

Targeting FcRn for immunomodulation: Benefits, risks, and practical considerations



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The neonatal fragment crystallizable (Fc) receptor (FcRn) functions as a recycling mechanism to prevent degradation and extend the half-life of IgG and albumin in the circulation. Several FcRn inhibitors selectively targeting IgG recycling are now moving rapidly toward clinical practice in neurology and hematology. These molecules accelerate the destruction of IgG, reducing pathogenic IgG and IgG immune complexes, with no anticipated effects on IgA, IgM, IgE, complement, plasma cells, B cells, or other cells of the innate or adaptive immune systems. FcRn inhibitors have potential for future use in a much wider variety of antibody-mediated autoimmune diseases. Given the imminent clinical use, potential for broader utility, and novel mechanism of action of FcRn inhibitors, here we review data from 4 main sources: (a) currently available activity, safety, and mechanism-of-action data from clinical trials of FcRn inhibitors; (b) other procedures and treatments that also remove IgG (plasma donation, plasma exchange, immunoadsorption); (c) diseases resulting in loss of IgG; and (d) primary immunodeficiencies with potential mechanistic similarities to those induced by FcRn inhibitors. These data have been evaluated to provide practical considerations for the assessment, monitoring, and reduction of any potential infection risk associated with FcRn inhibition, in addition to highlighting areas for future research. (J Allergy Clin Immunol 2020;146:479-91.)

Key words: FcRn, neonatal Fc receptor, immunoglobulin, IgG, albumin, hypogammaglobulinemia, autoantibody, antibody-mediated autoimmunity, FcRn inhibitors, infection risk

Autoantibody-mediated autoimmune diseases can result in tissue damage through IgG *immune complex* (IC) deposition^{1,2} or via monomeric pathogenic *autoantibodies*, which bind directly to target structures and induce damage through *complement* activation and/or recruitment of inflammatory phagocytes.²⁻⁷ Current therapeutic strategies for the treatment of chronic autoantibody-mediated diseases consist of reducing antibody production by immunosuppression or B-cell-targeting drugs, and removal of autoantibodies and IC via *plasma exchange* (PLEX) or *immunoadsorption* (IA).⁸⁻¹⁰ Alternatively, for monomeric IgG-mediated diseases, immunomodulatory high-dose intravenous immunoglobulin (IVIg) therapy acts via a number of mechanisms including increased catabolism of autoantibodies via the neonatal fragment crystallizable (Fc) receptor (FcRn), cytokine neutralization, blockade of activating Fc-gamma receptors (FcγRs), or inhibition of autoantibodies by binding of natural anti-idiotypes^{11,12} (see review by Shock et al¹³ in this issue).

In many regions, supply and cost of IVIg are important factors. It can be challenging for health care systems to meet the demand

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Terms in boldface and italics are detailed in the glossary on page 480.

Abbreviations used

B2M:	β_2 microglobulin
COVID-19:	Coronavirus disease 2019
Fc:	Fragment crystallizable
FcRn:	Neonatal Fc receptor
Fc γ R:	Fc-gamma receptor
FIH:	First-in-human
GI:	Gastrointestinal
Gm:	Gamma marker
HBV:	Hepatitis B virus
IA:	Immunoabsorption
IC:	Immune complex
IgRT:	IgG replacement therapy
ITP:	Immune thrombocytopenia
IV:	Intravenous
IVIg:	Intravenous immunoglobulin
MG:	Myasthenia gravis
PLE:	Protein-losing enteropathy
PLEX:	Plasma exchange
QMG:	Quantitative MG
QW:	Once-weekly
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus-2
SC:	Subcutaneous
SID:	Secondary immunodeficiency
TEAE:	Treatment-emergent adverse event
VL:	Viral load
WBC:	White blood cell

for IVIg, which is increasing due to growth in the number of patients requiring IgG replacement therapy (IgRT) for treatment of antibody deficiencies, and the expanding use of immunomodulatory high-dose IVIg (on- and off-label) in the context of a worldwide plasma shortage.¹⁴⁻¹⁶

IgG has one of the longest half-lives of serum proteins, sustained by a specialized recycling pathway involving FcRn (see Patel and Busnel¹⁷ review in this issue). FcRn is predominantly expressed on the endothelium, but has also been detected in a diverse range of tissues and cell types.² Because recycling is the principal mechanism for maintaining a high serum level of IgG (and albumin), modulation of this pathway by blocking

FcRn is an attractive mechanism for the reduction of pathogenic IgG autoantibodies. Inhibition of FcRn accelerates destruction of IgG via **lysosomal degradation**. Using this targeted mechanism to reduce tissue and serum concentrations of IgG has the potential to provide significant therapeutic benefit for patients with both monomeric and IC IgG autoantibody-mediated diseases.¹⁸⁻²¹ Should these therapies prove successful, they will provide an alternative to high-dose IVIg and PLEX, reducing treatment burden on health care systems and patients. FcRn inhibitors currently in clinical trials include efgartigimod,^{20,22,23} rozanolixizumab,^{19,21,24} nipocalimab (M281),²⁵ and orilanolimab (SYNT001)¹⁸; additional FcRn inhibitors in development include IMVT-1401/RVT-1401, CSL730/M230, and ABY-039 (see Patel and Busnel¹⁷ for further details).

In the absence of large data sets or long-term exposure to FcRn inhibitors, this review aimed to define the immunologic impact of decreasing levels of IgG through FcRn inhibitors. Furthermore, we will review procedures and treatments that also remove IgG (plasma donation, PLEX, and IA), diseases resulting in loss of IgG, and genetic disorders with potential mechanistic similarities to those of FcRn inhibitors, to better understand the risk of infection associated with this novel class of drugs currently in development. Finally, we aim to provide practical considerations on assessment, monitoring, and precautions necessary to ensure adequate humoral immunity in patients receiving an FcRn inhibitor (postapproval) in various clinical scenarios.

ACTIVITY AND SAFETY OF FcRn INHIBITORS IN DISEASE SETTINGS

Efgartigimod, currently in phase 3 trials for generalized myasthenia gravis (MG) and immune thrombocytopenia (ITP), is a monoclonal IgG₁ Fc fragment that has been mutated at 5 residues to increase its affinity for FcRn at both physiologic and acidic pH.²⁰ In a phase 2 randomized, placebo-controlled study in 24 patients with MG (see Table E1 in this article's Online Repository at www.jacionline.org),²⁰ following 4 once-weekly (QW) intravenous (IV) administrations of 10 mg/kg efgartigimod, mean maximum reductions in serum IgG of 70.7% from baseline were observed 1 week after the final infusion. Reductions

GLOSSARY

AUTOANTIBODIES: Antibodies that react with the host's own tissues.

COMPLEMENT: A cascade of plasma proteins that is activated directly by pathogens or indirectly by pathogen-bound antibody to enhance the ability of antibodies and phagocytic cells to clear microbes and damaged cells.

Fc REGION: The tail region of an antibody that contains the constant regions of the heavy chains and interacts with cell surface Fc receptors or serum complement molecules.

HYPOGAMMAGLOBULINEMIA: The presence of abnormally low IgG levels within the blood.

IMMUNE COMPLEX: A molecule composed of a cluster of interlocked antibodies and bound antigens.

IMMUNOADSORPTION: A procedure wherein separated plasma is passed through an adsorber column to remove specific antibodies and immune complexes. Because other plasma components are unaffected, it has the advantage of removing the need for plasma replacement.

IMMUNOGENICITY: The ability of a foreign substance to elicit an immune response.

LYSOSOMAL DEGRADATION: The digestion of macromolecules, including proteins, nucleic acids, lipids, and oligosaccharides, into their building block molecules within intracellular lysosomes.

OPPORTUNISTIC INFECTIONS: Microbial infections that exhibit increased frequency and severity in patients with compromised immune systems.

PLASMA EXCHANGE: A procedure wherein blood plasma is removed and exchanged with either donor plasma or a plasma substitute, such as albumin and saline.

PRIMARY IMMUNODEFICIENCY: A disorder that results from deficiency in the development and/or function of 1 or more components of the immune system. To be considered primary, the immunodeficiency must not be secondary in nature, such as being a result of other disease, drug treatment, or environmental exposure.

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in anti-acetylcholine receptor autoantibodies mirrored the observed reductions in total IgG. Efficacy assessments using the Quantitative MG (QMG), MG Activities of Daily Living, MG Composite, and the revised MG Quality of Life 15-Item scales consistently demonstrated that 75% of patients showed a rapid disease improvement; improvements in QMG, MG Activities of Daily Living, and MG Composite scores were sustained for the duration of the study (through day 78).

Most frequently reported treatment-emergent adverse events (TEAEs) in patients receiving efgartigimod were headache and reduced white blood cell (WBC) counts, all of which were mild in severity. Single TEAE reports considered possibly related to efgartigimod and temporally associated with its administration included decreases in total lymphocyte counts, T lymphocytes and B lymphocytes, and monocytes, and an increase in neutrophil counts (Table I).¹⁸⁻²⁵ Hematologic changes (ie, abnormal differential WBC counts) observed in 3 patients following treatment with efgartigimod were mild and asymptomatic, and most likely explained by concomitant use of immunosuppressants. However, the first-in-human (FIH) study of efgartigimod²³ also reported abnormal differential WBC counts (mild decrease in CD8, CD3, CD56, CD4, and CD19 lymphocyte counts) after receipt of the drug (3 of 4 healthy volunteers who received 25 mg/kg and 4 of 4 who received 50 mg/kg).

Data from a phase 2 trial of efgartigimod in adults with primary ITP reported clinically relevant increases in platelet counts with associated decreases in IgG levels.²² Patients were randomized to receive 4 QW doses of placebo ($n = 12$), or IV efgartigimod 5 mg/kg ($n = 13$), or 10 mg/kg ($n = 13$), with a total of 21 weeks' follow-up. Patients who experienced a relapse during the follow-up period (platelet count, $<30 \times 10^9$) had the option to enroll in a 1-year open-label extension (Table E1) during which they received efgartigimod 10 mg/kg QW for 4 weeks. In patients treated with IV efgartigimod 10 mg/kg, a maximum reduction in total serum IgG of 60% to 64% was achieved by day 25 (Table I), with levels returning to baseline over the first part of the study (80 days). Every patient achieved a decrease in all IgG subclasses; antiplatelet autoantibodies were identified in all patients and were reduced by treatment with efgartigimod. In patients receiving IV efgartigimod 10 mg/kg, platelet counts rose from a mean of less than $20 \times 10^9/L$ at baseline to approximately $40 \times 10^9/L$ at the end of the treatment phase. During the main part of the study, a platelet count of greater than or equal to $50 \times 10^9/L$ was achieved by a similar number of patients in the placebo group as in the combined efgartigimod 5 mg/kg and 10 mg/kg groups (54% and 50%, respectively). However, 46% of patients receiving efgartigimod reached this threshold on at least 2 occasions (25% placebo) and 39% maintained counts at or over this threshold for more than 10 cumulative days (0% placebo); 42% achieved a platelet count of greater than or equal to $100 \times 10^9/L$ (8% placebo).

Efgartigimod was well tolerated over the full duration of the study, with no dose-related safety observations, no increased risk of infection versus placebo, and a safety profile consistent with previous FIH and MG studies. Changes in serum albumin were similar between placebo and efgartigimod groups, mostly within $\pm 10\%$ to 15% of baseline, and changes were not considered clinically relevant, suggesting that efgartigimod does not interfere with albumin binding²² (Table I).

A recent study explored the consequences of engineering the **Fc region** of IgG₁, thus manipulating the FcRn-IgG₁ interaction

on Fc effector function.²⁶ All 4 recombinant human IgG₁ variants, one of which (MST/HN) carried the same 5 point mutations as efgartigimod (M252Y, S254T, T256E, H433K, N434F²³), markedly reduced binding to classical Fc γ Rs. Three of the 4 variants (including MST/HN) demonstrated significantly reduced binding to complement factor C1q. Reductions in Fc γ Rs and C1q binding limited the ability of these human IgG₁ variants to activate antibody-dependent mechanisms such as cell-mediated cytotoxicity, cellular phagocytosis, and complement-mediated cell lysis. Interestingly, previous successful attempts to treat acute childhood ITP with infusions of unmutated Fc γ fragments suggested a predominant blocking action on classical Fc γ Rs on mononuclear phagocytes.²⁷ To our knowledge, the effects of efgartigimod on classical Fc γ Rs- and C1q-mediated functions have not been published and more information is needed to determine whether efgartigimod, besides inhibiting FcRn, has a significant effect on Fc γ Rs and C1q binding.

Rozanolixizumab, currently in phase 3 trials for MG and ITP and a phase 2 trial for chronic inflammatory demyelinating polyneuropathy (CIDP), is a subcutaneously (SC) infused humanized IgG₄ mAb that binds to human FcRn, selectively inhibiting IgG binding without affecting albumin.²⁴ In a phase 2 placebo-controlled clinical trial, 43 patients with generalized MG were randomized equally to 3 QW SC infusions of rozanolixizumab 7 mg/kg or placebo in period 1; in period 2, patients were rerandomized to 3 additional QW SC infusions of rozanolixizumab 7 mg/kg or 4 mg/kg (Table E1).¹⁹ Treatment with rozanolixizumab 7 mg/kg resulted in rapid reductions in both total IgG and anti-acetylcholine receptor autoantibody concentrations, with a maximum decrease of approximately 68% observed in patients receiving SC rozanolixizumab 7 mg/kg/week throughout the study. Least-squares mean differences between rozanolixizumab and placebo groups at day 29 were -0.7 ($P = .221$) for the QMG score, -1.4 ($P = .036$) for the MG Activities of Daily Living score, and -1.8 ($P = .089$) for the MG Composite score. The most frequently reported TEAE in patients receiving rozanolixizumab was headache. The investigators concluded that despite not meeting the primary end point of change from baseline in the QMG score at day 29, proof of concept was achieved on the basis of clinically meaningful improvements in MG outcomes and reductions in autoantibody titers.¹⁹

A phase 2 open-label, multiple-dose clinical trial in 66 patients with persistent/chronic primary ITP²¹ assessed the effect of different dose schedules of SC rozanolixizumab for a similar total exposure of 15 to 21 mg/kg (Table E1). The primary objectives were safety and tolerability; secondary objectives were efficacy (change in platelet count) and pharmacodynamics (change in total IgG). The most common TEAEs were headache, diarrhea, and vomiting (all mild to moderate in intensity); no serious infections were observed. There were dose-dependent increases in platelet counts: by day 8, a platelet count of greater than or equal to $50 \times 10^9/L$ was achieved by 54% and 58% of patients in the 20 mg/kg and 15 mg/kg single-dose groups, respectively, with median peak counts exceeding $100 \times 10^9/L$ in both groups. Dose-dependent decreases in serum IgG concentration were observed by day 8, with the 20 mg/kg ($n = 12$) single-dose group achieving its nadir of a 60% mean change from baseline in total serum IgG at this time point, whereas the 5 \times 4 mg/kg ($n = 15$) group achieved its nadir of 43.6% change from baseline on day 29.

TABLE I. Summary of IgG, albumin, adverse event, and infection data for reported clinical trials of FcRn inhibitors

Indication	N	Intervention and comparator	Duration of follow-up	Mean maximum reduction in IgG (%)	Impact on albumin	TEAEs of interest (%)	Reported infections
Efgartigimod (IV)							
MG ²⁰ (NCT02965573)	24	<ul style="list-style-type: none"> ● 10 mg/kg QW × 4 ● Placebo 	8 wk	70.7 week 4	Not reported	<ul style="list-style-type: none"> ● Headache 33.3 ● Nausea 8.3 ● Diarrhea 8.3 ● Abdominal pain 8.3 ● Total lymphocyte count decrease 16.7 ● T- and B-lymphocyte decrease 16.7 ● Monocyte count decrease 16.7 ● Neutrophil count increase 16.7 	<i>Herpes zoster:</i> 1 efgartigimod-treated patient (also seen in SoC treatment with prednisone and mycophenolate mofetil)
ITP ²² (NCT03102593)	38	<ul style="list-style-type: none"> ● 5 mg/kg QW × 4 ● 10 mg/kg QW × 4 ● Placebo 	21 wk	60.4 D25 63.7 D25	Similar between groups and within ±10%-15% baseline	<ul style="list-style-type: none"> ● Vomiting (5 mg/kg group only) 15.4 ● Headache (10 mg/kg group only) 7.7 	1 pneumonia (deemed unrelated to efgartigimod treatment); no apparent increased risk of infection
FIH ²³ (NCT03457649)	MAD: 32	<ul style="list-style-type: none"> ● 10 mg/kg Q4D × 6 ● 10 mg/kg QW × 4 ● 25 mg/kg QW × 4 ● Placebo 	58-59 d	78.5 D24 E_{max} 73.0 D24 E_{max} 77.7 D24 E_{max}	No significant decrease	<ul style="list-style-type: none"> ● Headache n = 4 ● Abdominal discomfort n = 1 ● In the SAD part of the study, abnormal differential WBC count was reported by 3 of 4 healthy volunteers receiving 25 mg/kg and 4 of 4 receiving 50 mg/kg 	None
Rozanolixizumab (SC)							
MG ¹⁹ (NCT03052751)	43	Period 1 (D1-29): <ul style="list-style-type: none"> ● 7 mg/kg QW × 3 ● Placebo Period 2 (D29-43): <ul style="list-style-type: none"> ● 4 mg/kg QW × 3 ● 7 mg/kg QW × 3 ● Placebo 	55 d	68 D50 in patients receiving 7 mg/kg throughout the study	Not reported	<ul style="list-style-type: none"> ● Headache 57.1 	Not reported
ITP ²¹ (NCT02718716)	66	<ul style="list-style-type: none"> ● 15 mg/kg × 1 ● 20 mg/kg × 1 ● 4 mg/kg × 5 QW ● 7 mg/kg × 3 QW ● 10 mg/kg × 2 QW 	8 wk	60 D8 for single-dose 20 mg/kg	Not reported	<ul style="list-style-type: none"> ● Headache 39.4 ● Diarrhea 12.1 ● Vomiting 9.1 	No serious infections

(Continued)

TABLE I. (Continued)

Indication	N	Intervention and comparator	Duration of follow-up	Mean maximum reduction in IgG (%)	Impact on albumin	TEAEs of interest (%)	Reported infections
FIH ²⁴ (NCT02220153)	SAD SC: 24	● 1 mg/kg ● 4 mg/kg ● 7 mg/kg ● Placebo	79 d	43.4 for 7 mg/kg D10	Modest decrease, not significantly different from placebo	● Headache ● Nausea ● Diarrhea ● Vomiting ● Abdominal pain	27.8 0 16.7 11.1 5.6 Incidence of treatment-related infections was lower in the rozanolixizumab total group (13.9%) than in the placebo group (23.1%)
Nipocalimab (IV)							
FIH ²⁵ (NCT02828046)	MAD: 16	● 15 mg/kg QW × 4 ● 30 mg/kg QW × 4 ● Placebo	Up to 14 wk	D20*: 83 E_{max} D24*: 84 E_{max}	Asymptomatic and transient reduction in total serum protein and albumin	● Headache ● Nausea ● Gastroenteritis	8.3 8.3 8.3 Incidence of treatment- emergent infections and infestations was similar between nipocalimab (41.7%) and placebo (50%) groups
Orilanolimab (IV)							
FIH ¹⁸ (NCT03643627)	SAD: 31	● 1 mg/kg ● 3 mg/kg ● 10 mg/kg ● 30 mg/kg ● Placebo	27 d	46.21 median for 30 mg/kg dose group within 5 d	No significant changes	● Headache ● Nausea ● Diarrhea ● Abdominal pain ● Decreased appetite	34.8 4.3 4.3 4.3 4.3 Not reported

D, Day; E_{max} , maximum percentage reduction value; MAD, multiple ascending dose; Q4D, every 4 d; SAD, single ascending dose; SoC, standard of care. For FIH studies, data are presented for multiple doses if available. *Median time to E_{max} .

Nipocalimab (M281), a high-affinity, fully human monoclonal IgG₁ anti-FcRn antibody engineered to have no Fc effector potential (no C1q binding, and no binding to activating FcγR), and *orilanolimab* (SYNT001), a humanized IgG_{4κ} mAb, are 2 additional FcRn inhibitors with published FIH data^{18,25} (Table I). *Nipocalimab* is currently in phase 2 trials for autoimmune hemolytic anemia, hemolytic disease of the fetus and newborn, and MG. The *orilanolimab* FIH study assessed the impact on C1q-associated circulating IgG ICs measured by the MicroVue CIC-C1q EIA Kit, in addition to demonstrating reductions in serum IgG. The investigators report that administration of *orilanolimab* to 31 healthy male volunteers resulted in significant dose-dependent reductions in circulating ICs, and *ex vivo*, *orilanolimab* inhibited the ability of IgG ICs to induce secretion of innate inflammatory cytokines by human peripheral blood leukocytes.¹⁸ Whether these promising initial findings translate into clinically meaningful therapeutic effects in patients with IgG IC-mediated disease remains to be seen.

Areas where further data are required to contribute to our understanding of the impact of FcRn inhibitors on immune function remain, in addition to data sets anticipated from unpublished phase 2 studies and forthcoming phase 3 trials. It would be of interest to understand details of specific antibody titers before and after inhibition of FcRn, booster responses during treatment, and responses to neoantigens (eg, hepatitis A or rabies vaccine). The impact of dose and route of administration on safety, efficacy, and patient satisfaction with treatment also needs to be evaluated. As patient numbers increase, analyses of

bacterial, viral, and fungal infections relative to placebo groups should become possible, as should understanding the impact of previous and concomitant therapies on changes in serum IgG and risks of infection. Further studies should also shed light on the impact of FcRn inhibitors on antigen presentation and follicular dendritic cells, which will be relevant to the understanding of potential FcRn inhibitor-associated infection risk. Finally, more information will emerge on interindividual or age-dependent variability in FcRn expression and, in turn, how this affects response to FcRn inhibitors.

THE MECHANISTIC BASIS OF FcRn INHIBITION: POTENTIAL IMPACT ON IMMUNE FUNCTION

Current evidence shows that inhibition of FcRn selectively reduces serum IgG, with no relevant reductions in IgM, IgA, IgE, or albumin^{18,23-25} (Table I). Reduction in IgG is transient and reversible, with mean maximum reductions in serum IgG of 45% to 85% from baseline, returning to near-baseline levels 50 to 57 days (28 days for *orilanolimab*) after single doses,^{18,24,25} and 50 to 80 days after multiple doses,^{20,22,23,25} indicating that function of the memory B- and plasma-cell compartments remains unaffected by inhibition of FcRn (Table I). During clinical trials of FcRn inhibitors, no rebound effect on levels of total IgG has been observed; for specific antibodies and autoantibodies, rebound is unknown and considered unlikely.

Any differential impact of FcRn inhibitors on reductions in IgG subclasses is of interest due to their potential utility for the

treatment of IgG₄-related disease.²⁸ An FIH study of efgartigimod reported that following administration of both single and multiple doses of efgartigimod, reductions in IgG₁₋₃ followed a similar pattern, with slightly smaller reductions observed for IgG₄.²³ This pattern of lower reductions for IgG₄ in comparison with IgG₁₋₃ was also observed in the phase 2 studies of efgartigimod,^{20,22} suggesting perhaps less efficient FcRn blockade by efgartigimod (a mutated Fc portion of IgG₁) for IgG₄. In contrast, FIH studies of rozanolizumab and orilanolimab both reported that administration of single doses resulted in dose-dependent reductions in IgG₁₋₄, with the most pronounced changes seen for IgG₃.^{18,24} A fourth phase 1 study found that each IgG subclass exhibited similar decreases in serum levels after the administration of single doses of nipocalimab; this observation was highly consistent across subjects.²⁵ Although a detailed structure-function analysis is beyond the scope of this review, factors such as half-life of subclasses, *gamma marker* (Gm) allotypes, and binding characteristics to FcRn deserve some mention. Histidine at position 435 (H435) provides for optimal FcRn-IgG binding and a long half-life (21 days). IgG₁, IgG₂, and IgG₄ carry the H435 variant, whereas an arginine at position 435 (R435) is more common in the IgG₃ subclass, leading to reduced binding affinity for FcRn, a shortened half-life (8 days), and reduced transplacental IgG₃ transfer.^{29,30} Interestingly, the H435 variant of IgG₃ has a different prevalence among Europeans (1%), Asians (10%-25%) and Africans (30%-60%), an observation that has been found to be important in the transplacental transfer of IgG₃ antibodies in antimalarial immunity.^{29,31} Similarly, the high number of codominantly inherited Gm allotypes in the IGHG3 locus (13 of all 20 Gm allotypes reside here) suggests a strong functional selection pressure in this part of the genome.³² Whether differences in IgG₃ H435/R435 and Gm3 allotype markers (such as G3m5, G3m6, G3m15, G3m16, G3m21 or G3m24, all encoded by 1 or several IGHG3 alleles) could influence its blockade through FcRn inhibitors and the clinical relevance of such a potential effect requires monitoring.

The main TEAEs reported to date appear to be gastrointestinal (GI) disturbances and headache—predominantly mild to moderate in severity, and, in the case of headache, manageable with standard therapies. More data are needed to clarify the effect of FcRn inhibitors on lymphocyte, monocyte, and neutrophil counts given the effects reported in the phase 1 FIH²³ and phase 2 trial of efgartigimod in MG²⁴ and ITP.^{20,22} As with all immunomodulatory therapies, there is a concern of increased risk of infection, although there is no evidence of increased infections for FcRn inhibitors reported so far. However, data are still limited, and increased rate of infection is perhaps the greatest theoretical risk associated with these new therapies. By inducing transient reduction in IgG, inhibition of FcRn has interesting parallels with several primary and secondary immunodeficiencies as well as procedures that reduce serum IgG. Assessing data from these examples may aid our understanding of the immunologic impact of FcRn inhibition and thus the potential risk of infection.

Hypogammaglobulinemia and infection risk

Increasing the rate of IgG removal via therapeutic inhibition of FcRn does not distinguish between pathogenic and nonpathogenic IgG and could be considered a type of novel secondary immunodeficiency (SID) (for overview, see Fig E1 in this article's Online Repository at www.jacionline.org).³³ Although SID can

result in increased risk of infection, potential severity varies widely, ranging from a modest increase in mild infections to a more serious profile, including opportunistic pathogens.³³ In patients with autoimmune diseases, antibody deficiencies can be multifactorial, from underlying disease processes and subsequent treatments. Patients who experience loss of IgG while antibody production and quality remain unaltered (eg, renal or GI losses, or antibody removal by PLEX) retain specific antibody production, and have a lower infection risk and less severe symptoms compared with patients with genetic disorders that result in global deficiency of antibody production.³³ Patients with genetic disorders resulting in low IgG who retain normal IgA and/or IgM levels may experience a more benign infection and complication profile.³⁴⁻³⁸ SID with a high risk of infections may occur, particularly when antibody production is impaired such as in lymphoid malignancies^{33,39,40} or prolonged treatment with B-cell-depleting therapies (eg, rituximab).⁴¹⁻⁴⁶

To assess the infection risk in SID or after therapeutic removal of immunoglobulin, it is important to consider which immunoglobulin class(es) has been reduced, where and how they function, and the mechanism and degree of reduction achieved.³³ Although FcRn is key to homeostatic regulation of both IgG and albumin, it does not bind to the other immunoglobulin classes (Fig 1). As observed in the FcRn inhibitors trials to date, inhibition of FcRn would be expected to induce a transient reduction in IgG with no relevant loss of IgM, IgA, or IgE. FcRn binds to albumin and IgG at 2 distinct sites in its $\alpha 1$ and $\alpha 2$ domain, respectively,⁴⁷ FcRn inhibitors bind only to the $\alpha 2$ domain; therefore, specific FcRn inhibitors should not impact serum albumin concentrations.

Inhibition of FcRn is not expected to affect plasma cells, B-cell repertoire, or memory B cells, or to interfere with other cells of the innate and adaptive immune systems, or complement. Because of its discrete mechanism of action, FcRn inhibition is less likely to be associated with increased risk of infection compared with other immunomodulators such as glucocorticoids or rituximab, and unlikely to lead to *opportunistic infections* with intracellular pathogens, particularly those requiring granulomatous inflammation for control (eg, mycobacteria, fungi). However, as a result of the selective loss of IgG, some recipients may be at increased risk for certain sinopulmonary infections, including those caused by respiratory viruses, *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Inhibition of FcRn results in a selective and reversible reduction of IgG that would be predicted to have a lower risk of infection than the impaired production of multiple immunoglobulin classes that results from some genetic disorders. We will therefore also consider infection data associated with procedures that remove IgG, diseases that result in loss of IgG, and genetic disorders with mechanistic similarities to inhibition of FcRn.

WHAT CAN WE LEARN FROM OTHER CONDITIONS AND THERAPIES?

Procedures that remove IgG

Plasma donation, PLEX, and IA all involve removal of blood components with greater or lesser degrees of selectivity for IgG (Table II).^{18,23-25,48-64} These procedures result in the reduction of existing antibodies, while leaving production of immunoglobulins by plasma cells intact (Table II). Levels of serum proteins,

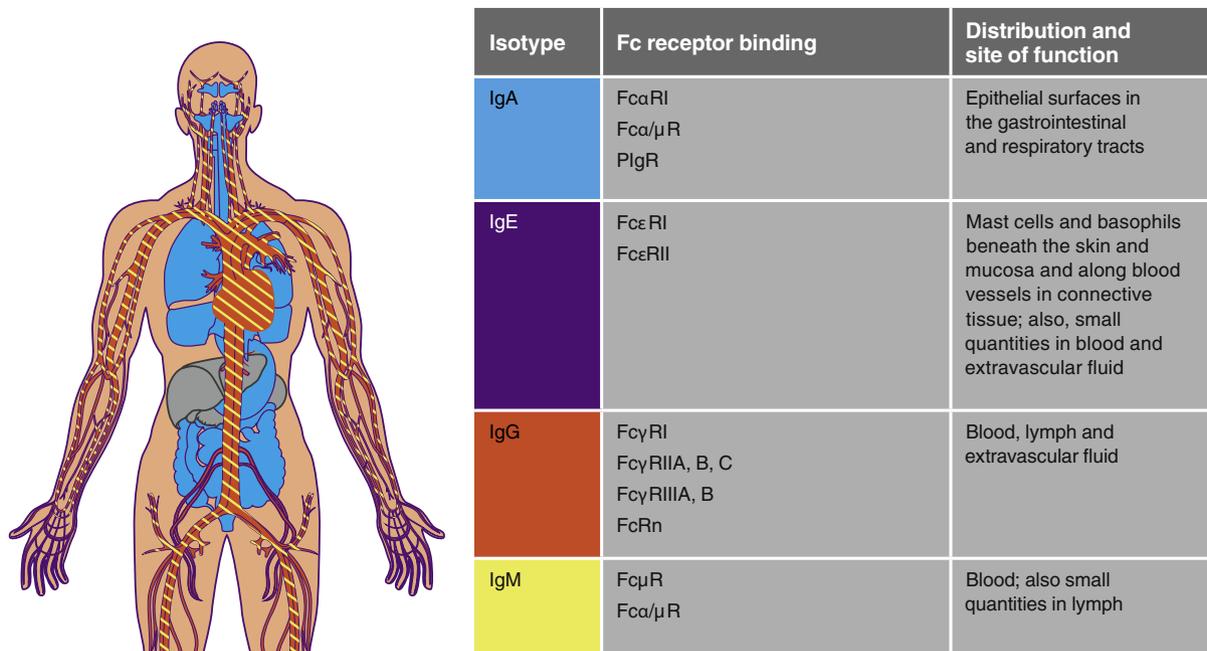


FIG 1. Distribution and function of immunoglobulin isotypes. *PIgR*, Polymeric immunoglobulin receptor.

including IgG, are subsequently restored by new production and redistribution from the extracellular space.

Plasma donation is perhaps the most common and least documented in terms of understanding the impact on the immune system and the subsequent infection risk. Plasma derivatives, including IVIg and albumin, are derived by processing a large number of pooled plasma donations.^{65,66} Apheresis plasma donations are generally restricted to 400 to 900 mL/donation (anticoagulant excluded) at a frequency of 13 to 104 donations per individual per year,⁶⁶ with data suggesting a 13% reduction from baseline in donor serum IgG levels over the course of an 800 mL donation.⁴⁸ A limited number of studies have prospectively assessed the safety of long-term intensive plasmapheresis on donors.^{49,67,68} Even with intensive plasmapheresis, there is no evidence of reduced immune responses; donors have normal IgG production and respond normally to antigenic stimulation (Table II).

PLEX involves the removal of 1 to 1.5 plasma volumes (30 to 40 mL/kg) per exchange using centrifugation or filtration-based devices, and replacing volume with isotonic albumin or a mixture of saline and albumin to avoid hypotension.⁵¹ The procedure requires large-caliber venous access and may be associated with cardiovascular disturbance; close monitoring of electrolytes is also needed.⁵¹ Therapeutic effect is based on the removal of circulating pathogenic immune factors, including autoantibodies and ICs; however, nonpathogenic IgG, IgA, and IgM are also removed, as well as complement components (Table II). *PLEX* is predominantly used in the acute treatment of several antibody-mediated disorders such as MG, lupus crisis, Guillain-Barré syndrome, and pulmonary-renal syndrome.⁵¹ *PLEX* does not always provide clinical benefit in chronic diseases,⁶⁹ and may not be the most effective or targeted approach to the treatment of autoantibody-mediated diseases, because it removes all circulating proteins. In addition, as IgG is distributed throughout the extravascular space, its removal from serum by

PLEX results in rapid redistribution back into the intravascular space.⁶⁹

IA is a therapeutic procedure for the specific removal of proteins by passing separated plasma through an adsorption column. Immunoglobulins can be targeted for removal through binding to selected ligands on the backing matrix surface (membranes or beads) of the adsorption column (Table II). Although *IA* is effective for the treatment of pemphigus vulgaris^{70,71} and CIDP,^{72,73} *IA* systems are used less frequently than *PLEX* for the treatment of IgG autoantibody-mediated diseases, due to the availability and complexity of the procedure, and regulatory and economic differences between health care systems.⁵¹

The American Society for Apheresis, the American Academy of Neurology, and other organizations have published guidelines and commentaries for *PLEX* and *IA*,^{51,74,75} noting that side effects and complications of *PLEX* and *IA* mostly relate to the procedure itself.^{75,76} Both treatments are used in patients with a range of heterogeneous disorders alongside varied previous therapies and differing numbers of exchanges. Thus, teasing out the specific impact on infection risk of using these procedures to remove serum proteins is challenging, with few studies assessing the risk of infection for these procedures in patients with antibody-mediated autoimmune diseases. Schmaldienst et al⁷⁷ evaluated the infection risk of *IA* with and without IVIg substitution. Overall, rates of infection were low and similar between groups (*IA* + IVIg, 1.3 per patient-year, interquartile range, 0-2; *IA* alone, 0.9 per patient-year, interquartile range, 0-2).⁷⁷ In 2012, Som et al⁷⁸ reported data for *PLEX*-related complications from the Oklahoma thrombocytopenic purpura-hemolytic uremic syndrome Registry, which provides data from a population-based inception cohort of consecutive patients with a diagnosis of thrombocytopenic purpura or hemolytic uremic syndrome. Over 15 years, the percentage of patients with major complications attributed to *PLEX* decreased—because of reduced frequency of catheter-related complications, rather than

TABLE II. Procedures and conditions causing excessive loss of antibodies

Procedure/ condition	T cells	B cells	NK cells	IgA	IgM	IgE	IgG	Albumin	Infection risk	References	
Procedures that remove IgG											
Plasma donation		Normal humoral and cellular immunity					Decreased (Ab loss)	Normal or reduced	No risk		48-50
PLEX	Possible alterations in lymphocyte function due to mechanical damage			Decreased (with rapid recovery)	Decreased (with rapid recovery)		Decreased (Ab loss), recovery may be delayed by weeks		NR		51,52
IA				Decreased (Ab loss). Dependent on the ligands used to bind different Ig classes					NR		51
FcRn inhibitors	Normal	Normal	Normal	Normal	Normal	Normal	Decreased (Ab loss)	Normal or modest decrease	No increased risk of infection reported		18,23-25
Conditions that result in loss of IgG											
Protein loss	T-cell abnormalities	B-cell abnormalities	NR	NR	Normal to elevated levels	NR	Decreased (Ab loss)	Decreased; synthesis may be increased	Increased susceptibility, particularly to bacterial infections		53-55
● Renal loss											
○ Nephrotic syndrome											
● Gastrointestinal loss*	Decreased	Decreased	NR	Decreased	Normal or decreased	Normal	Normal or decreased (Ab loss)	Reduced, synthesis normal or increased	NR		56,57
● Fontan procedure	Normal or decreased	Normal	Normal	Variable	Variable	NR	Decreased (Ab loss)	Normal or increased	Delayed clearance of cutaneous viral infections		58
CD55 deficiency	Normal	Normal	Normal	Decreased (Ab loss)	Decreased (Ab loss)	Decreased (Ab loss)	Decreased (Ab loss)	Decreased	Recurrent respiratory infections		59
Genetic disorders resulting in the increased catabolism of IgG											
● FcRn defect	Normal; altered differentiation of CD8 T cells	Decreased	Decreased; but functionally inactive	Normal to elevated	Variable	NR	Decreased (Ab loss)	Decreased	Infections include RTIs; granulomatous dermatitis; recurrent otitis media		60,61 62
○ B2M deficiency											
○ Myotonic dystrophy											
● Glycosylation type IIb defect	Normal	Normal or increased	Normal	Decreased (Ab loss) Shortened half-life of Igs due to a glycosylation defect			Decreased because of reduced half-life of Igs	Normal	Paradoxical increased resistance to some viral infections, due to glycosylation defects in viral receptors and viral envelope (n = 3 patients)		63,64
○ MOGS-CDG											

The literature was also assessed for changes to antigen-presenting cells, but no data were reported for this cell type in the articles cited.

Ab, Antibody; CDG, congenital disorders of glycosylation; MOGS, mannosyl-oligosaccharide glucosidase; NK, natural killer; NR, not reported; RTI, respiratory tract infection.

*Early onset inflammatory bowel disease caused by single gene defects associated with immune dysregulation.

complications related to plasma removal. The researchers make no mention of increased infection risk as a consequence of *hypogammaglobulinemia*.⁷⁸

Overall, PLEX and IA appear to be associated with a low risk of infection, and infections that do occur are mainly associated with venous access. In the case of PLEX, which removes IgA, IgM,

complement, and other blood components in addition to IgG, the low level of reported infections offers some reassurance regarding the impact of procedures that leave antibody production intact. In clinical practice, the use of these therapies and the duration and degree of IgG reduction that can be realistically achieved may be limited by their other side effects and the burden of treatment on

both patient and health care system. The targeted ability of FcRn inhibitors to reduce serum IgG while leaving all other serum constituents intact, and without the associated risks with extended venous access/central venous catheters, anticoagulants, and donor blood products, would suggest a similar or lower infection risk than with PLEX or IA.

Diseases that result in loss of IgG

Further insights into the potential impact of FcRn inhibition on risk of infection can be obtained from conditions associated with loss of fully functional IgG (Table II). *Nephrotic syndrome* is typically associated with proteinuria, resulting in peripheral edema and hypoalbuminemia due to increased glomerular permeability caused by a number of primary and secondary glomerular diseases.⁵³ Because of its large molecular weight (150 kDa) compared with albumin (70 kDa), only a subset of patients with nephrotic syndrome experience loss of IgG. Nephrotic syndromes with nonselective protein loss that includes IgG have less favorable prognoses than those with selective loss of small proteins, because they frequently lead to tubulointerstitial damage and decreased likelihood of remission.⁷⁹ Patients with nephrotic syndrome have increased susceptibility to infection due to hypogammaglobulinemia, reduced complement activity, and treatment-related (corticosteroids, immunosuppressive agents) decrease in T-cell function,⁸⁰ as well as increased risk of clotting disorders and cellulitis due to peripheral edema (Table II). Infections have been reported in up to 20% of adult patients, with bacterial infections such as pneumonia and cellulitis being the most common.⁵³

Protein-losing enteropathy (PLE) can result in loss of all serum proteins, including immunoglobulins, and sometimes WBC into the gut lumen (Table II). PLE has been observed in a range of GI and non-GI conditions including cardiac disease, liver disease, and systemic lupus erythematosus, and, rarely, arises after the Fontan procedure for single-ventricle congenital heart disease.⁵⁶ Because albumin and IgG contribute to most of the total osmotic effect of human serum, peripheral edema, ascites, and pleural effusions are the most common clinical complications of PLE. The loss of immunoglobulins and coagulation factors increases the risk of bacterial infections and clotting disorders.⁸¹ The Fontan procedure leads to increased central venous pressure, hypogammaglobulinemia, and lymphopenia secondary to chronic GI loss of lymph. However, severe bacterial infections are infrequent and only a minority require IgRT.⁵⁸

CD55 deficiency is an autosomal-recessive syndrome that results in hyperactivation of complement, angiopathic thrombosis, and PLE. All patients described to date have normal lymphocyte subsets and antibody production. The PLE-induced decrease in IgA, IgM, IgG, IgE, and albumin is directly related to primary intestinal lymphangiectasia, intestinal inflammation, and thromboses (Table II).⁵⁹ Five of 11 patients experienced recurrent respiratory infections associated with hypogammaglobulinemia; infections were reduced in 2 patients after treatment with IVIg.⁵⁹

Although patients with nephrotic syndrome, PLE, and CD55 deficiency have extensive protein loss in common, their antibody production is normal, suggesting that most symptoms are associated with protein loss. The infection susceptibility profiles observed in these conditions are typically mild and limited to sinopulmonary infections and cutaneous cellulitis, and are less

frequent than in patients with abnormal antibody production. In contrast to FcRn inhibitors, the protein loss in these conditions is not limited to IgG but, depending on disease severity, can include low- and high-molecular-weight proteins such as albumin, IgA, IgM, IgG, IgE, and complement, as well as cellular elements. Loss of albumin and associated peripheral edema is the dominant risk factor for cellulitis, and therefore unlikely to be a concern for treatment with FcRn inhibitors.

Genetic disorders with mechanistic similarities to inhibition of FcRn

The β_2 microglobulin (*B2M*) gene is required for cell-surface expression of nearly all members of the MHC-I family, including FcRn. *B2M deficiency* has been described in 2 pairs of siblings.^{60,61} Although the genetic mutations and subsequent levels of B2M expression differed between the pairs of siblings, all 4 patients had normal-to-high IgA levels, variable IgM levels, and low serum albumin and IgG levels due to a lack of functional FcRn (Table II). Because of its role in mediating cell-surface expression of MHC-I molecules, the impact of B2M deficiency was not limited to humoral immunity. The patients had a complex immunodeficiency impacting both the innate and the adaptive immune systems, characterized by altered differentiation of CD8 T cells and a lack of functional natural killer cells.⁶¹ Clinically, patients presented with recurrent bacterial respiratory tract infections, bronchiectasis, and inflammatory skin lesions, all of varying severity, resembling transport associated with antigen processing deficiency and other MHC-I deficiencies.^{60,61}

Myotonic dystrophy is an autosomal-dominant disorder characterized by muscle weakness, myotonia, cataracts, and cardiac conduction defects. Hypogammaglobulinemia is a lesser-known symptom of myotonic dystrophy type 1, with patients typically having low IgG₁ and IgG₃, with normal levels of IgM, IgA, IgG₂, IgG₄, and albumin; patients retain the ability to produce protective specific vaccine-related antibody titers (Table II).⁶² It has previously been proposed that alterations to the FcRn receptor in myotonic dystrophy type 1 lead to impaired recycling and hypercatabolism of IgG.⁸² Although patients with myotonic dystrophy type 1 and hypogammaglobulinemia have been reported to experience increased infection risk, the resulting burden of infection in these patients does not appear to correlate directly with serum levels of IgG, and the mechanism by which IgG levels are reduced remains unclear.⁶²

Mannosyl-oligosaccharide glucosidase mutations represent 1 of more than 100 types of congenital disorders of glycosylation identified to date and caused by defects in protein or lipid glycosylation.⁶³ N-glycosylation disorders such as mannosyl-oligosaccharide glucosidase-congenital disorders of glycosylation result in intrinsic defects, affecting immunoglobulin structure and stability, and can alter IgG function and half-life (Table II).⁸³ Case studies of 6 patients have reported variable infection rates and a complex influence on vaccine responses.^{63,64,84}

B2M deficiency presents with a complex immunologic picture, myotonic dystrophy, and mannosyl-oligosaccharide glucosidase-congenital disorders of glycosylation selectively shorten the half-life of IgG without impacting IgA, IgM, IgE, or other components of the immune system. In addition, in each of these conditions, reductions in IgG do not appear to correlate directly with infection risk.

PRACTICAL CONSIDERATIONS

Inhibition of FcRn reduces both pathogenic and nonpathogenic IgG (but does not change the production or quality of IgG), without affecting other components of the innate or adaptive immune systems. Based on the multiple lines of evidence reviewed, it would be expected that patients receiving an FcRn inhibitor will have limited risk of increased infection. Here, we provide our considerations for clinicians in terms of diagnostic assessments, monitoring of patients, and vaccination, before and during FcRn inhibition. These principles are based on the limited currently available clinical evidence and are driven by theoretical and scientific deliberations, because FcRn inhibitors are still in clinical development and yet to be licensed for use. We expect these principles to evolve as clinical trial data and real-world evidence emerge, and in accordance with future individual drug labels.

Diagnostic assessments before FcRn inhibition

Establish any possible preexisting risks for infection from the clinical history and with the following assessments:

- WBC count with differential; C-reactive protein, liver, and renal function profiles; serum albumin; and IgG, IgA, and IgM.

Establish presence of hepatitis B virus (HBV), hepatitis C virus, and/or HIV in patients at risk for infection:

- Serologic and/or PCR screening may need to be performed.
- Capacity for seroconversion may be affected by a primary immune defect or by previous therapies; therefore, assessment of the corresponding viral load (VL) may be the preferred approach.
 - Where possible, storage of serum for future analysis should be considered, because serology testing may be less reliable after treatment.

In patients with a family history and/or clinical suspicion of *primary immunodeficiency* or SID, additional testing beyond immunoglobulin levels could be considered—including (but not limited to) T-, B-, and natural killer-cell enumeration and subset differentiation.

These immunologic tests provide a baseline assessment of the patient to facilitate interpretation of potential changes in these parameters, which is useful because patients with primary immunodeficiency may present with autoimmune complications.

Prophylactic antibiotics before FcRn inhibition

Routine antibiotic prophylaxis for patients before or during FcRn inhibition was not recommended for the clinical trials.

- Specific approaches may be required for some underlying conditions (eg, CD4⁺ T lymphopenia, splenectomy, or multilobar bronchiectasis) or if there is a burden of infection before initiation of an FcRn inhibitor.

Vaccination

The *immunogenicity* of vaccines is not currently expected to be compromised by FcRn inhibition. However, the ability to respond to vaccines may be impaired because of other recent immunosuppressant therapy.

For FcRn inhibition in treatment-naive patients, we would recommend the following:

- Recombinant or inactive vaccinations be up-to-date more than or 2 to 4 weeks before commencing treatment, allowing time for adaptive immunity to develop.
- Live attenuated vaccines be administered more than or 8 weeks before initiating an FcRn inhibitor, to ensure enough time for clearance of vaccine-associated viremia.
 - Live attenuated vaccines are generally contraindicated in patients with proven or suspected immunodeficiency, because of the potential for vaccine-related complications.

For patients already receiving an FcRn inhibitor:

- There is currently no evidence against administering inactivated and recombinant vaccines.
- Kinetics of IgG restoration, following single or multiple dosing of an FcRn inhibitor, suggest that vaccines should be given 2 months or more after the last dose, and more than or 2 to 4 weeks before the next.
- Inactivated influenza vaccine should be administered annually, with the timing based on the scenarios described above.

The safety of live attenuated vaccines in patients receiving an FcRn inhibitor is currently unclear; some clinical trials stipulated that they should be avoided during the trial. Given the current lack of evidence, they should therefore be generally avoided.

Management of infections during long-term FcRn inhibition

Although bacterial respiratory tract infections are thought to be the most likely consequence of FcRn inhibitors, any infection should be thoroughly investigated to establish the anatomical site and microbial etiology, and reported while we gain experience with these agents. Reassessment of the baseline immunologic parameters may also help to determine any changes in immunophenotype that may be associated with the infection.

Novel, rare, or recurring viral infections are always concerning. Measles, influenza, and HBV are vaccination preventable and immunity may be boosted before or during FcRn inhibition, whereas for some other viruses, including the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), at the time of writing there exists no vaccine and no effective antiviral treatment. A case report of nonsevere coronavirus disease 2019 (COVID-19) demonstrated recruitment of immune cell populations and IgM and IgG SARS-CoV-2-binding antibodies before the resolution of symptoms.⁸⁵ Although the primary antiviral immune response involving IFNs, IgM, IgA, complement, and natural killer and T cells is unlikely to be affected by FcRn inhibition, the presence and the degree of low IgG levels and the potential impact on the primary immune response when exposed to a new virus or the clinical course and severity of COVID-19 is unknown. It is therefore prudent to pause the FcRn inhibitors if a diagnosis of COVID-19 or other severe respiratory virus is confirmed, to mitigate against any consequences of reduced IgG in this scenario.

The risk of FcRn inhibitors in the setting of HBV, hepatitis C virus, and HIV is unknown but would be theorized to be favorable to that of some other immunosuppressive options.

For patients with active viral infection (eg, detectable VL in blood):

- It may be prudent to initiate antiviral treatment before the use of FcRn inhibitors.
- Monitor VL while on an FcRn inhibitor.

For chronic HBV (characterized by persistence of HBV surface antigen):

- Antiviral prophylaxis may be considered before and during FcRn inhibition.
- HBV VL monitoring should be considered.
- Active monitoring (eg, with liver enzymes and HBV VL), with preemptive initiation of antiviral therapy as required.
- Possible referral to an infectious disease specialist.

Appropriate antimicrobial therapy should be implemented if needed—the choice dependent on severity of infection, anatomical site, microbial etiology, local epidemiological pattern of antimicrobial resistance, and, where possible, microbiological sensitivities. For severe infections (ie, requiring hospitalization or IV therapy), withholding any immunosuppressant treatment should be considered; this decision likely also applies to FcRn inhibition. In nonsevere cases, it is possible that FcRn inhibitors can be continued with concomitant antimicrobial therapy and close monitoring of IgG levels, particularly if the patient demonstrates a favorable evolution. Where an FcRn inhibitor is continued during or reinstated after treatment of infection, close monitoring for clinical and/or laboratory evidence of disease recurrence is recommended. In cases of severe infection that cannot be controlled with other specific treatments (eg, antibiotics), IgRT may be considered. Any subsequent decision about continued FcRn inhibition would need to be based on individual assessment of the patient, considering also any anticipated further need for IgRT.

As with other novel biologic modulators, the emergence of unanticipated side effects such as opportunistic infections should be monitored in the real-world setting by building registries. Opportunistic infections will need to be reported to the manufacturer and/or regulatory agency for safety purposes and the cases published.

Patients with primary or secondary immune deficiency: Specific considerations

Patients who require IgRT because of primary or secondary immune deficiency may be at risk of serious infections. FcRn inhibition is unlikely to be appropriate for these patients.

Patients who have undergone splenectomy: Specific considerations

Splenectomy remains a treatment option for patients with ITP or common variable immune deficiency with severe autoimmune cytopenias who have not responded to other therapies.^{86,87} In the absence of any FcRn inhibitor–specific recommendations, standard guidelines for patients undergoing splenectomy⁸⁸ should be followed.

Patients with splenectomy are at risk of overwhelming postsplenectomy infection, a life-threatening sepsis. Where overwhelming postsplenectomy infection develops despite appropriate vaccination, chronic FcRn inhibitor therapy is unlikely to be appropriate and alternative treatments for the underlying condition should be considered.

Monitoring during long-term FcRn inhibition

Postapproval, monitoring of patients receiving repeat cycles of an FcRn inhibitor may include the following:

- A questionnaire-derived score to identify patients with elevated risk of respiratory tract infections.⁸⁹⁻⁹²
- Measurement of incidence of infections, headache, and GI symptoms; quality-of-life measures; body weight; and laboratory data, including serum immunoglobulins and serum albumin.

SUMMARY AND CONCLUSIONS

Based on the evidence available to date, hypogammaglobulinemia caused by FcRn blockade is transient and reversible, and affects only the IgG isotype. Despite the absence of data on specific vaccine and infection-induced antibody titers before, during, and after FcRn blockade, we do not expect that this inhibition impacts plasma cells or B cells, or cells of the innate and adaptive immune systems. By harnessing the IgG salvage and recycling pathway, FcRn inhibitors have the potential to meet an urgent need for a more targeted therapeutic approach to pathogenic IgG reduction and provide a less invasive and time-consuming alternative to PLEX, IA, and immunomodulatory high-dose IVIg therapies.

Key concepts and therapeutic implications

- Inhibition of FcRn is a promising therapeutic approach for the treatment of IgG-mediated autoimmune diseases that has the potential to provide an alternative to immunomodulatory high-dose IVIg therapy, PLEX, IA, and other less targeted immunosuppressive therapies.
- Successful treatment with an FcRn inhibitor will induce transient low levels of IgG, including a lowering of IgG autoantibodies and IgG-containing ICs.
- There are no anticipated effects of FcRn inhibitors on IgA, IgM, IgE, complement, plasma cells, B cells, or other cells of the innate or adaptive immune systems.
- Short-term treatment experiences with FcRn inhibitors currently in development do not indicate an increased infection risk.
- Described treatment-related side effects of FcRn inhibitors are headaches and mild GI symptoms (diarrhea, vomiting).

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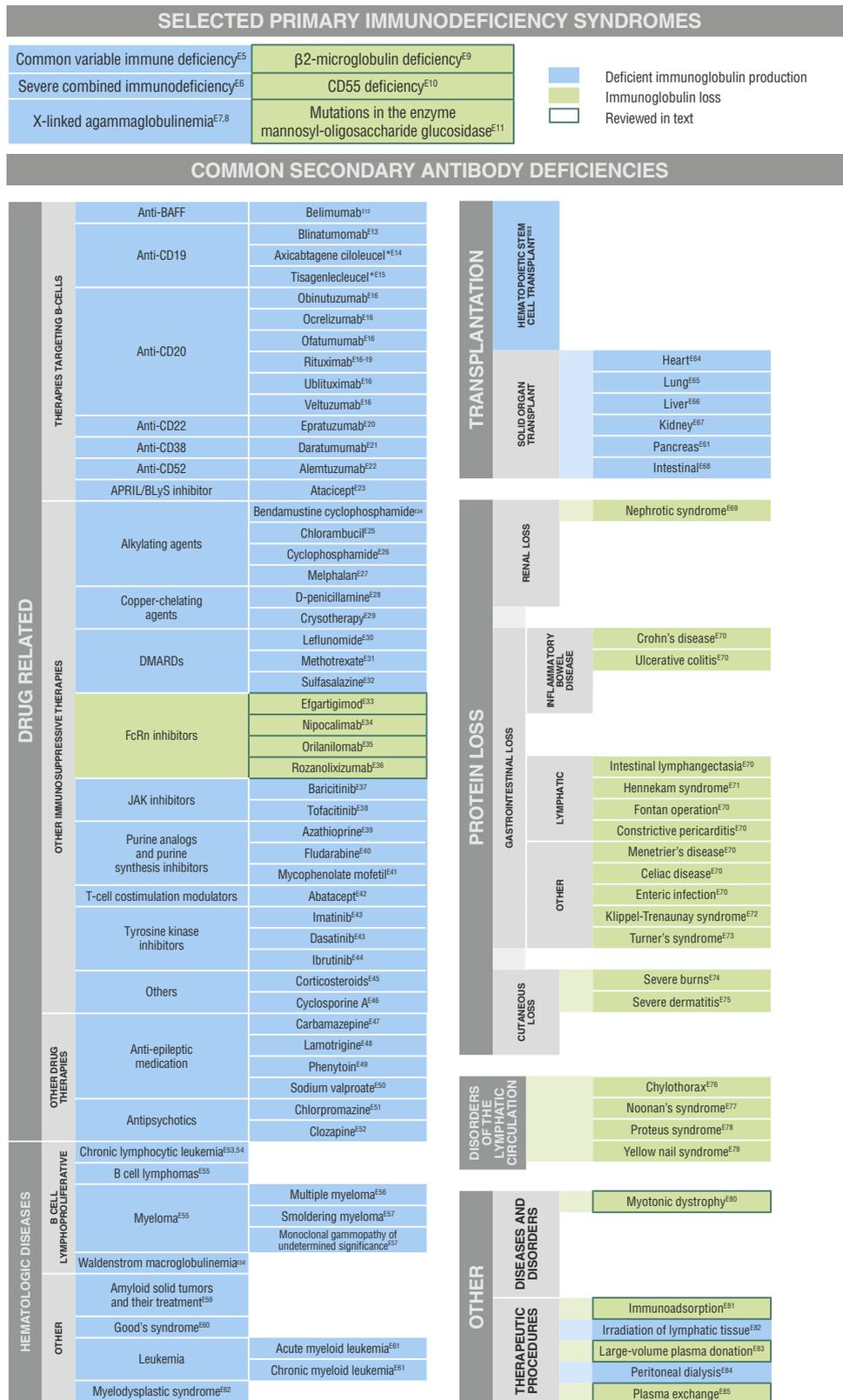


FIG E1. Impact of selected primary and secondary antibody deficiencies on IgG. ^{E5-E85} APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; BLyS, B-lymphocyte stimulator; DMARD, disease-modifying antirheumatic drug; JAK, Janus kinase.

TABLE E1. Summary of methodology for reported phase 2 clinical trials of FcRn inhibitors

Indication	No. of patients randomized	Intervention and comparator	Primary end point	Duration of follow-up	Geographical region of recruited patients	Methodology for infection screening before enrollment	Reported infections*	Reference
Efgartigimod: IgG ₁ Fc fragment modified by 5 point mutations								
MG (NCT02965573)	24	IV efgartigimod 10 mg/kg QW vs placebo	Safety and tolerability	11 wk	Canada, Europe, US	<p>Exclusion criteria</p> <ul style="list-style-type: none"> ● Active infection ● Recent serious infection within the 8 wk before screening ● History of or known infection with HIV, HBV, HCV, or TB <p>At screening patients must have had negative test results for</p> <ul style="list-style-type: none"> ● HBV surface antigen ● HBV core antibody ● HCV antibody ● HIV 1 and 2 antibodies <p>QuantiFERON-TB Gold</p>	<i>Herpes zoster</i> : 1 efgartigimod-treated patient (also on SoC treatment with prednisone and mycophenolate mofetil)	E1
ITP (NCT03102593)	38	IV efgartigimod 5 mg/kg or 10 mg/kg, QW (4 doses) vs placebo	Safety and tolerability	Main study: 21 wk OLE: 1 y	Europe, Ukraine	Not provided	<p>Pneumonia: 1 efgartigimod-treated patient who was deemed unrelated to treatment.</p> <p>No increased risk of infection was apparent</p>	E2
Rozanolixizumab: IgG ₄ mAb with a S241P stabilizing hinge mutation								
MG (NCT03052751)	43	<p>Period 1: 3 doses of SC rozanolixizumab 7 mg/kg QW</p> <p>Period 2: 3 doses of SC rozanolixizumab 4 mg/kg QW or 7 mg/kg QW vs placebo</p>	<p>Clinically meaningful improvements in MG outcomes and reductions in autoantibody titers</p> <p>Safety and tolerability</p>	99 d	Canada, Europe, US	Not provided	Not reported	E3

(Continued)

TABLE E1. (Continued)

Indication	No. of patients randomized	Intervention and comparator	Primary end point	Duration of follow-up	Geographical region of recruited patients	Methodology for infection screening before enrollment	Reported infections*	Reference
ITP (NCT02718716)	66	Single (15 or 20 mg/kg) or multiple (5 × 4 mg/kg, 3 × 7 mg/kg, 2 × 10 mg/kg weekly) doses of SC rozanolixizumab; total dose in each group ranged from 15 to 21 mg/kg No comparator	Safety and tolerability	12 wk	Australia, Europe	Exclusion criteria: ● Clinically relevant active infection ● Serious infection within 6 wk before the first dose of rozanolixizumab	No serious infections were seen	^{E4}

HCV, Hepatitis C virus; Ig, immunoglobulin; OLE, open-label extension; SoC, standard of care; TB, tuberculosis.

*Although neither FcRn inhibitor appears to increase in risk of infection, limitations of these data include small sample sizes and trial duration.