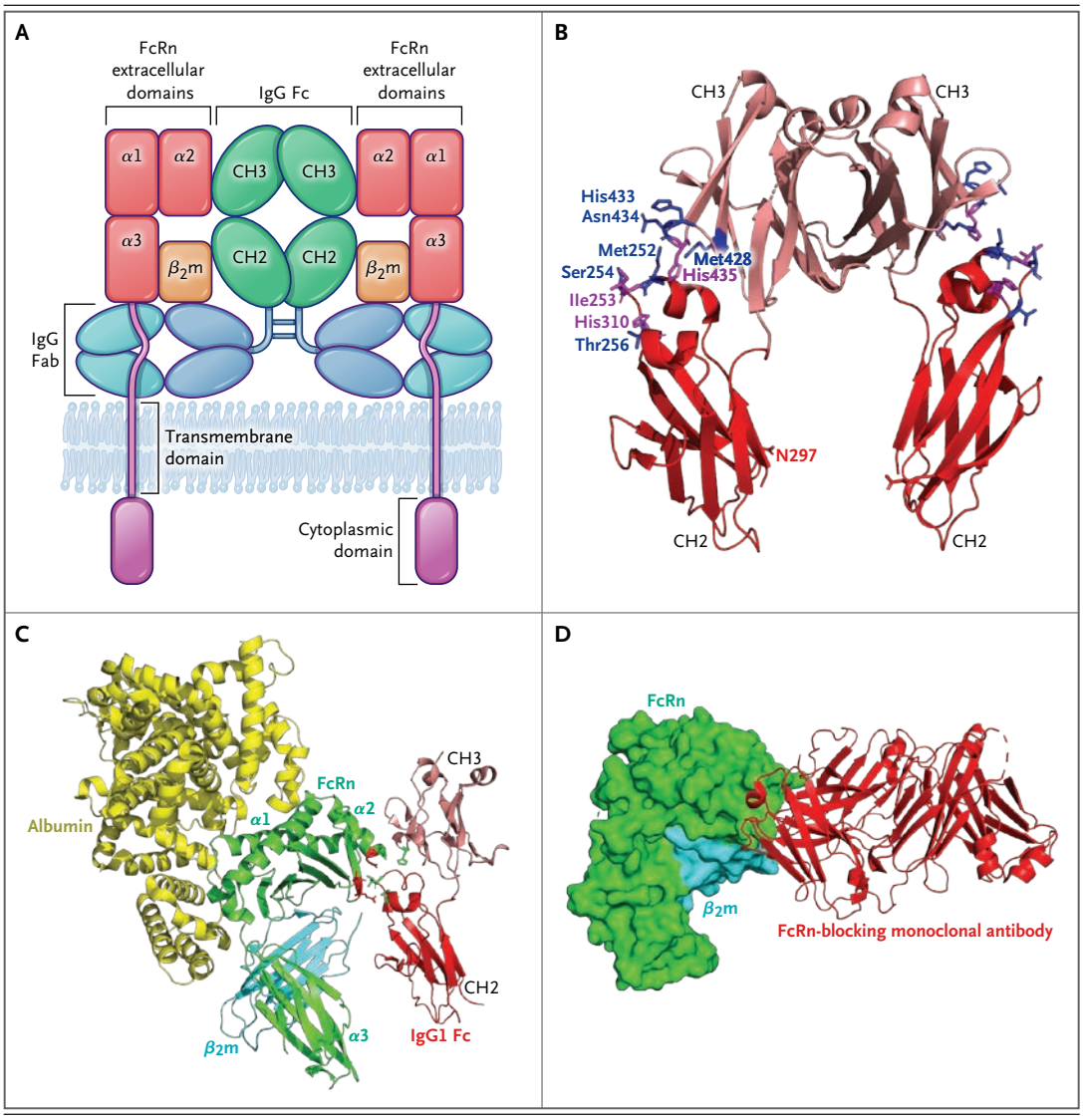
importance of FcRn in IgG transport.[31] Studies in humanized mouse models show that maternal–fetal acquisition of IgG is mainly mediated by FcRn rather than by classical FcγRs.[32]

Not all human IgG antibodies are handled in the same way, as shown by the diminished transplacental transport of IgG antibodies with bulky Fab fragments owing to their glycosylation (more common among patients with autoimmunity)[33] or IgG3 allotypes that contain arginine 435 (more common in western populations).[34] Transplacental passage of IgG antibodies from mother to fetus is initiated by binding of IgG to FcRn in placental syncytiotrophoblasts, specialized placental epithelial cells that express high FcRn levels and are active in transcytosis.[10] IgG is then delivered to and released at the basal surfaces of syncytiotrophoblasts; from there, it traverses the underlying stroma and is transported across the fetal endothelium, possibly by means of FcRn, to the fetal circulation (Fig. 2B).[10]

These activities present many therapeutic opportunities and challenges. Transplacental transport of biologic agents such as rituximab, for example, can cause hypogammaglobulinemia in a neonate owing to depletion of the infant's B cells.[35] FcRn-mediated IgG transport by way of the placenta into the human fetus can, however, deliver protective antibodies after maternal vaccination,[36] therapeutic proteins to replace missing factors (such as beta-glucuronidase for mucopolysaccharidosis),[37] or proteins such as factor VIII to potentially induce immunologic tolerance in patients with hemophilia A to forestall the development of inhibitors.[38] Conversely, transfer of maternal alloantibodies and autoantibodies can cause death and serious complications of hemolytic disease of the fetus and newborn,[39] fetal and neonatal alloimmune thrombocytopenia,[40] and fetal heart block in maternal Sjögren's disease and systemic lupus erythematosus (Table 1).[41]

FCRN AS A PROTECTION RECEPTOR

On the basis of findings in animal models that the half-life of IgG was inversely related to its serum concentration and dependent on the Fc domain, Brambell drew critical parallels to IgG transport across the epithelium in neonatal rodent models. They hypothesized that a related "protection" receptor was also involved in preventing IgG catabolism.[42] Evidence that FcRn was the factor responsible for preventing IgG catabolism came from studies in mice[43] and humans who lacked β2-microglobulin[44] and conclusively from studies involving *Fcgrt*-deficient mice[45] and analysis of mutant IgG in humans that is unable to bind FcRn in vivo.[14] They all showed that FcRn interactions with IgG and albumin[17]



are responsible for the long half-life of IgG and albumin, and in the absence of FcRn, hypogammaglobulinemia (and hypoalbuminemia) ensues.

Studies of bone marrow transfer in chimeric mouse models[46] and mouse models with deletion of *Fcgrt* in specific cell types[47] showed that macrophages and endothelial cells contribute equally to protecting IgG and albumin from catabolism. Mechanistically, FcRn functions as a recycling receptor after IgG internalization by fluid-phase endocytosis (or a more active process that involves fluid "gulping" or macropinocytosis in macrophages),[48] whereupon it binds FcRn in acidic early endosomes that shuttle the FcRn–IgG complex to recycling endosomes for exocytosis and IgG release in the neutral pH environment of the cell surface.[49] When the binding capacity of FcRn is exceeded, such as after the administration of intravenous immunoglobulin, the internalized IgG antibodies are no longer protected and instead are degraded in lysosomes (Fig. 3A).[4,5]

These protection pathways account for the long half-life of IgG-based biologic agents and Fc- and albumin-based fusion proteins used in clinical practice.[3,4] In addition, the Fc domain of IgG can be modified to enhance binding to FcRn at acidic pH, but not neutral pH, which

Figure 1 (facing page). Structure of IgG and Interaction with FcRn.

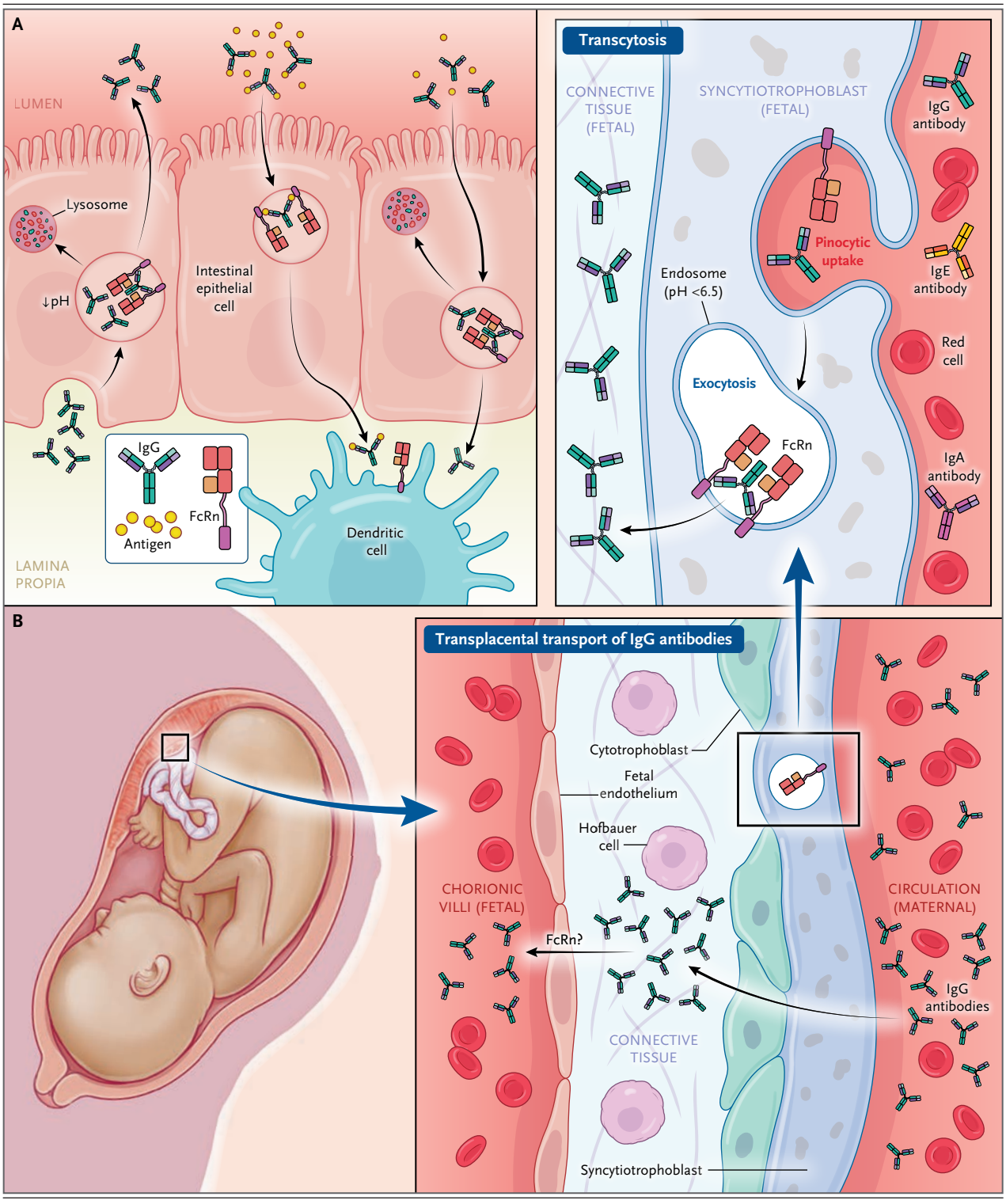
An IgG molecule consists of two heavy chains and two light chains that together form two variable (or Fab [fragment antigen binding]) arms and one constant (or Fc [fragment crystallizable]) region, as shown in Panel A. The Fc consists of two constant heavy (CH) domains (CH2 and CH3) for binding Fc gamma receptors such as the Fc neonatal receptor (FcRn). Each Fc heavy chain (green) binds to an FcRn (red)–β_2m (orange) heterodimer. The FcRn extracellular domains α1, α2, and α3 (red) are linked to a transmembrane domain and cytoplasmic tail (purple). The Fab domains of the IgG are oriented toward the membrane (light blue). Panel B depicts a ribbon diagram of IgG Fc (Protein Data Bank [PDB] identifier, 1FC1) with indicated CH2 (red ribbons) and CH3 (pink ribbons) domains. IgG residues Ile253, His310, and His435, indicated by purple lines, are critical for binding to FcRn. When the IgG1 MST-HN residues — Met252, Ser254, Thr256, His433, and Asn434 (blue lines) — are mutated to Tyr252, Thr254, Glu256, Lys433, and Phe434, the result is a mutant Fc, the IgG1$^{YTE\text{-}KF}$ variant, which exhibits higher binding to FcRn at acidic pH and retains binding at neutral pH. The IgG1$^{YTE\text{-}KF}$ Fc represents efgartigimod. Mutation of IgG1 MN residues Met428 and Asn434 (blue lines) to Leu428 and Ser434 results in an IgG1^{LS} variant, which shows substantially higher binding to FcRn at acidic but not basic pH. The IgG1^{LS} variant is incorporated into therapeutic antibodies to extend their half-life.[16] Each Fc fragment of the Fc domain contains a site for glycosylation at Asn297 (red lines). All residues described are shown in the left half of the IgG Fc domain but are also contained in the other Fc fragment (but not labeled). Panel C depicts a ribbon diagram of human FcRn–albumin–IgG1^{YTE} Fc as a ternary complex (PDB identifier, 4N0U), wherein albumin (yellow ribbon), FcRn heavy chain (α1, α2, α3; green ribbon), β_2m (turquoise ribbon), and half of the high-affinity IgG1^{YTE} Fc mutant CH2 (red ribbon) and CH3 (pink ribbon) are shown. Human FcRn and IgG–Fc residues that mediate FcRn–IgG1 binding are Glu115, Glu116, and Glu133 (red lines) and Ile253, His310, and His435 (green lines). Efgartigimod, by way of modified Fc domain, and therapeutic antibodies such as rozanolixizumab, nipocalimab, and batoclimab, by way of Fab domains, bind to the region of FcRn where an IgG Fc docks and block this interaction. Panel D shows surface (left) and ribbon (right) diagrams of human FcRn–anti-FcRn antibody complex (PDB identifier, 5WHK), in which FcRn heavy chain (green area) and β_2m (blue area) and anti-human FcRn antibody Fab (red ribbon) are shown. All four panels are adapted from Pyzik et al.[4] Ile or I denotes isoleucine, His or H histidine, Met or M methionine, Ser or S serine, Thr or T threonine, Asn or N asparagine, Leu or L leucine, Glu or E glutamic acid, Tyr or Y tyrosine, Lys or K lysine, and Phe or F phenylalanine.

augments FcRn-mediated protection and results in longer half-life and prolonged pharmacodynamic activity (Fig. 1B).[16] In contrast, the blockade of FcRn-mediated protection of IgG, which forces the degradation of IgG, is desirable to treat IgG-mediated autoimmune diseases.

FCRN AS A REGULATOR OF CELLULAR IMMUNITY

Human monocytes, macrophages, dendritic cells, and neutrophils express high levels of FcRn[50] and various classical FcγRs.[11] The low-affinity activating human FcγRs (FcγRIIa and FcγRIII) bind IgG as a soluble or cell-associated immune complex; the latter occurs, for example, when a microbe or cell, such as a platelet or red cell, is bound by an antibody or autoantibody, respectively.[2] An IgG immune complex bound to a classical FcγR stimulates phagocytosis or production of cytokines. Low-affinity FcγRs can also internalize an IgG immune complex into intracellular organelles of myeloid cells that enable regulated degradation of IgG-associated antigens into peptides for presentation by class I HLA molecules to CD8+ cytolytic T cells or by class II HLA molecules to CD4+ helper T cells, resulting in the stimulation of a T cell. FcRn participates in many of the same cellular activities and acts cooperatively with classical FcγRs.[51] IgG immune complex bound to FcRn can regulate phagocytosis by neutrophils[52] and stimulate the production of soluble inflammatory mediators and procoagulant activity by antigen-presenting cells.[53,54]

When FcRn encounters IgG as an immune complex containing a bound antigen, FcRn and its associated immune complex are diverted away from recycling pathways to intracellular compartments involved in class I HLA[55] and class II HLA[46] antigen-processing pathways for activation of CD8+ and CD4+ T cells, respectively. This action can lead to increased B-cell responses and IgG production.[4] These FcRn-regulated cellular pathways are involved in tissue responses that are associated with autoimmune diseases, as shown in models of inflammatory bowel disease[4] and rheumatoid arthritis,[51] or immune responses to cancer (Fig. 3B).[53] By their nature, these pathways probably sustain autoimmunity and may be amenable to therapeutic blockade with anti-FcRn agents.[50]



FCRN AS A THERAPEUTIC TARGET FOR IGG-MEDIATED AUTOIMMUNE DISEASE

The evidence that FcRn plays a role in the pathogenesis of autoimmune disorders was first provided by genetic models. Mice lacking β2-microglobulin, and thus functional FcRn, are less susceptible to the development of a spontaneous lupus-like autoimmune syndrome.[56] Mice deficient in β2-microglobulin[57] or FcRn[58] are re-

Figure 2 (facing page). FcRn in Transcytosis and Transplacental Transfer of IgG.

Panel A depicts transcytosis across polarized epithelial cells in adults. In intestinal epithelial cells abutting the lumen of the gut, pinocytosis of IgG from the tissues allows internalization into intracellular acidic vesicles. There, it binds FcRn and is transported to the opposite cell surface facing the lumen, where the FcRn-bound IgG is released. At this point, the IgG antibody can bind luminal antigens, such as those from bacteria, and the reverse cycle of transcytosis takes place, enabling delivery of antigens bound to IgG for uptake by tissue dendritic cells that also express FcRn. Panel B depicts transplacental transfer of maternal IgG to the fetus. In humans, the maternal and fetal circulation are separated by a polarized layer of epithelium (the syncytiotrophoblast). There, maternal IgG is transported from the maternal bloodstream into the stroma and subsequently transmitted across the fetal endothelium to the fetal bloodstream. FcRn is responsible for this transport in the syncytiotrophoblast and possibly in the endothelium. Panel B is adapted from Pyzik et al.[4]

sistant to a bullous pemphigoid disorder caused by injection of anti-hemidesmosome antibodies. FcRn-deficient mice are resistant to antibody-induced autoimmune arthritis.[59] Moreover, the efficacy of intravenous immune globulin in these autoimmune disease models is dependent on FcRn.[58,59] The first evidence that an IgG-mediated autoimmune disease could be targeted by pharmacologic blockade of FcRn with a therapeutic antibody was provided in an active and a passive model of myasthenia gravis.[60] These studies and others laid the foundation for developing therapeutics that target FcRn to treat IgG-mediated autoimmune disease,[4] as discussed below.

THERAPEUTIC AGENTS TO BLOCK FCRN

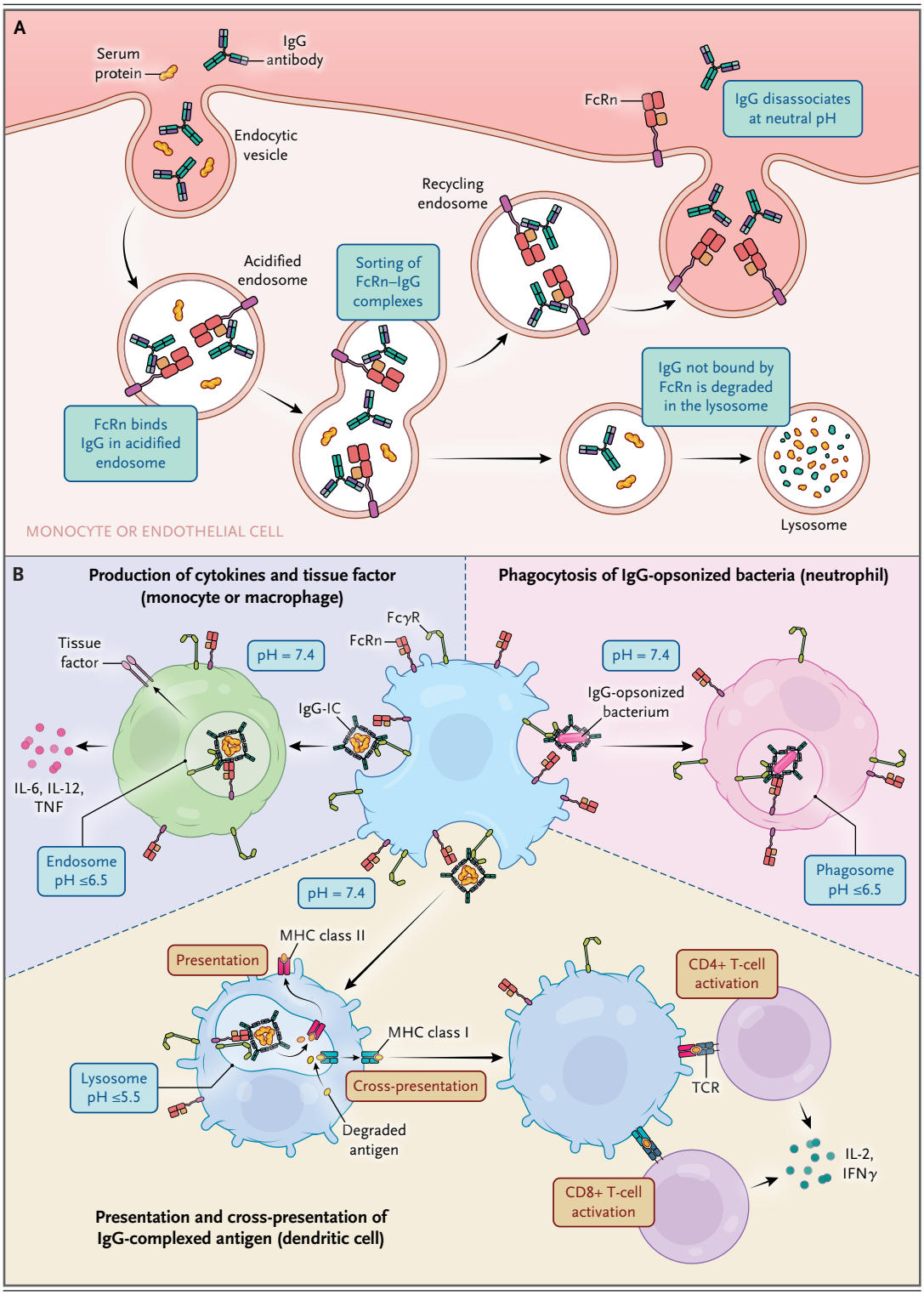
Several approaches have been pursued to obtain therapeutic blockade of FcRn by selectively targeting the IgG binding interface (Fig. 1C). The first involves engineering a human IgG1 Fc domain with five mutations (Fig. 1B) that increase binding to FcRn at acidic and neutral pH values.[61] The crystal structure of this mutated Fc in a complex with human FcRn shows that it binds like a natural Fc fragment but, because it lacks Fab domains (Fig. 1A), does not abut the membrane of endosomes.[62] In combination with the increased affinity for FcRn binding conferred by mutations, this mutated Fc outcompetes endogenous IgG antibodies for FcRn-mediated protection. It is thus a high-affinity antibody fragment that acts as a decoy and induces IgG degradation (e.g., the FcRn antagonist efgartigimod[63]).

Several therapeutic antibodies that bind FcRn by means of the Fab (or antigen-binding) fragment and block IgG–FcRn interactions are also in clinical development (Fig. 1C and 1D). Each binds with high affinity and is linked to either a human IgG4 Fc domain (rozanolixizumab[64]) or a mutated human IgG1 Fc domain (nipocalimab[65] and batoclimab[66]) to limit interactions with other Fcγ receptors and their effector functions. Peptide mimetics possessing sequences unrelated to human Fc that can block FcRn, small-molecule inhibitors of FcRn, and IgG-degrading enzymes are also in development.

THERAPEUTIC BLOCKADE OF FCRN IN CLINICAL PRACTICE

A major benefit of anti-FcRn therapies is that circulating IgG levels provide a pharmacodynamic biomarker. Inhibition of FcRn decreases all IgG subtypes and autoantibodies within the first week of administration, a change that typically plateaus at a reduction of 50 to 70% after multiple doses, depending on the dose and schedule of administration (Fig. 4).[4] All FcRn blockers cause prolonged IgG depletion notwithstanding their pharmacokinetic half-lives of 1 to 4 days.[63,64] Pretreatment levels of gamma globulin may not return for 1 to 3 months after completion of therapy.[67,68] Preexisting protective antibodies to tetanus toxoid, varicella zoster, or pneumococcus are also decreased by FcRn blockade but return to baseline with global IgG recovery.[69]

Although vaccine responses are not thought to be appreciably affected — a conclusion based on early clinical experience[69] — separation of anti-FcRn therapy and vaccination by at least 2 months may be prudent.[70] Studies involving patients with primary immunodeficiency (e.g., chronic variable immunodeficiency) who also have other immune deficits have shown that a prolonged decrease of IgG to a level of 3 to 5 g per liter or less is associated with an increased risk of infection.[71] However, the clinically approved anti-FcRn therapies have not shown a substantial increase in serious infections to date despite IgG reductions to levels seen in immunodeficiency. FcRn inhibition does not affect IgA or IgM levels, which may explain the absence of serious infections with anti-FcRn therapy thus far. Clinically approved



anti-FcRn therapies are generally safe, with headache being the most frequent adverse event. Whereas efgartigimod does not lower albumin levels, certain therapeutic antibodies can do so, owing to steric hindrance of the albumin-binding site of FcRn (Fig. 1C) or receptor degradation, or

Figure 3 (facing page). FcRn in Immune Activities.
Panel A depicts the recycling and protection of IgG from catabolism. Fluid-phase uptake of IgG by endothelial and monocytic cells allows binding to FcRn in acidified intracellular endosomal vesicles. These vesicles recycle the FcRn-bound IgG to the plasma membrane, where IgG dissociates from FcRn at the neutral pH of the extracellular milieu. IgG that is not bound by FcRn is transferred to lysosomes for degradation. Panel A is adapted from Roopenian et al.[5] Panel B depicts the immune activities of FcRn. When FcRn on a professional antigen-presenting cell, such as a monocytic or myeloid cell, binds IgG as an immune complex with antigen, several FcRn-regulated functions may be engaged. These include the production of cytokines and other mediators, such as tissue factor, which is associated with the induction of thrombosis; phagocytosis of the IgG-opsonized microbe or cell; and the internalization and transport of the IgG-bound antigens to intracellular compartments where the processing of IgG-associated proteins enables the generation of peptides. These peptides bind to class I and class II HLA molecules for stimulation of CD8+ and CD4+ T cells and their downstream consequences. These cellular pathways occur in cooperation with classical Fcγ receptors. Panel B is adapted from Pyzik et al.[4]

both.[72] A possible reduction in albumin levels warrants continued monitoring of albumin and lipid levels and drugs carried by albumin.[3]

Numerous clinical trials are currently under way to examine the therapeutic efficacy of these approaches in many clinical indications (Table 1). The clearest benefits of FcRn inhibition are seen in cases of myasthenia gravis caused by IgG autoantibodies to the acetylcholine receptor (Table 1); this observation is consistent with findings from studies in animal models.[60] Findings from studies of the use of intravenous immune globulin in the treatment of myasthenia gravis suggest that a 20 to 30% reduction in autoantibody levels may be a threshold for observing clinical improvement.[73] Phase 3 clinical trials of FcRn inhibition in myasthenia gravis showed that a 60 to 70% reduction of autoantibody levels was associated with significant clinical benefit as compared with placebo. Notable concordance was seen between decreased clinical disease activity (as reflected by the Myasthenia Gravis–Activities of Daily Living score and the Myasthenia Gravis–Quality of Life score) and overall IgG and IgG antiacetylcholine receptor levels after FcRn inhibition in both the ADAPT and the MycarinG trials (Fig. 4).[67,68] These findings resulted in approval by the Food and Drug Administration of both efgartigimod (Vyvgart) and rozanolixizumab (Rystiggo) for this indication. In the recent phase 2 ADHERE trial of efgartigimod in chronic inflammatory demyelinating polyneuropathy (CIDP), a disease that is associated with autoantibodies to myelin-associated antigens, 70% of the patients had evidence of clinical improvement and had fewer relapses while receiving therapy.[74] These findings led to FDA approval of efgartigimod for treatment of CIDP (Table 1).

Studies of FcRn inhibitors in immune thrombocytopenic purpura (ITP), another well-known IgG-mediated autoimmune disease, have resulted in clinical benefit, but to a lesser extent than that seen in myasthenia gravis. In a phase 2 trial, rozanolixizumab therapy increased platelet counts from 20×10^9 per liter to 80×10^9 per liter within 72 hours after administration of the highest single dose, coincident with a fall in total plasma IgG levels of only 40%.[75] This result suggests a lack of concordance of IgG reduction and platelet augmentation as well as an unanticipated immediacy of response. A phase 2 trial of efgartigimod in ITP showed responses of 46% with efgartigimod as compared with 25% with placebo.[76] A phase 3 trial of intravenous efgartigimod (ADVANCE IV) showed a significant primary response of 21% with efgartigimod ($\geq50\times10^9$ per liter for at least four of the six visits between weeks 19 and 24) as compared with 5% with placebo, with criteria met for multiple secondary end points, in a patient population with difficult-to-treat disease.[77] On the basis of these results, efgartigimod as an intravenous formulation has been approved in Japan for the treatment of ITP. However, a second phase 3 trial of subcutaneously administered efgartigimod (ADVANCE SC; ClinicalTrials.gov number, https://clinicaltrials.gov/study/NCT04687072) met neither the primary nor secondary outcome criteria despite reductions in IgG of greater than 60% by week 17, similar to those in the ADVANCE IV trial.

These trials and others illustrate the complexity of IgG-mediated autoimmune diseases — complexity that is reflected in the response observed with anti-FcRn agents. Myasthenia gravis and CIDP involve the direct effects of the autoantibody on target cells (the neuromuscular junction and nerve cell, respectively); therefore,

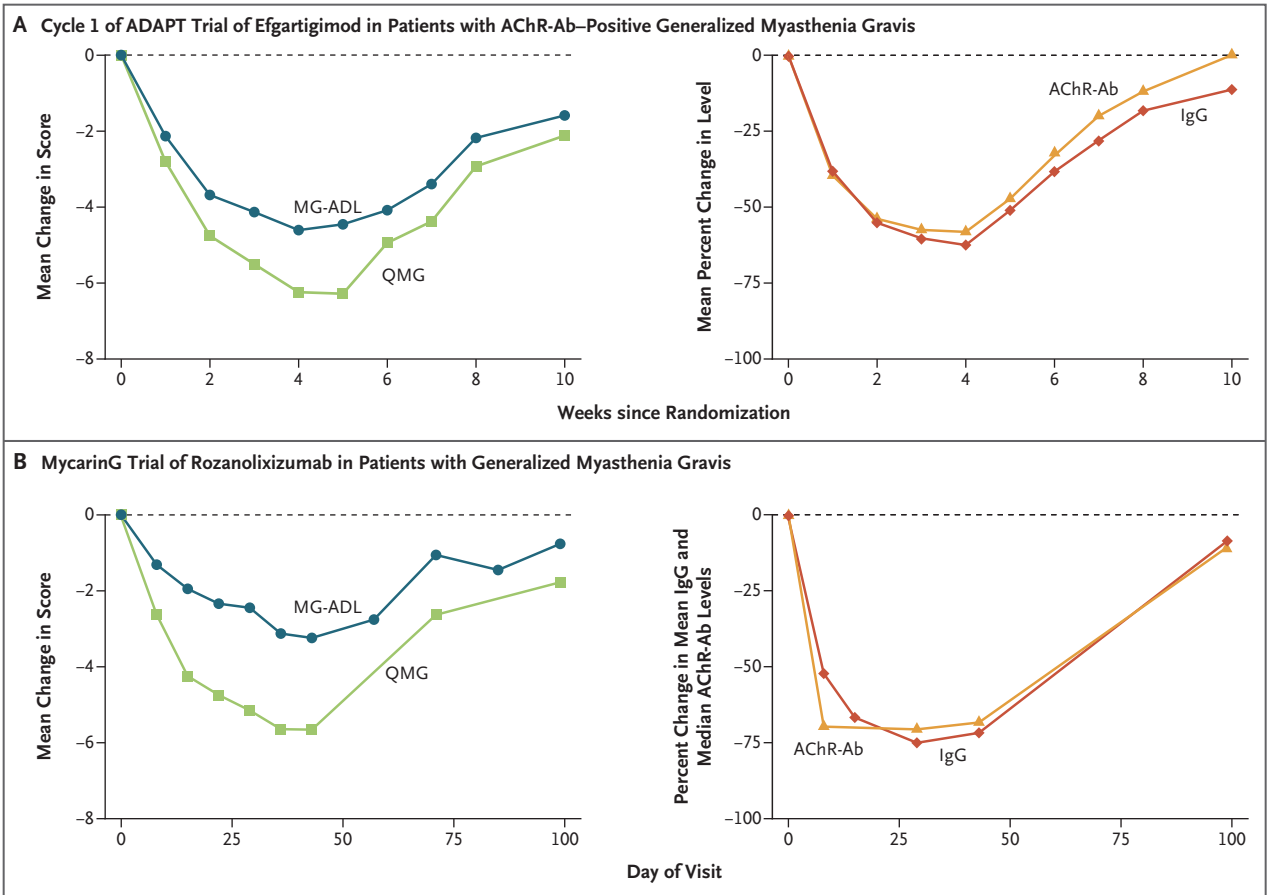


Figure 4. MG-ADL and QMG Scores and IgG and AChR-Ab Levels in ADAPT and MycarinG Trials.

Panel A shows the mean change in the Myasthenia Gravis–Activities of Daily Living (MG-ADL) score (blue circles; higher scores indicate more severe disease) and the Quantitative Myasthenia Gravis (QMG) score (green squares; higher scores indicate more severe disease) and the levels of IgG (red diamonds) and acetylcholine receptor antibody (AChR-Ab; orange triangles) from baseline during cycle 1 of the ADAPT trial of efgartigimod (at a dose of 10 mg per kilogram of body weight per week for 4 weeks) in patients with AChR-Ab–positive generalized myasthenia gravis.[67] The mean changes in MG-ADL and QMG scores reflect decreases (indicating clinical improvement) from baseline. Changes in AChR-Ab and IgG levels are reported as percent decreases from baseline. Panel B shows the mean changes in the MG-ADL score and the QMG score and the percent changes in levels of IgG and AChR-Ab from baseline to day 43 of the treatment period and through the final visit of the MycarinG trial of rozanolixizumab at a dose of 10 mg per kilogram of body weight per week for 6 weeks in patients with generalized myasthenia gravis.[68] The mean changes in MG-ADL and QMG scores reflect decreases from baseline. The changes in levels of AChR-Ab and IgG are reported as percent decreases from baseline; a decrease of 2 or more in the MG-ADL score and a decrease of 3 or more in the QMG score are considered clinically important. In all graphs, each point represents 46 to 69 observations.

clinical status correlates with circulating IgG levels. In contrast, ITP has more complex pathophysiological features that involve rapid phagocytosis of IgG autoantibody-coated platelets in the spleen and liver and autoantibody-mediated damage to megakaryocytes, thereby reducing platelet production.[40] A direct relationship between levels of circulating autoantibodies and clinical status has not been shown in ITP, and platelet-bound autoantibodies are not identified in all patients. Clearance mechanisms not based on FcRn, such as the asialoglycoprotein receptor, T-cell mediated cytotoxicity, or classical FcγRs, may limit the response to this approach in patients with ITP. These findings indicate the uncertain benefit of IgG reduction alone in certain IgG-mediated autoimmune diseases. It is not yet known whether clinically important disease-

specific differences exist among FcRn inhibitors or how FcRn inhibitors affect the tissue levels of IgG or activities of FcRn.[53]

Recently, FcRn inhibition has been used to inhibit maternal–fetal transfer of IgG anti-D and anti-Kell antibodies in severe, early-onset hemolytic disease of the fetus and newborn (HDFN).[39] Nipocalimab, at weekly doses intended to completely block FcRn, led to dramatic responses in 7 of 13 fetuses,[39] 8 of which had had siblings that died in previous pregnancies. The 7 fetuses with responses received no other antenatal treatment, in particular no intrauterine transfusions, and only 1 postnatal transfusion, unlike their preceding, severely affected siblings. The 6 other fetuses had lesser responses, showing delays in but not complete absence of in utero transfusion, with one fatality at 22 weeks of gestation. The underlying pathophysiological features that distinguish fetuses with a response from those without a response are unclear and could involve variations in properties and titers of antibodies against red cells or variations in FcRn expression levels in the placenta, or could involve an ancillary role of other Fcγ receptors in the transplacental transport mechanism, among other possibilities.

CONCLUSION

Insights from foundational studies that deciphered the transport of immunity from a mother to her offspring has led in the ensuing years to delineation of FcRn as a critical factor in determining the transport, lifespan, and activity of its two ligands, IgG and albumin. This understanding has enabled, and now validated, FcRn as a therapeutic target in the treatment of IgG-mediated alloimmune and autoimmune diseases. Manipulation of FcRn, whether by inhibition or augmentation, may prove to be an important part of the therapeutic armamentarium in the prevention and treatment of infectious diseases, autoimmunity, and cancer.

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