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Review

Next-generation Fc receptor–targeting biologics for autoimmune diseases

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ABSTRACT

In recent years, there has been a surge in the research and development of novel molecules as potential therapeutic alternatives to traditional treatments (such as intravenous immunoglobulins) for autoimmune disorders. The aim of this review is to describe different drug development strategies and evaluate how various molecules have performed in clinical trials to date. Broadly, three main approaches have been pursued. Recombinant fragment crystallisable (rFc) multimers primarily target Fcγ receptors (FcγRs) but may also affect the complement system. These include PF-06755347 (GL-2045), CSL730 (M230), CSL777 and Pan Fc Receptor Interacting Molecule (PRIM). Neonatal Fc receptor (FcRn)-targeting therapeutics block the FcRn receptor and are represented by candidate drugs such as the Fc fragment efgartigimod and the monoclonal antibodies rozanolixizumab (UCB7665), M281 and SYNT001. Finally, Fc and FcγR-targeting therapeutics, comprise molecules that target the Fc of IgG, such as the recombinant soluble FcγIIb receptor valziflocept (SM101/SHP652) and various monoclonal antibodies directed against the receptors. The developmental status of these three classes of molecules ranges from preclinical to ongoing phase 3 clinical studies. Efgartigimod and rozanolixizumab are the most advanced and have demonstrated encouraging results from phase 2 trials in immune thrombocytopenia and myasthenia gravis. Although initial results are promising, further long-term data and a better understanding of the unique mechanisms of action of the different molecules are needed. The efficacy, safety, convenience of administration, duration of effects, and cost will all contribute to determining which of the molecules will be successful in the clinic.

1. Introduction

Plasma-derived human immunoglobulin (Ig)G products such as intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) have a long history of use as replacement therapies in primary and secondary immunodeficiencies, and as immunomodulatory therapies in autoimmune disorders such as immune thrombocytopenia (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP) [1].

Although IVIG and SCIG products are generally considered safe and effective, they have certain inherent limitations including dependence on the supply of human plasma and the large doses of product of up to 2 g/kg body weight needed for therapy [2,3]. These challenges may potentially be overcome by novel alternative treatments, which can be categorised based on either structure or function. For this review, we have classed the molecules into the following groups:

- Recombinant fragment crystallisable (rFc) multimers
- Neonatal Fc receptor (FcRn)-targeting therapeutics
- Fc/Fcγ receptor (FcγR)-targeting therapeutics

The rFc multimers are a novel class of therapeutics designed to have multiple, organised, and structured IgG-Fc moieties (e.g. trivalent or hexavalent molecules) to produce a range of different immunomodulatory effects. FcRn-targeting therapeutics are designed to

Abbreviations: ABD, albumin binding domain; ADCC, antibody-dependent cell-mediated cytotoxicity; APC, antigen-presenting cells; CAIA, collagen antibody-induced arthritis; CDC, complement-dependent cytotoxicity; CIA, collagen-induced arthritis; CIDP, chronic inflammatory demyelinating polyneuropathy; CP, classical complement pathway; DoE, Design of Experiments; EAE, experimental autoimmune encephalomyelitis; EBA, epidermolysis bullosa acquisita; Fc, fragment crystallisable; FcRn, neonatal Fc receptor; FcγR, Fcγ receptor; Ig, immunoglobulin; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MAC, membrane attack complex; MAD, multiple ascending dose; MG, myasthenia gravis; NMO, neuromyelitis optica; PRIM, Pan Fc Receptor Interacting Molecule; rFc, recombinant Fc; SAD, single ascending dose; SCIG, subcutaneous immunoglobulin; SLE, systemic lupus erythematosus; TEAE, treatment-emergent adverse events; WAIHA, warm autoimmune haemolytic anaemia.

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Table 1
Overview of compounds, their clinical development stage and target indications.

Compound	Manufacturer	Clinical Development Stage	Target Indication(s)
Recombinant Fc Multimers			
PF-06755347 (GL-2045)	Pfizer/Gliknik	Phase 1 (ongoing)	CIPD (assumed*)
CSL730 (M230)	CSL/Momenta	Phase 1 (ongoing)	Unknown
PRIM	AB Bioscience/Shire (now Takeda)	Preclinical	Unknown
HexaGard™	Liverpool School of Tropical Medicine	Unknown	Unknown
Hexavalent Fc multimer	UCB	Preclinical	Unknown
CSL777	CSL	Preclinical	Unknown
FcRn-targeting therapeutics			
Efgartigimod (ARGX-113)	argenx	Phase 3 (ongoing)	gMG, ITP, CIDP, PV
Rozanolixizumab (UCB7665)	UCB	Phase 3 (planned)	gMG, ITP, CIDP
SYNT001	Syntimmune/Alexion	Phase 1b/2a (ongoing)	WAIHA, PV, PF
M281	Momenta	Phase 2 (ongoing)	gMG, HDFN
RVT-1401 (HL161)	Immunovant/Roivant/HanAll Biopharma	Phase 2 (ongoing)	MG
ABY-039	Affibody	Phase 1 (ongoing)	Unknown
FcγR-targeting therapeutics			
Valziflocept (SM101/SHP652)	Baxalta/Shire/Takeda	Phase 2a (completed)	ITP, SLE
VIB9600	VielaBio	Phase 1 (ongoing)	Unknown
Monovalent 3G8 variant	Canadian Blood Services	Preclinical	Unknown
XMAB-5871	Xencor	Phase 2 (ongoing)	RA, IgG4-RD
MGD010	MacroGenics	Phase 1 (completed)	Unknown

CIDP, chronic inflammatory demyelinating polyneuropathy; gMG, generalised MG; HDFN, haemolytic disease of the fetus and newborn; IgG4-RD, IgG4-related disease; ITP, immune thrombocytopenia; MG, myasthenia gravis; PF, pemphigus foliacus; PV, pemphigus vulgaris; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; WAIHA, warm autoimmune haemolytic anaemia. *Based on orphan drug designation for CIDP granted to GL-2045 by the Food and Drug Administration [76].

specifically and selectively target FcRn using a variety of possible approaches (e.g. Fc fragments or monoclonal anti-FcRn antibodies), which increase the catabolism of autoantibodies. Finally, FcγR-targeting therapeutics include all non-rFc therapeutics designed to block the interactions of IgG with FcγRs (e.g. recombinant soluble FcγRs or antibody approaches).

The aim of this review is to describe the different drug development strategies and approaches attempted and evaluate how the molecules have performed in clinical trials to date. An overview of all molecules discussed in this review, including developmental status and target indications, is summarised in Table 1.

2. Recombinant Fc multimers

The primary mechanism of action of the rFc multimers reviewed in this section (see overview in Fig. 1A) is to inhibit immune-complex mediated FcγR activation; however, some of the molecules were also shown to target the complement system. The functional consequences of the interaction of rFc multimers with FcRn have not been explored in-depth. These features may lend a functional advantage to rFc multimers compared to other strategies (e.g. those described in Sections 3 and 4). For example, the combined effects of the multiple mechanisms of action of a single drug, such as inhibition of FcγR activation, inhibition of full complement activation, and FcRn blockade, may result in more robust efficacy. Conversely, molecules with multiple mechanisms of action may also have greater potential for induction of unwanted side effects.

2.1. *Pf-06755347 (GL-2045)*

PF-06755347 (GL-2045) [4], initially called “Stradomer”, was one of the first rFc multimers to be developed. GL-2045 is currently being developed by Pfizer under a licensing agreement with Gliknik. Using the human IgG2 hinge as a multimerisation element, GL-2045 consists of a heterogeneous mixture of IgG1-Fc oligomeric structures (Fig. 1A). Preclinical data demonstrated that GL-2045 was efficacious in treating collagen-induced arthritis (CIA) [5], experimental autoimmune neuritis [6] and experimental autoimmune myasthenia gravis (MG) [7]. It also prevented ITP in a mouse model [5]. No significant increase of proinflammatory cytokines was observed when administered at up to 1000 mg/kg intravenously to cynomolgus monkeys [8]. However, a transient increase of the complement activation fragments C4a, C3a, sC5b-9 and fBb was observed [8].

Recently published mechanistic studies showed that in addition to blocking FcγRs, GL-2045 effectively inhibits complement-dependent cytotoxicity (CDC) by interfering with activation of the classical complement pathway (CP) on the target. This is achieved by binding to complement component C1q resulting in fluid-phase activation with high levels of C4a, low levels of C3a, no C5a, reductions in C4b and membrane attack complex (MAC) on the target, and generation of inactive C3b by potentiation of factor H activity at high concentrations of GL-2045 (i.e. > 5 mg/mL) [9]. Whether the interaction with factor H is of physiological relevance needs to be further investigated. In 2015, GL-2045 received orphan drug status in the US for the treatment of CIDP. The safety, tolerability and pharmacokinetics of this drug candidate are currently being evaluated in a phase 1 clinical trial (NCT03275740) [10]. Recently, two “evolved” analogues of GL-2045 with similar properties have been described. G207/G211 (presumably equivalent to GL-0719) was purportedly designed for increased binding to C1q and reduced interaction with FcγRs, making it a specific complement inhibitor (particularly of the CP) (Fig. 1A). G207/G211 blocked CDC in vitro and was protective in complement-dependent rat models of glomerulonephritis (i.e. anti-Thy1 glomerulonephritis and passive Heyman's nephropathy) and antibody-induced acute red blood cell haemolysis (Fig. 1B) [11,12]. However, while reduced binding to FcγRs was clearly demonstrated [10], no actual increase in C1q binding compared to GL-2045 was reported. Further, no functional data has been published demonstrating superior complement inhibitory properties of G207/G211 compared to GL-2045. Furthermore, G207/G211 binding to FcγR induced lower amounts of tumour necrosis factor α in human peripheral blood mononuclear cells in vitro than GL-2045. A second GL-2045 analogue, a more specific FcγR-inhibitor termed GL-0806 (Fig. 1A), has been suggested to be efficacious in an experimental autoimmune encephalomyelitis (EAE) mouse model by inhibition of maturation and migration of antigen-presenting cells (APC); however, no peer-review publications with further details on this molecule are available to date [12].

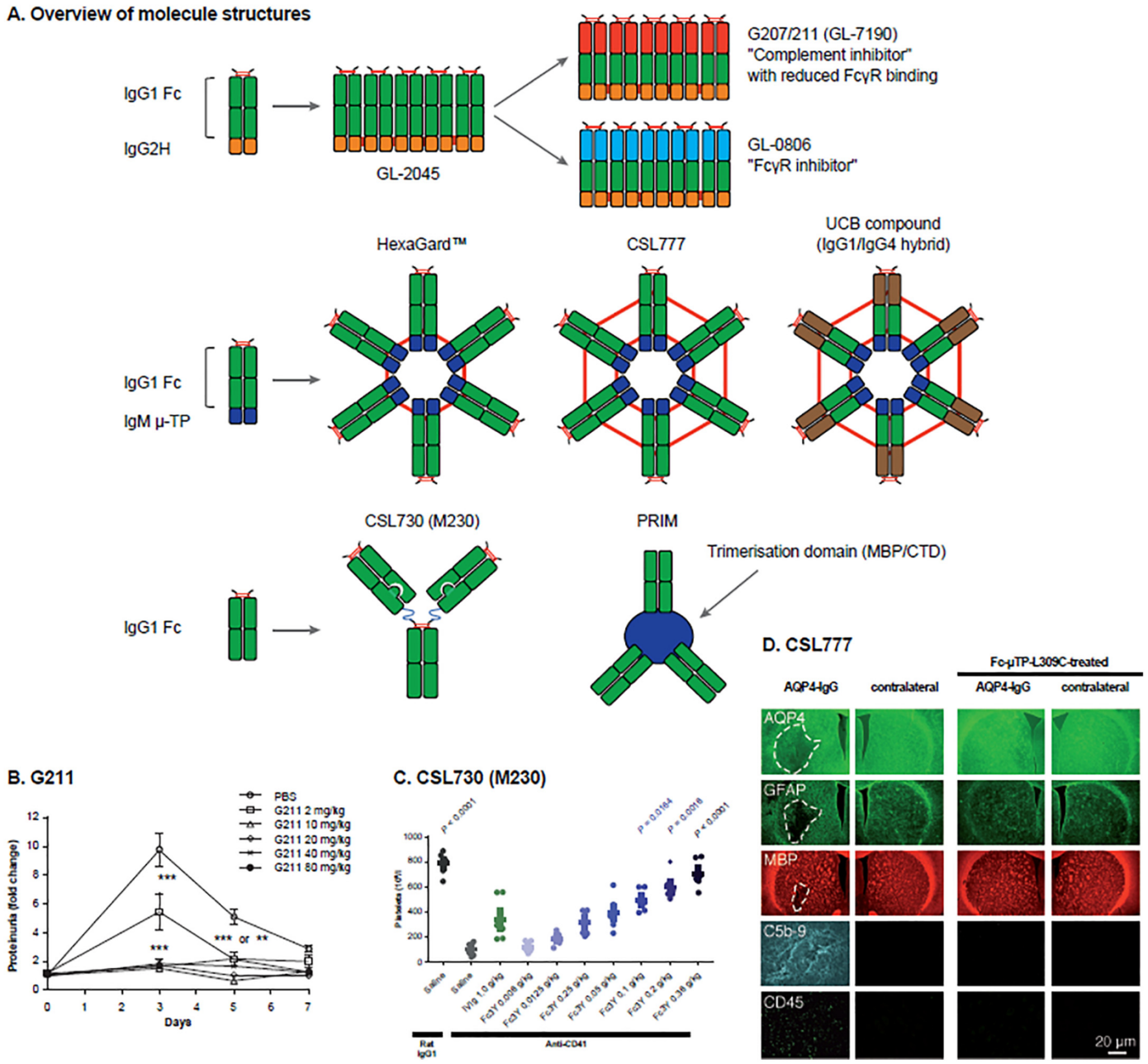

Fig. 1. Overview of the structure of recombinant Fc multimers and key preclinical data. A) Overview of recombinant Fc multimers discussed in Section 2. B) Time course of the daily urinary protein excretion in anti-Thy-1 nephritis rats pre-treated with different doses of G211. The start time of anti-Thy-1 antibody injection was designated as day 0. Data are summarised from three separate experiments and are shown as the mean ± SEM of the fold change of urinary protein levels, compared with baseline (pre-anti-Thy-1 Ab injection), at the time points indicated. N = 8 per group [11]. C) Platelet numbers after therapeutic treatment with IVIG and Fc3Y (CSL730) in an ITP model. Mean ± SEM are shown for biological replicates (N = 6). Statistical differences between anti-CD41/saline and the indicated group were calculated by one-way analysis of variance with Dunn's multiple comparison test [13]. D) Brain immunofluorescence of indicated markers of NMO pathology at day 5 showing AQP4-IgG-injected and control contralateral hemispheres from non-treated and FcμTP-L309C (CSL777)–treated rats. Representative of experiments on 3 rats per group [22]. Panel B and D copyright Elsevier Ltd.; panel C copyright The American Association for the Advancement of Science. Reprinted with permission. AQP4, aquaporin-4; CTD, collagen trimerisation domain; Fc, fragment crystallisable; GFAP, glial fibrillary acidic protein; Iba-1, ionised calcium-binding adaptor molecule–1; IgG, immunoglobulin G; IgM, immunoglobulin M; MBP, myelin basic protein; PBS, phosphate-buffered saline; SEM, standard error of the mean; TP, tail piece.

2.2. CSL730 (M230)

CSL730, licensed from Momenta Pharmaceuticals, is being developed by CSL in collaboration with Momenta (Fig. 1A). The molecule is composed of three human IgG1 Fc fragments linked in a Y-configuration, connected by a flexible linker between the hinge of the lower Fc fragment and the C-termini of the upper Fc fragment. CSL730 has been shown to inhibit immune complex-mediated activation of immune cells, suppress antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis, yet it does not induce CDC via the classical complement pathway [13]. In preclinical studies, CSL730 demonstrated efficaciousness in multiple animal models of autoimmune disease induced by exogenous antibodies, including ITP (Fig. 1C), collagen antibody-induced arthritis (CAIA), and epidermolysis bullosa acquisita (EBA) [13]. The safety, pharmacokinetics and pharmacodynamics of CSL730 are currently being assessed in a phase 1 clinical study (NCT03375606)

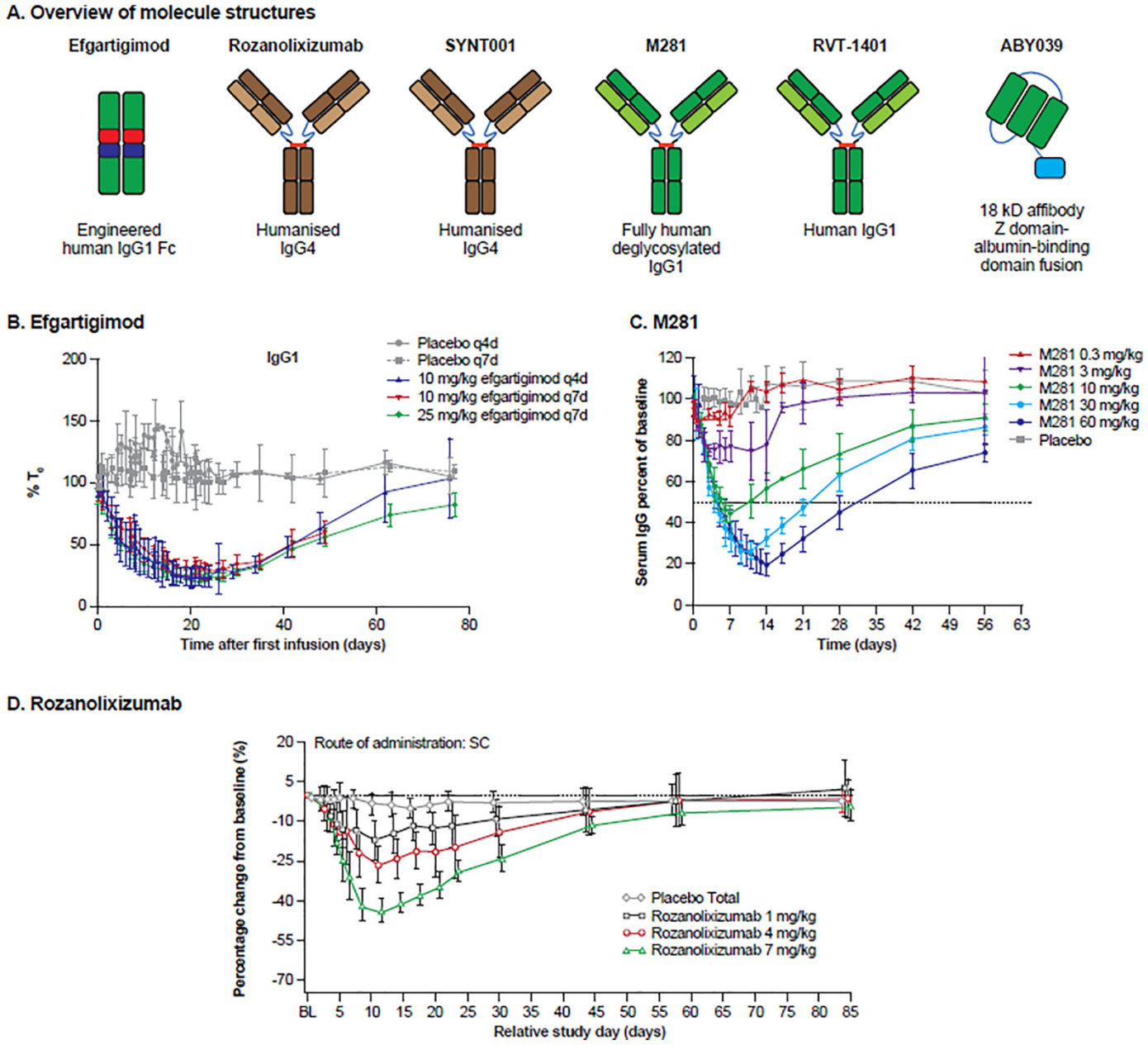

Fig. 2. Overview of the structure of FcRn-targeting therapeutics and key clinical data. A) Overview of FcRn-targeting therapeutics discussed in Section 3. B) Serum levels of IgG1 over time in the MAD part of first-in-human study. Healthy subjects (N = 6/group) were dosed with 0.2, 2, 10, 25, or 50 mg/kg efgartigimod or placebo. Efgartigimod or placebo (randomised at a 4:2 ratio) was administered intravenously in a 2-h infusion. Percentage change versus baseline in IgG1 serum concentration (%T_0) is shown. Values are shown as mean ± SD [26]. C) Serum IgG percentage relative to baseline following treatment with M281. M281-treated cohorts are represented by N = 3 (0.3 or 3 mg/kg), N = 6 (30 mg/kg), and N = 5 (60 mg/kg). Placebo controls from each single-dose cohort were combined (N = 10). Values are shown as mean ± SD [35]. D) The effect of single-dose rozanolixizumab on IgG concentration in healthy subjects. Mean percentage change from baseline in serum IgG concentrations over time, after a single dose of rozanolixizumab by subcutaneous administration. Baseline is defined as the pre-dose day 1 concentration. Mean percentage change and SD are shown; N = 13 for placebo and N = 6 for rozanolixizumab (full analysis set) [44]. Panel A adapted from A.M. Manning, Momenta Pharmaceuticals, corporate presentation; Panel B copyright American Society for Clinical Investigation; Panel C under an Attribution-Non-Commercial 4.0 International license; Panel D copyright The American Association for the Advancement of Science. Reprinted with permission. Fc, fragment crystallisable; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; kD, kilodalton; SAD, single ascending dose; SC, subcutaneous; SD, standard deviation.

[14].

To our knowledge, CSL730 and GL-2045 are the only two rFc multimers to progress into human trials to date. The following molecules have also been identified, although they have not progressed into clinical development at this time or their status has not been published.

2.3. PRIM

In 2018 it was announced that AB Bioscience and Shire had entered into an agreement for the development of a molecule known as Pan Fc Receptor Interacting Molecule (PRIM) (Fig. 1A) [15]. No peer-reviewed publications describing this molecule are available, but in a patent application it was disclosed that PRIM is composed of three human IgG1 domains that can bind to all FcγRs and FcRn [16]. Specifically, PRIM (P8003Z/ P80020Z) is a fusion protein comprising a single-chain IgG constant light chain, a CH1 region, followed by two Fc domains (Hinge-CH2-CH3) connected by a flexible linker that allows pairing of the first and the second Fc domain. A mannose-binding protein or a

collagen trimerisation domain leads to the formation of a trivalent Fc multimer (Fig. 1A) [16]. Preclinical testing demonstrated therapeutic effects of PRIM in the CIA mouse model [16].

2.4. HexaGard™

HexaGard™ was the first hexameric rFc multimer (Fig. 1A) described in the literature. It is an engineered molecule, which uses the IgM μ-tailpiece as a multimerisation element, as previously described for hexamerisation of full-length IgG [17,18]. These proteins have been shown to bind with high avidity to all low-affinity FcγRs, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and C1q, and to activate complement via the classical pathway (when immobilised/coated on a plate) [19,20].

2.5. CSL777 (FcμTP-L309C)

Spirig et al. [21] recently described a similar hexameric rFc molecule, termed FcμTP-L309C (CSL777) (Fig. 1A), which also uses the μ-tailpiece from human IgM for multimerisation, but with a slightly different sequence compared to HexaGard™ [21]. In-depth functional analyses revealed that CSL777 binds to FcγRs and to FcRn, leading to the inhibition of FcγR-mediated cell activation by IgG immune complexes and a potential increase in autoantibody degradation [21]. Moreover, CSL777 blocks the full activation of the classical complement pathway by blocking C2 cleavage, thus preventing the activation of downstream complement proteins (C5a, C3b, MAC or sC5b–9) [21]. In vitro analysis showed partial activation of the complement pathway including cleavage of C4 but no downstream activation [21,22]. In vitro, CSL777 has been shown to inhibit ADCC and CDC, and in vivo it has demonstrated good efficaciousness in acute and chronic murine models of arthritis (CAIA and CIA), ITP and exogenous antibody-induced neuromyelitis optica (NMO) (Fig. 1D) [22].

2.6. Hexavalent molecules by UCB

Rowley et al. further evolved the basic hexameric concept by developing a hybrid IgG1/IgG4 rFc molecule (Fig. 1A) [23,24]. The goal in generating this protein was to create a molecule able to retain FcγR-blocking activity while reducing functions such as induction of cytokine production, C′ activation, and platelet activation that might lead to off-target effects and adverse events. Indeed, it has been shown that the hexavalent Fc multimer binds FcγR and blocks FcγR function both in vitro and in vivo [23]. Moreover, the molecule also binds to C1q and partially activates the complement pathway (i.e. C4d and C3a are generated), but sC5b–9 are only weakly elevated [24]. A mutagenesis strategy powered by Design of Experiments (DoE) statistical design, was employed to explore the different combinations of IgG1 versus IgG4 CH2 domain variants. This identified the key amino acids involved in IgG1-induced cytokine release, platelet activation and C1q binding, and receptor interactions [24]. Preclinical testing demonstrated that the hexavalent Fc multimer was efficacious at blocking FcγR in murine models of ITP [24].

3. FcRn-targeting therapeutics

The mechanistic concept of FcRn-targeting therapeutics is to accelerate IgG catabolism by blocking the FcRn-mediated intracellular IgG recycling pathway, thereby reducing overall plasma IgG levels, including the levels of pathogenic autoantibodies. Several structurally distinct therapeutics that target FcRn are currently in clinical development (Fig. 2A).

3.1. Efgartigimod (ARGX-113) and ARGX-117

Efgartigimod (ARGX-113) from argenx is the furthest advanced molecule of its class in terms of clinical development. It is a human IgG1-derived Fc fragment developed using argenx's proprietary mutation technology to induce mutations at five separate residues, resulting in increased Fc/FcRn binding at neutral and acidic pH [25,26]. In preclinical testing, it showed efficaciousness in murine K/B × N serum-transfer arthritis [27] and EAE models [28]. A subsequent phase 1 trial demonstrated its ability to reduce serum IgG levels by an average of 75% following repeated dosing, an effect that was surprisingly sustained for approximately 8 weeks before IgG levels returned to baseline (Fig. 2B) [25,26]. The dosing schedule in the human multiple ascending dose (MAD) study was 10 or 25 mg/kg every 4 or 7 days; the drug was well tolerated in healthy subjects.

Efgartigimod is currently being investigated in MG, ITP and pemphigus vulgaris. In MG, a phase 2 trial showed that efgartigimod conveyed a clinically meaningful and statistically significant improvement lasting at least 6 consecutive study weeks in 75% of patients, compared with 25% of patients treated with placebo [29]. A subsequent phase 3 trial is currently recruiting (NCT03669588) [30]. In ITP, a phase 2 trial demonstrated clinically meaningful improvements in platelet counts that coincided with reductions in overall serum IgG levels; the overall response rate was 46–58% [30,31]. At the time of this writing, a phase 2 trial in patients with pemphigus vulgaris (NCT03334058) is ongoing and no results have been posted [32]. In addition to the above studies, argenx plans to initiate a phase 2 study in CIDP in the second half of 2019.

3.2. Monoclonal antibodies against FcRn

Several companies are currently pursuing monoclonal antibody approaches to target the FcRn (Fig. 2A); the molecules are at various stages of clinical development up to the completion of phase 2.

3.2.1. M281

M281 is a fully human deglycosylated IgG1 anti-FcRn monoclonal antibody (Fig. 2A) currently under development by Momenta. M281 has been demonstrated to be efficacious in mouse ITP and antibody-induced arthritis models [33,34]. In a phase 1 single ascending dose (SAD) study, the highest dose tested (60 mg/kg) induced a reduction in serum IgG levels of 80% compared with baseline (Fig. 2C) [35]. In a MAD study, in which M281 was administered every 7 days for a total of 4 doses, full receptor occupancy was achieved for 7–9 days (15 mg/kg dose) or for 9–10 days (30 mg/kg dose); here, the doses of 15 and 30 mg/kg reduced circulating IgG levels by an average of 85%. As with the other FcRn blockers, a mild-to-moderate treatment-emergent adverse event (TEAE) profile was reported [36]. Momenta recently started a phase 2 trial in generalised MG as well as another phase 2 trial in haemolytic disease of the fetus and newborn [37,38].

3.2.2. SYNT001

SYNT001 is another anti-FcRn monoclonal antibody under development by Syntimmune (recently acquired by Alexion). SYNT001 is a humanised, IgG4 monoclonal antibody with a stabilising hinge mutation designed to block the interaction between FcRn and the Fc portion of IgG molecules, at both acidic and neutral pH (Fig. 2A) [39].

Data from a phase 1a trial demonstrated rapid, durable and clinically significant reductions in all IgG subclasses in healthy volunteers [39,40]. A subsequent phase 1b study in patients with warm autoimmune haemolytic anaemia (WAIHA) (NCT03075878) [41] and a phase 1b/2a study in patients with pemphigus (vulgaris or foliaceus) (NCT03075904) [42] are currently ongoing. Preliminary results from the pemphigus study suggest a good safety profile and the ability of SYNT001 to reduce clinical disease severity scores as well as IgG levels [43].

3.2.3. Rozanolixizumab (UCB7665)

Rozanolixizumab (UCB7665) from UCB is a humanised, high-

affinity, human IgG4 anti-FcRn monoclonal antibody (Fig. 2A) [44]. A detailed recent report described how the molecule was selected and engineered and summarised its biochemical and functional characteristics [45].

In a phase 1 study [44], rozanolixizumab at doses of 1–7 mg/kg effectively reduced plasma IgG levels when given intravenously (14.5–47.6% reduction) or subcutaneously (16.8–43.4% reduction) (Fig. 2D). The absolute reductions achieved with the 7 mg/kg dose were − 4.3 g/L (intravenously) or − 4.2 g/L (subcutaneously). Mild-to-moderate TEAEs (such as headache or back pain) were more frequent after intravenous than subcutaneous dosing, leading to discontinuation of development of the intravenous route of administration. Rozanolixizumab is the only drug in this class for which subcutaneous data have been reported so far. Data from phase 2 trials in MG [46] and ITP [47] patients suggest that rozanolixizumab is well tolerated and efficacious in patients with these autoimmune conditions. In the MG trial, rozanolixizumab resulted in a 68% decrease in serum IgG and IgG autoantibodies together with a clinically meaningful improvement in multiple disease-related endpoints; a phase 3 trial is planned to start in 2019 [48]. Interim data from the ITP trial showed rozanolixizumab to be associated with a 24–69% decrease in serum IgG levels and a clinically relevant improvement in platelet count in 31–54% of subjects [49]. In addition to further clinical development for MG and ITP target indications, UCB recently initiated a phase 2 study in CIDP patients [50].

3.2.4. RVT-1401 (HL161)

RVT-1401 is a human recombinant anti-FcRn monoclonal antibody. It was originally conceived by HanAll Biopharma (as HL161) but is currently being developed by Immunovant/Roivant.

Publicly available preclinical data on RVT-1401 is limited, although data from the HanAll website describe a reduction in serum IgG levels in cynomolgus monkeys dosed with the molecule [51]. Currently, RVT-1401 is being investigated in a phase 2 study in patients with MG [52].

3.2.5. ABY-039

Affibodies are peptide mimetics derived from phage display libraries in which 13 amino acids of a bacterial receptor protein are randomised [53]. One such peptide that specifically binds to FcRn in a pH-dependent fashion [54] was expressed either alone (termed Z_{FcRn}) or fused to an albumin binding domain (ABD, termed Z_{FcRn}-ABD) for half-life extension [55]. This yielded an 18 kD protein able to inhibit IgG-FcRn interaction and to lower IgG levels in vivo [55]. The Swedish company Affibody is currently pursuing a phase 1 proof-of-principle study (NCT03502954) for treatment of B-cell driven autoimmune diseases with a molecule termed ABY-039 which is presumed to be equivalent to Z_{FcRn}-ABD [56,57].

4. Fc/FcγR-targeting therapeutics

The FcγR-targeting therapeutics are a diverse group of molecules that target Fcs or FcγRs in various ways; broadly, these can be divided into recombinant soluble FcγRs and monoclonal antibody approaches [58]. Other approaches include targeting the Fc-glycosylation of IVIG or Fc fragments [59,60]. An example of the latter is M254, a plasma-derived IgG with enzymatically sialylated Fc-glycans, which is currently being investigated in a phase 1/2 study [61].

4.1. Recombinant soluble FcγRs

The rationale behind this approach was based on the hypothesis that soluble FcγRs could bind to and neutralise pathogenic IgG, thereby forming a “decoy” or “scavenger” receptor capable of reducing the severity and progression of autoimmune diseases; a hypothesis that was confirmed in animal models [62,63]. Valziflocept (SHP652, also known as SM101 or BAX1810) is an example of this approach that has proceeded to clinical trials. Valziflocept is a recombinant, soluble human FcγRIIb developed by Suppremol (and later acquired by Baxalta/Shire/Takeda). Phase 2 study data from separate trials in patients with ITP and systemic lupus erythematosus (SLE) published in 2012 and 2014, respectively, were encouraging [64,65]; however, there do not appear to be any ongoing phase 3 activities.

4.2. Monoclonal antibodies

Historically, the development of anti-FcγR monoclonal antibodies such as 3G8 has been hampered by poor tolerability. For instance, the FcγRIII antibody GMA161 was associated with severe infusion reactions in preclinical testing [66]. Although the reasons have not been disclosed, development of VielaBio's VIB9600, an FcγRIIa monoclonal antibody that advanced into a phase 1 trial (NCT03621605) [67], was recently stopped. The Canadian Blood Services described the development of a monovalent 3G8 variant in single-chain variable fragment format, recombinantly fused to human serum albumin. In preclinical testing, it demonstrated efficaciousness in an ITP model without inducing noticeable adverse events [58].

Bi-specific antibodies represent another approach as highlighted by Xencor's XMAB-5871, a bi-specific anti-FcγRIIb/anti-CD19, and MacroGenics' MGD010, a bi-specific anti-FcγRIIb/anti-CD79b. XMAB-5871 and MGD010 together represent a conceptually separate approach unique to bi-specific antibodies, which attempts to inhibit B-cell function [68,69] through inhibitory “negative feedback” (immunoreceptor tyrosine-based inhibitory motif–associated) signalling via FcγRIIb. Data from phase 2 trials of XMAB-5871 suggested efficaciousness in rheumatoid arthritis and IgG4-related disease [70,71]; however, a phase 2 trial in SLE did not reach statistical significance as assessed by its primary endpoint [72]. For MGD010, phase 1 data showed good tolerability and demonstrated a downregulation of B-cell induced signalling and B-cell expression [69].

5. Indications and clinical development

An overview of the molecules reviewed in this article, including their clinical trial status and target indications is shown in Table 1. As shown by this table and the discussion above, multiple approaches are currently being used to target a wide range of immune-complex mediated autoimmune diseases, including ITP, SLE, MG and CIDP. One could conclude that all approaches have potential merit, with molecules in each class having successfully completed phase 1 studies, while some molecules have already reported encouraging results from phase 2 studies. It will therefore, be of interest to see how these various molecules and approaches will perform in future phase 3 trials. The FcRn blocker efgartigimod is currently the furthest advanced in clinical trials, with some of the anti-FcRn monoclonals following not far behind.

With significant mechanistic differences between approaches, it is important to carefully consider disease pathophysiology when selecting target indications and designing phase 2 and 3 studies. Based on our current understanding, rFc multimers may be preferable for use as therapeutics in diseases mediated by complement activation and IgG-mediated phagocytosis, ADCC and inflammation. Meanwhile, FcRn-targeting approaches may be the most effective with regards to decreasing levels of pathogenic IgG, i.e. in diseases where plasma levels of autoantibodies correlate with disease activity or severity. However, data to confirm such direct relationships is limited. ITP and MG have become “typical” indications for proof-of-concept studies with FcRn blockers, presumably due to their well-described pathophysiology, with critical involvement of autoantibodies (or exogenous antibodies in animal models) against platelets and neuromuscular junction proteins, respectively, in the initiation and progression of these diseases; the relatively quick readout measures (within days or a few weeks) in these conditions may also play a role. FcRn-targeting molecules may also have indirect protective effects on complement activation,

phagocytosis, ADCC and inflammation. Approaches that very specifically target one receptor subtype are likely to focus on diseases where this subtype is known to play a substantial role in pathophysiology as they may not produce sufficiently broad immunomodulatory effects to target multifactorial autoimmune diseases. On the other hand, such molecules, or other molecules with only one particular inhibitory function (e.g. inhibiting only FcRn or complement) may show favourable safety profiles compared with molecules with multiple functions that produce broader immunomodulatory effects. Specificity versus breadth of the mechanism(s) of action of various molecules may also be a factor to consider when targeting acute vs chronic diseases. In this context, the long-term safety of the various classes of molecules will be of particular relevance. For example, while initial safety profiles of FcRn-targeting molecules have been encouraging, no long-term data are available yet. Long-term reduction of total plasma IgG levels by > 80% with chronic FcRn blockade may potentially render patients hypogammaglobulinaemic, a condition known to be associated with increased infection risk and classically treated with IVIG or SCIG [73].

6. Conclusions

In recent years several research groups have initiated programmes to develop molecules targeting Fc receptors, including FcRn, for autoimmune indications. The development stage of individual molecules varies widely, with some in the preclinical phase while others have already shown promising results in phase 2 trials and have planned or even ongoing phase 3 trials.

These molecules have the potential to provide therapeutic advances as well as to help address the dependence on the supply of plasma for current IgG products. From the current perspective, the novel molecules may be associated with significant benefits, as well as potential risks. These include issues such as potential immunogenicity or the development of bioactive anti-drug antibodies that may result in unknown adverse events. Moreover, the consequences of long-term treatment with potent FcRn-targeting molecules are unknown but could potentially engage homeostatic mechanisms, decreasing drug efficacy. Conversely, Ig products have proven their safety throughout decades of clinical practice [74], although some patients may have tolerability issues. If safety can be demonstrated, these new molecules may have some specific advantages compared to current plasma-derived IgG products. For instance, the doses and consequent infusion volumes of Fc multimers or monoclonal antibodies are much lower than those required with IgG products, and thus, may allow for more rapid and convenient subcutaneous self-administration. Nevertheless, while the doses of efgartigimod (10 or 25 mg/kg) and M281 (15 or 30 mg/kg) were clearly lower than standard IVIG doses (1–2 g/kg), they are still high for recombinant biologics.

Overall, results with many of the molecules and approaches discussed in this review are promising. In addition, it is worth noting that there are also other possible approaches not detailed here, such as specific inhibitors of the complement system [75] or intracellular kinase inhibitors, may also be effective against phagocytosis and inflammation. The availability of a growing spectrum of novel molecules is an interesting and positive development. The fact that the molecules in question have multiple, distinct, and therefore potentially additive or synergistic mechanisms might also enable broader application of combination(s) of biologics. This practice is already very common in oncology but less established in the treatment of autoimmune diseases. It is conceivable that in some conditions, a combination of therapies will be required for successful maintenance treatment or to treat acute disease flare-ups.

The relationship between factors such efficacy, safety, convenience of administration, duration of effects, and cost will ultimately determine which molecules will be successful. A better understanding of the mechanisms of action through additional pre-clinical and clinical data will provide better knowledge of how to use these novel molecules for the treatment of complex autoimmune diseases.

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Declaration of Competing Interest

AWZ, RSP and FK are employees of CSL Behring AG; ABM and TR are employees of CSL Ltd.

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