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RAPID REVIEW

TRANSFUSION

Targeting the neonatal Fc receptor (FcRn) to treat autoimmune diseases and maternal-fetal immune cytopenias

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Key Ideas

- FcRn, a non-classical Fc gamma (γ) receptor (FcγR) with near ubiquitous expression, plays key roles in disease pathogenesis and progression though immunoglobulin G (IgG) transport, IgG recycling, and IgG-immune complex clearance.
- FcRn function can be inhibited using IgG-based and non-IgG-based antagonists, by exploiting the pH-dependent binding affinity of FcRn for the IgG Fc region.
- FcRn therapeutics have shown promise in murine models and human clinical trials for autoimmune diseases and maternal-fetal immune cytopenias; they appear safe, well-tolerated, and reduce circulating IgG levels.
- Compared to traditional therapeutics, inhibiting FcRn has fewer adverse side effects and represents a new approach that is less invasive, time-consuming, and costly.

KEYWORDS
AIHA/drug-induced IHA, HDN, immune thrombocytopenia

1 | INTRODUCTION

Current methods to treat humoral auto- and allo-immune diseases include suppressing antibody production with corticosteroids and B-cell targeting drugs, inducing "immunomodulation" by infusing intravenous immunoglobulin, or physically decreasing antibody levels using plasmapheresis or immunoadsorption. Although reasonably effective, their benefits are offset by broad immunosuppression, increased infection risk, cost, time requirements, and/or invasiveness.[1–3] Because the neonatal Fc receptor (FcRn) has recently become a therapeutic target, this review discusses its mechanisms, ongoing studies, and limitations.

1.1 | FcRn and its mechanism of action

FcRn, a non-classical Fc gamma (γ) receptor (FcγR) with near-ubiquitous expression, is detected on multiple cell types (e.g., epithelial cells), in secondary lymphoid organs (e.g., spleen), and in the placenta[4,5] Functionally, FcRn binds the Fc region of immunoglobulin G (IgG); its initial discovery involved the transport of maternal IgG across the placenta (Figure 1), and other roles in shaping immune responses were subsequently identified.[6] For example, FcRn prolongs IgG circulatory half-life via rescue from lysosomal degradation in endothelial cells (Figure 1), induces macrophage phagocytosis of IgG-opsonized antigens, and initiates adaptive immune

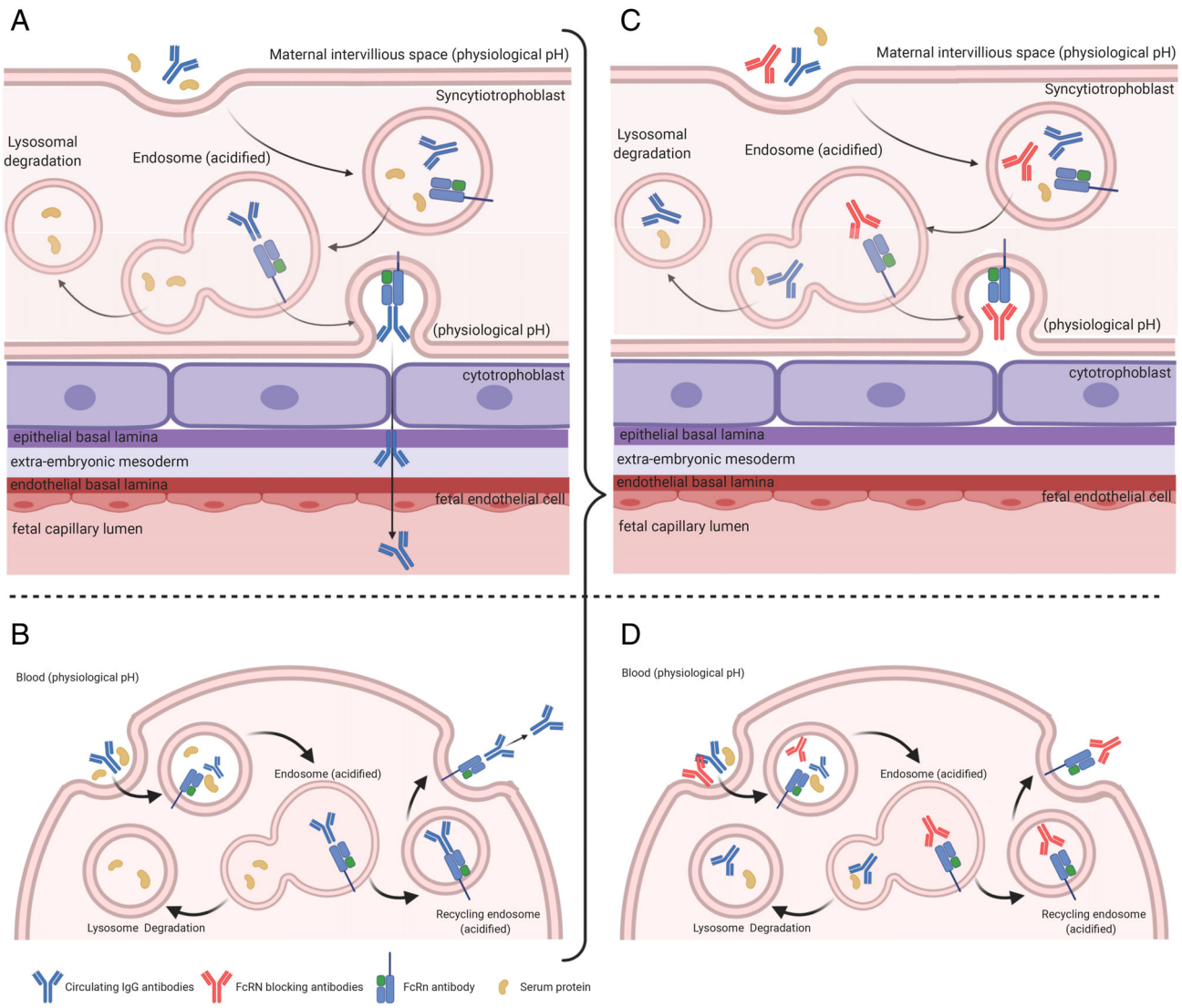

FIGURE 1 Inhibiting FcRn can prevent IgG transfer and recycling. FcRn binds the IgG fc region with high affinity at acidic pH and with low affinity at physiological pH.[6] After IgG internalization, endosomal FcRn binds IgG during acidification, preventing IgG sorting into lysosomes and subsequent degradation.[6] (A) Following IgG internalization at the maternal, apical surface of syncytiotrophoblasts, endosomal acidification, and vesicular transport to the basolateral surface, membrane fusion occurs, and maternal IgG is released into the fetal circulation.[6] (B) Following IgG internalization and endosomal acidification in endothelial cells, IgG is recycled into the circulation after vesicular fusion with the plasma membrane. Inhibiting FcRn function can be achieved with IgG-based and nonIgG-based antagonists, which exploit the pH-dependence of the IgG Fc region binding to FcRn.[17] For example, IgG monoclonal antibody antagonists strongly bind FcRn at acid pH and disrupt IgG-FcRn immune complexes.[15] Of note, it appears these antagonists may have minimal transfer across the placenta or limited recycling capabilities due to their high-affinity FcRn binding at both intracellular and extracellular pH, which prevents release from FcRn.[11] (C) In syncytiotrophoblasts, FcRn antagonists displace bound circulating IgG, and newly liberated IgG is rapidly cleared.[17] (D) A similar process prevents IgG recycling in endothelial cells.[17] Image created with BioRender.com

responses by retrieving and presenting immune complexes in lymphoid structures.[6] Although FcRn does not bind other immunoglobulin isotypes, it does bind albumin, thereby protecting albumin from lysosomal catabolism and prolonging its circulatory half-life.[6]

1.2 | FcRn in disease initiation and as a therapeutic target

FcRn's role in disease pathogenesis results from its affinity for IgG. In maternal-fetal immune cytopenias, FcRn

transports maternal autoantibodies and alloantibodies across the placenta to react with fetal antigens, such as blood group antigens on circulating red blood cells in hemolytic disease of the fetus and newborn.[6,7] In antibody-mediated autoimmunity (e.g., myasthenia gravis [MG]), FcRn exacerbates disease by maintaining pathogenic autoantibodies in circulation.[6,7] FcRn also supports tissue damage by targeting immune complexes for destruction (e.g., platelet-bound autoantibodies in immune thrombocytopenia [ITP]).[6,7] Therefore, blocking FcRn function by diminishing IgG circulatory half-life or placental transport may prevent or ameliorate antibody-mediated disorders. Indeed, one of the mechanisms of action of intravenous immunoglobulin in certain autoimmune diseases (e.g., ITP) relies on the inhibition of FcRn effects.[8]

1.2.1 | Maternal-fetal immune cytopenias

Targeting FcRn successfully prevented placental transport of pathogenic antibodies in murine models. For example, fetal neonatal immune thrombocytopenia (FNIT) was prevented in fetal FcRn-knockout mice; additionally, anti-FcRn monoclonal antibody treatment prevented FNIT in pups of alloimmunized B3-deficient mothers and FNIT-related miscarriage in immunized GPIba-deficient mothers.[9,10] These results were complemented by ex vivo human placental perfusion studies demonstrating that anti-FcRn monoclonal antibody blocked transfer of an immunosuppressive biologic into the fetal circuit.[11]

1.2.2 | Autoimmunity

Inhibiting FcRn successfully reduced IgG antibodies in murine models, indicating a potential therapeutic benefit in autoimmune diseases.[12] For example, anti-FcRn agents reduced circulating IgG and demonstrated efficacy in mouse models of ITP, arthritis, and encephalomyelitis[13–15] Thus, blocking FcRn represents a novel therapeutic approach for both autoimmune cytopenias and other autoantibody-mediated diseases.

1.2.3 | Inhibiting IgG-FcRn interactions

Inhibiting FcRn function can be achieved with IgG-based and non-IgG-based antagonists. Efgartigimod, an anti-FcRn monoclonal IgG1 Fc fragment, strongly binds cell surface FcRn at physiological pH, preventing interactions with endogenous IgG; it also competes more efficiently for FcRn binding in acidic endosomes, thereby directing unbound endogenous IgG toward lysosomal degradation.[7] In contrast, other agents (e.g., MOG-Seldeg) contain IgG Fc-regions fused to pathogenically relevant antigens (e.g., myelin oligodendrocyte glycoprotein [MOG]).[16] Pathogenic antibodies then bind MOG while the Fc fragment binds FcRn, prompting degradation of MOG-specific autoantibodies; this strategy decreases circulating disease-relevant antibody levels while preventing loss of beneficial IgGs.[16] Finally, non-IgG-based antagonists include synthetic peptides (e.g., SYN1436) and small molecules that bind to, or mimic, IgG Fc-regions, competing for FcRn binding and preventing endogenous IgG recycling or transport.[17]

Several ongoing clinical trials evaluating FcRn inhibitors were recently reviewed in detail (see Table 1 for ClinicalTrials.gov identifiers).[7] Rozanolixizumab, a humanized IgG4 anti-FcRn monoclonal antibody, significantly reduced pathogenic autoantibodies and improved clinical outcomes in patients with MG and ITP.[18,19] It is now in Phase 3 trials for MG and ITP and in Phase 2 trials for chronic inflammatory demyelinating polyneuropathy (CIDP). Efgartigimod significantly reduced anti-acetylcholine receptor autoantibodies and achieved associated clinical improvement in patients with MG.[20] Efgartigimod also demonstrated efficacy in refractory ITP.[21] It recently completed a Phase 3 trial for MG and is now in Phase 3 trials for ITP and in Phase 2 trials for CIDP, MG, pemphigus vulgaris or foliaceus, and ITP. M281, a human monoclonal anti-FcRn antibody, is in Phase 2 trials for autoimmune hemolytic anemia, hemolytic disease of the fetus and newborn, and MG. Finally, SYNT001, a humanized IgG4 FcRn-blocking monoclonal antibody, is in Phase 2 trials for patients with warm autoimmune hemolytic anemia and pemphigus vulgaris or foliaceus.

1.2.4 | Adverse effects and unintentional consequences

Although anti-FcRn clinical trials are promising, potential adverse effects exist. For example, FcRn inhibition reduces both pathogenic and nonpathogenic IgGs; although reductions are restricted to the IgG isotype, there may be an infection risk from hypogammaglobulinemia.[6,7] Additionally, anti-FcRn treatment during pregnancy blocks placental transfer of protective IgG maternal antibodies; because IgG is the only isotype transported to the fetus, it is essential for fetal and neonatal humoral immunity.[6,10] Finally, anti-FcRn biologics are potentially immunogenic; although

TABLE 1 Summary of reported clinical trials for selected FcRn inhibitors

	Phase II	Phase III
Rozanolixizumab	• *CIDP*: NCT04051944, NCT03861481	• *ITP*: NCT04596995, NCT04224688, NCT04200456 • *MG*: NCT0465085, NCT04124965, NCT03971422
Efgartigimod	• *CIDP*: NCT04280718, NCT04281472 • *ITP*: NCT04188379 • *MG*: NCT03770403 • *Pemphigus vulgaris or foliaceus*: NCT04598451	• *ITP*: NCT04225156, NCT04687072 • *MG (completed)*: NCT03669588
M281	• *Autoimmune hemolytic anemia*: NCT04119050 • *Hemolytic disease of the fetus and newborn*: NCT03842189, NCT03755128 • *MG*: NCT03772587	
SYNT001	• *Pemphigus vulgaris or foliaceus*: NCT03075904 • *Warm autoimmune hemolytic anemia*: NCT03075878	

immunogenicity was evaluated in initial trials, additional studies are needed, especially for patients receiving multiple dose protocols.[7]

2 | CONCLUSIONS

FcRn functions include IgG transport, IgG recycling, and IgG-immune complex clearance. FcRn-targeted therapeutics demonstrated promise in murine models and human clinical trials for maternal-fetal immune cytopenias and autoimmune diseases; they appear safe and well-tolerated, and are transient, reversible, and specifically reduce circulating IgG levels. Together, FcRn-targeted therapeutics may have fewer adverse effects than standard treatments, presenting an alternative that is less invasive, time-consuming, and costly. Overall, FcRn-targeted therapeutics may be an important addition to the transfusion medicine practitioner's therapeutic armamentarium.

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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