Targeting interleukin-6 to treat neuromyelitis optica spectrum disorders: Implications from immunology, the FcRn pathway and clinical experience

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Neuromyelitis optica spectrum disorder (NMOSD) is a rare disease of the central nervous system (CNS) that is associated with poor outcomes for patients. Until recently, when complement inhibitors were approved, there was no approved therapy. Most recently, clinical trials of interleukin-6 (IL-6) blockade showed a therapeutic benefit for NMOSD. In this review, we introduce the immunological basis of IL-6 blockade in NMOSD and summarize current knowledge about the clinical use of the IL-6 receptor inhibitors tocilizumab and satralizumab. The aim of extending the half-life of monoclonal antibodies (mAbs) has been actualized by successful clinical translation for Satralizumab, achieved via the neonatal Fc receptor (FcRn) pathway. The basic principles of FcRn are highlighted in this review together with the potential therapeutic benefits of this emerging technology.

Keywords: Neuromyelitis optica; NMOSD; Interleukin-6; Monoclonal antibody; Disease-modifying therapy; Neonatal pathway; Aquaporin antibody

Introduction

NMOSD comprises a group of rare inflammatory disorders of the CNS with relapse-associated accumulation of neurological disability. The predominant sites affected by this rapidly disabling disease include the spinal cord and optic nerves. Lesions can also be found in the hemispheric white matter, diencephalon, and brainstem [1]. In addition, the occurrence of chronic fatigue, neuropathic pain, depression, sleep disorders, and cognitive impairment are additional challenges for the management of patients with NMOSD. The histopathological correlates include blood–brain barrier (BBB) breakdown, necrosis and demyelination, infiltration of macrophages and granulocytes, widespread axonal swelling and spheroids, and cavitation [2]. Furthermore, astrocytes are characterized by loss of the water channel aquaporin-4 (AQP4) and glial fibrillary acid protein (GFAP), and complement deposition occurs around blood vessels [3].

NMOSD can be associated with antibodies against AQP4 (AQP4-Ab), an integral membrane protein found in astrocytic foot processes, glia limitans, and ependyma [4]. The identification of IgG1 autoantibodies against AQP4 as a sensitive and highly specific serum diagnostic biomarker for NMOSD in 2004 was a pivotal milestone for enhancing the understanding of the pathogenic mechanism, fostering early diagnosis and improving management [5]. This antibody is found in up to 80% of patients with NMOSD [6]. AQP4-Ab can enter the CNS by passive diffusion at sites lacking a proper BBB, including the area postrema, or through a disrupted BBB [7]. Indeed, disruption of neurovascular units can be caused by acute infections, which were shown to precede NMO attacks in up to 35% of patients

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[8,9]. AQP4-IgG$^-$ NMOSD is likely to be a mixed diagnostic entity comprising conditions with antimyelin oligodendrocyte glycoprotein (MOG) Abs or yet unidentified entities [10]. MOG is a minor myelin component exclusively expressed on the surface of myelin sheaths in the CNS [11]. Histopathological studies of MOG-IgG-associated disease revealed distinct findings of macrophages in perivascular spaces and demyelinating lesions, and immune cells surrounding blood vessels in and around demyelinating lesions [12]. Moreover, activation of humoral immunity, as evidenced by perivascular deposits of activated complement components and immunoglobulins (Igs), was only occasionally observed.

Plasma cells in the systemic circulation are the main source of AQP4-Ab [13,14]. In this regard, AQP4 peptides have been shown to be recognized by T cells, mainly T helper subtype 17 (Th17) cells, and to contribute to B cell activation by conformationally intact AQP4 proteins [6]. These B cells then differentiate into plasmablasts, which secrete AQP4-Ab of the IgG1 subtype (AQP4-IgG). Indeed, there is a selective increase in plasmablasts with the $CD19^{int}CD27^{high}CD38^{high}CD180^-$ phenotype in the peripheral blood of patients with NMOSD [15]. Although B cells have a crucial role in the production of AQP4-IgG, the role of T cells in the immunopathogenesis of the disease is increasingly recognized. Indeed, emerging evidence indicates that NMOSD is associated not only with humoral immunity involving B cells, but also with Th17 cytokines, including IL-6 and IL-17 [16].

The diagnostic criteria for NMOSD are based on the detection of AQP4-Ab in serum, major clinical symptoms, and characteristic magnetic resonance imaging (MRI) findings [17]. A timely diagnosis with aggressive treatment of relapses with steroids and even plasma exchange as first-line treatment decreases the risk of permanent disability [18,19]. To date, treatment of NMOSD has largely been based on the results of observational studies, case reports, and retrospective analyses, and has included empiric use of off-label treatments. Indeed, immunosuppressive therapy has been shown to prevent acute attacks effectively and improve long-term outcome in many patients. The treatment options include B cell depletion by targeting CD20 with mAbs and administration of azathioprine, mycophenolate mofetil, mitoxantrone, or cyclophosphamide [20]. Reports also show efficacy of autologous hematopoietic stem cell transplantation [21]. However, a considerable number of patients experience breakthrough disease on these therapies, and alternative treatment options need to be considered. Thus, five pivotal Phase III studies on therapies for NMOSD were published in 2019–2020. These emerging treatments include eculizumab, a complement C5 inhibitor [22,23], inebilizumab (MEDI-551), a mAb that depletes CD19-expressing B cells [24,25], and two mAbs targeting the IL-6 receptor (IL-6R; tocilizumab and satralizumab). Satralizumab has since been approved for the treatment of NMOSD by the US Food and Drug Administration (FDA) [26] and the European Medicines Agency (EMA) [27] (Table 1).

Here, we provide details on NMOSD and the importance of the IL-6 signaling pathway for the pathophysiology of this disease. By discussing the neonatal Fc receptor (FcRn) signaling pathway and its interaction with Igs/antibodies as an emerging target in the treatment of autoimmune diseases and for biomolecular engineering, we present the most recent developments in the treatment of NMOSD and in pharmacology. In addition, we provide insights into the emerging 'antibody recycling technology' via the FcRn pathway, which is a novel feature of satralizumab. Finally, the results of studies with mAbs against IL-6R in NMOSD are presented.

Interleukin-6

Interleukin-6: General aspects

Human IL-6 comprises 212 amino acids, including a 28-amino acid signal peptide, and its gene has been mapped to chromosome 7p21 [28]. Although the core protein is ~20 kDa, naturally occurring IL-6 has a molecular weight of 21–26 kDa because of glycosylation.

IL-6 was initially identified as a soluble factor that is secreted by T cells and induces antibody production by B cells [29]. Since then, the involvement of IL-6 in various pathways of immune regulation both under physiological conditions and in inflammatory disorders has been recognized. IL-6 has been shown to be a soluble mediator with pleiotropic effects on inflammation, the immune response, and hematopoiesis. For this purpose, IL-6 activates a receptor complex comprising IL-6R and the signal-transducing receptor subunit gp130. IL-6 can bind to both the transmembrane and a soluble forms of IL-6R [30]. Thus, three modes for IL-6 signaling may occur, in which IL-6 binds to mIL-6R (classical), binds to sIL-6R (*trans*-signaling), or is joined through IL-6R to gp130 on nearby cells (*trans*-presentation)

TABLE 1

Completed Phase III trials in NMOSD.[a]

Drug	Study	Enrolled patients[b]	Target antigen	Usage	Approved[c]	Refs
Eculizumab	PREVENT	$Aqp4^+$	C5 complement inhibition	i.v. 900 mg initiation phase (weekly), 1200 mg maintenance dose every 14 days	FDA*; EMA**	[22,23,114]
Satralizumab	SAkuraSky; SAkuraStar	$Aqp4^{-/+}$	IL-6R blockade	s.c. 120 mg week 0, 2, 4 and afterwards every 4 weeks	FDA^+	[26,27,105,106]
Ineblizumab	N-Momentum	Aqp4+	CD19	i.v. 300 mg week 0 and 2 and every 6 months afterwards	FDA^{++}	[24,25]

[a] Abbreviations: i.v., intravenous; s.c., subcutaneous.

[b] Eculizumab and inebilzumab were only studied in patients with antibodies to aquaporin 4 (Aqp4), whereas satralizumab was also tested in seronegative patients ($Aqp4^-$), but was only for approved for seropositive patients based on the Phase III trials result.

[c] *, approved by the FDA for the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody positive; **, approved by the EMA for treatment of NMOSD in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease; +, approved by the FDA for the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody positive; ++, approved by the FDA for the treatment of NMOSD in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

[31]. The downstream signaling cascade includes the Janus kinase (JAK), signal transducer and activator of transcription factor 3 (STAT3), and JAKSHP-2 mitogen-activated protein kinase pathways [32]. STAT3 also induces the expression of suppressor of cytokine signaling 1 and 3, which bind to phosphorylated JAK and gp130, respectively, leading to the termination of IL-6 signaling via a negative feedback loop [30].

Monocytes and macrophages are the main sources of IL-6, but T cells, B cells, hepatocytes, endothelial cells, fibroblasts, keratinocytes, mesangial cells, and adipocytes, as well as several tumour cells, can produce IL-6 constitutively or after stimulation [33]. In general, IL-6 is rapidly synthesized in response to tissue injury or infection and exerts proinflammatory effects by stimulating hepatocytes to produce acute-phase proteins (C-reactive protein, serum amyloid A, fibrinogen, and a1-antichymotrypsin) [34]. By contrast, the synthesis of fibronectin, albumin, and transferrin is reduced [28]. In addition, many inflammatory responses in tissues are initiated by IL-6, which promotes the infiltration and activation of mononuclear leukocytes while suppressing neutrophil infiltration [30]. Furthermore, IL-6 signaling is associated with the upregulation of antiapoptotic factors that promote T cell survival [35,36]. IL-6 induces the production of vascular endothelial growth factor (VEGF), which enhances angiogenesis and increases vascular permeability [37]. Furthermore, there is evidence that supports the modulation of IL-6 responses in the CNS [38]. Most types of human cell are not responsive to IL-6 because expression of the 80-kDa transmembrane IL-6R is limited to hepatocytes, neutrophils, monocytes/macrophages, and some lymphocyte subsets [30].

IL-6 dysregulation has been shown to be crucial for the development of autoimmune diseases. Importantly, IL-6 promotes the specific differentiation of naïve CD4+T cells to proinflammatory Th17 cells [39]. Moreover, IL-6 inhibits TGF-β-induced regulatory T cell (Treg) differentiation [40]. An altered Th17/Treg balance is considered to be responsible for the disruption of immunological tolerance and, thus, is pathologically involved in the development of autoimmune and chronic inflammatory diseases [41]. Furthermore, IL-6 has been shown to promote T follicular helper cell differentiation as well as the production of IL-21, which regulates immunoglobulin synthesis [42]. IL-6 also induces the differentiation of CD8+T cells into cytotoxic T cells [43] and can induce the differentiation of activated B cells into antibody-producing plasma cells.

Therapeutic mAbs in different stages of development that target the IL-6/Il6-R axis include satralizumab (Roche), tocilizumab (Roche), sarilumab (Sanofi), sirukumab (Janssen), clazakizumab (Adler Biopharma), olokizumab (UCB), vobarilizumab (Ablynx), olankicept (Ferring Pharma), and NI-1202 (Tiziana) [32].

Interleukin-6 in the pathogenesis of NMOSD

Emerging *in vivo* and *in vitro* evidence indicates that the IL-6 signaling pathway has an important role in the pathogenesis of NMOSD. IL-6 protein levels are increased in the serum and cerebrospinal fluid (CSF) of patients with NMOSD compared with healthy controls [44–47]. Another study showed that the CSF sIL-6R level was higher in patients with NMOSD than in those with multiple sclerosis (MS) and was correlated with clinical severity [48]. The CSF levels of IL-6 are higher during relapses, and higher levels are associated with poorer recovery [49,50]. Moreover, one study correlated IL-6 levels in CSF with markers of neuroaxonal damage [51]. Thus, elevations in CSF IL-6 levels might reflect the degree of inflammation and direct destruction of the CNS. IL-6 levels in CSF are also correlated with matrix metalloproteinase-2 levels and BBB disruption [52]. IL-6 signaling decreases BBB function, increases chemokine production, and enhances leukocyte migration *in vitro* [53]. Moreover, IL-6 prolongs the survival of CD19-, CD27- and CD38-positive plasmablasts and plasma cells, including AQP-4-Ab-secreting cells [15].

Anecdotal reports have proven that therapeutic inhibition of IL-6 reduces the serum level of AQP-4-Ab in the setting of NMOSD [54,55]. In addition, IL-6 might be involved in the mechanisms mediating pain and fatigue, frequent complications of NMOSD [54,56].

The FcRn pathway and possible therapeutic considerations

Immunology and therapeutics: General aspects

Based on the findings of Edward Jenner [57] and since the days of Louis Pasteur and Robert Koch, when the discipline of immunology was beginning to be established, knowledge of immunological processes has gone hand in hand with their therapeutic application, as readily exemplified by vaccinations [58]. In recent decades, there has been a previously inconceivable gain in knowledge about immunological processes. Based on these findings, the era of mAbs, which have interdisciplinary applications and have revolutionized treatment approaches in these disciplines, has begun [59]. Pharmaceutical engineering enables the manufacture of products in addition to mAbs, such as fusion proteins, which are termed 'biologics' because of their biological source [60]. Currently, >20 different classes of biologics and >350 products can be distinguished [60,61].

Immunoglobulins and the neonatal Fc receptor

Antibodies (or Igs) are components of the humoral immune response and the adaptive immune system. Antibodies can be divided into five classes (isotypes) (IgM, IgG, IgA, IgD, and IgE), with further subclasses of IgG and IgA. Igs differ in their molecular weight (ranging from 150 kDa for IgG to 900 kDa for IgM), half-life (from 3 days for IgA and IgD to 23 for IgG), and specific immunological properties (e.g., complement fixation ability, immune cell binding, site of action, or the extent to which they can cross the placenta). Genes encoding immunoglobulins are located on chromosomes 14 [heavy (H) chains], 2 [κ light (L) chains], and 22 (λ L chains) [62]. Igs comprise two H and two L chains. Both the H and L chains consist of constant (C) and variable (V) regions. An antigen-binding fragment (Fab) and a crystallizable fragment (Fc) can be distinguished. Fab comprises the L chains and part of the H chains containing the V regions and one C region each. The C regions of the H chain determine the Ig class: IgG has a γ H chain, IgM has a m H chain, IgA has an α H chain, IgD has a δ H chain, and IgE has an ε H chain. Although Fab, with its variability, is responsible for antigen binding, the effector function is mediated by Fc (Fig. 1a). The effector functions of each Ig class and subclass vary [62]. The different IgG subclasses differ in the hinge region and in the number of

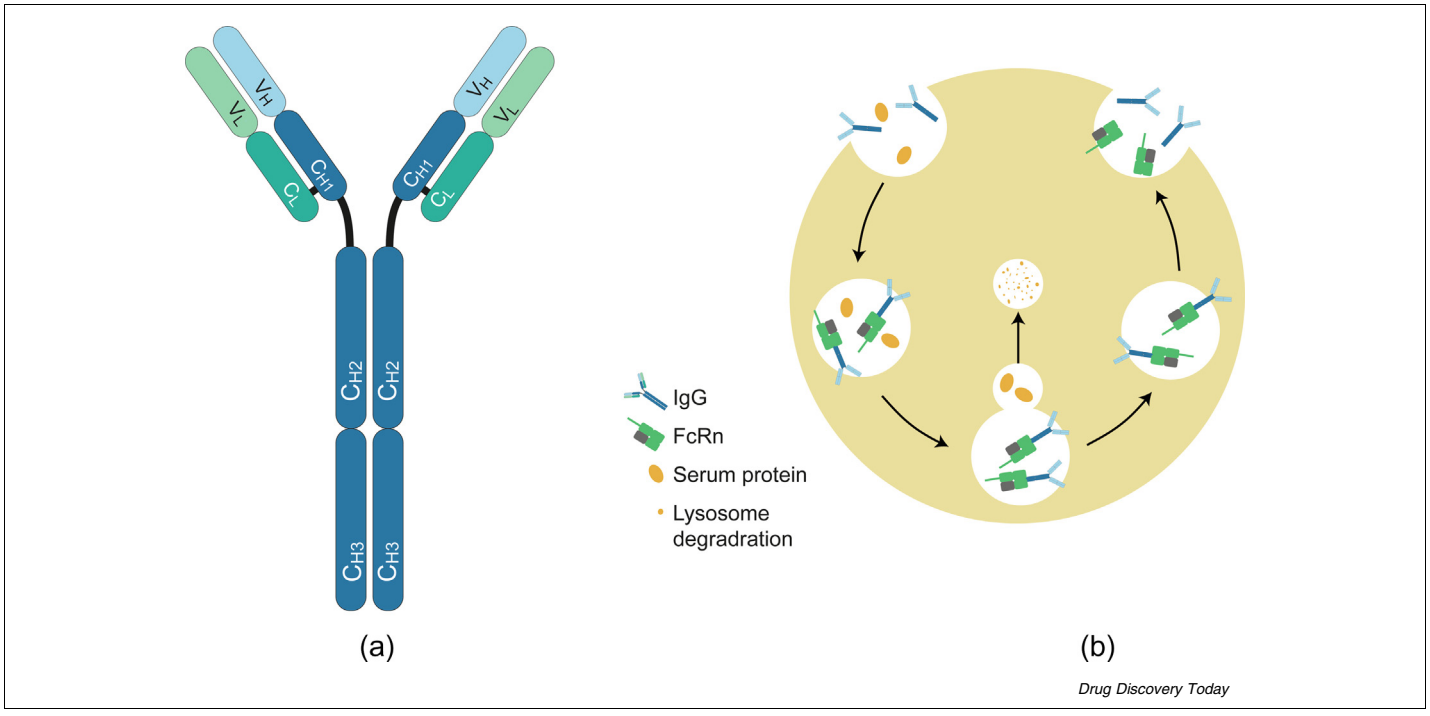

FIGURE 1

(a) An immunoglobulin G (IgG) antibody. The variable regions (VH and VL) are mainly responsible for antigen binding, whereas the constant regions (CH3 and 2) are responsible for effector functions. (b) Recycling of an IgG antibody by pinocytosis, binding to the FcRn, detachment, and release. For further details, see the main text.

disulfide bonds between the chains. These difference, in turn, are responsible for various conformational changes and immunological reactions [62]. The functions of Igs are triggered by binding to corresponding Fc receptors (FcRs) located on the surface of cells (not only immune cells). FcRs are Ig specific and can be distinguished by their notation; for example, FγRI (CD64), which binds IgG (in the order IgG1, IgG3 > IgG4 > IgG2), is found on different cells (macrophages, neutrophils, eosinophils, and dendritic cells). In addition, their functions differ depending on which immune cells they are found on. The immune system can be activated or inhibited by FcR binding in a manner dependent on the FcRs and their triggered mechanisms [63,64].

Another receptor to which only the IgG isotype can bind is FcRn. In neonates, the plasma IgG level corresponds with that of the mother, and FcRn has been hypothesized to be responsible for the transfer of IgG from the mother to the fetus via the placenta [8,65]. More recently, studies have suggested that FcγRs mediate transplacental IgG transport, because some Fc glycoforms are detected in the fetal circulation [66,67]; however, modeling maternal–fetal transport in FcγR/FcRn humanized mice supports the hypothesis that *trans*-placental transport of IgG can be sustained only by FcRn [68]. Therefore, it is safe to conclude that IgG is selectively bound by FcRn, resulting in enhanced accumulation of maternal antibodies in the fetus [69].

The molecular structure of FcRn is similar to that of major histocompatibility complex class I (MHC-I) molecules. However, in contrast to MHC-I, FcRn does not bind to processed peptides (because this binding site is blocked) but binds to IgG. By binding to FcRn, IgG is transported via the placenta. Similarly, after birth, FcRn is responsible for uptake of IgG via absorption of breast milk from the intestinal lumen into the circulation of the newborn. FcRn can be found not only in the placenta, but also in the intestinal epithelium, liver, and other endothelial cells, and persists in adults. In addition to IgG, albumin is recycled via this pathway. Both IgG and albumin are absorbed into the vascular endothelium via FcRn by pinocytosis and bind to FcRn in a pH-dependent manner. Thus, they are not degraded via lysosomes and are returned to the cell surface. At a physiological pH of 7.4, IgG and albumin detach from the FcRn and are again made available to the blood circulation [70] (Fig. 1b). However, unbound proteins are degraded. Collectively, albumin and IgG account for 90% of serum proteins. Thus, a constant serum level of IgG and albumin is maintained [71,72]. Indeed, the different Igs differ in their half-lives; IgGs have the longest half-life. The half-life of the IgG subclasses (except for IgG3) is extended via this pathway to ~23 days [73,74].

Separate from these aspects of the FcRn pathway, the role of FcRn in viral diseases is being investigated. Reports indicate that FcRn could be vital for viral replication. This importance has been shown for enteric cytopathic human orphan (ECHO) viruses, but the exact mechanism needs to be elucidated [75]. In addition, viruses can be transcytosed via mucosa through the FcRn pathway, and this mechanism might be a new target for vaccination against HIV or herpesviruses [76].

Possible applications in human disease and therapeutics

The mechanisms of the FcRn pathway have recently been investigated in more detail, and possible effects on diseases (especially autoimmune diseases) or on therapeutics, especially biologicals, have been more precisely revealed [77].

The interaction between FcRn and IgG can be modified by altering the affinity of the Fc of an antibody for FcRn. Furthermore, in animal models, overexpression of FcRn has been shown to reduce the catabolism of IgG, leading to higher plasma IgG levels [61]. Consequently, two questions arise: first, to what extent can FcRn blockade lower IgG levels? Second, how can improved docking to FcRn prolong the half-life of monoclonal antibodies? Although the first strategy is primarily intended for use in (auto)immune-mediated diseases, the second strategy is suitable for all therapies involving mAbs.

Hence, the FcRn mechanism could be used therapeutically in two ways: (i) to reduce the half-life of pathological antibodies or (ii) to increase the half-life of therapeutic antibodies [78]. Both alterations lead to changes in IgG levels. The aim in autoimmune diseases might be a reduction in pathological antibodies, whereas extension of the half-life leads to an increase in the therapeutic benefit.

Reduction in pathological antibodies

Intravenous Ig (IVIg) substitution has a long history of therapeutic use. IVIg contains mainly IgGs and, to a lesser extent, IgAs and IgMs, and is collected and processed for therapeutic purposes from a large number of donors. These polyvalent Igs are used in the treatment of Ig deficiencies, but they have also been shown to be effective in the treatment of autoimmune diseases, such as Guillain–Barré syndrome [79]. Although the benefit of these therapies in immunodeficiency diseases is obvious, their benefit in autoimmune diseases is not as self-evident. In addition to exerting effects on T cells, complement, and B cells (downregulation via FcRs), IVIgs compete with endogenous IgGs in the patient for FcRn binding. The excess of polyvalent IgGs leads to receptor saturation and decreases the half-life of endogenous pathological antibodies [80].

FcRn is being investigated as a target antigen in numerous autoimmune diseases. Whereas all IgG mAbs affect FcRn, only biologics that explicitly exploit this pathway to generate an additional therapeutic benefit are discussed herein.

The largest amount of data is available for myasthenia gravis, with blockade of FcRn in myasthenia gravis being recently investigated. The half-life of IgG should be reduced by antagonization. Inhibition of IgG binding to FcRn leads to a selective decrease in IgG levels and can alleviate the effects of pathological IgG. This effect is expected to be similar to those of plasmapheresis or IVIg supplementation but with a more selective component. One possibility for FcRn blockade is direct attachment of mAbs to FcRn. Over the past few years, fusion proteins have been the main focus for therapeutic use. Recombinant proteins are fused with the Fc region of IgG and are taken up via the FcRn pathway.

One FcRn inhibitor has already shown a dose-dependent benefit in the acetylcholine receptor-ab and muscle-specific kinase (MuSK)-positive mouse model, and several drugs are in clinical development. Efgartigimod is an altered human IgG1 Fc fragment that binds with high affinity to FcRn. In a Phase I study, IgG levels were reduced by 50–75%, and no effects on albumin levels were seen [71]. A Phase II trial showed a rapid and long-lasting benefit in 75% of treated patients [77]. In addition, a Phase III trial showed improvement in activities of daily in patients with myasthenia gravis [81]. Nipocalimab is an IgG1 anti-FcRn mAb that reduced IgG levels by up to 90%, with a slight reduction in total protein and serum albumin levels. Serum IgG was decreased by up to 48%, but various adverse effects, such as headache and fever, occurred; thus, the tolerability of nipocalimab needs improvement. RVT-1401 is a fully human mAb that also binds to FcRn. When RVT-1401 was administered weekly, IgG levels decreased by up to 78% and remained up to 35% below baseline levels 1 month after the final administration. Furthermore, albumin levels were decreased by 31% [71]. All these drugs have reached Phase II study status, and rozanolixizumab is in an active Phase III study [82]. Positive results from a Phase III trial with efgartigimod in myasthenia gravis have also been announced.

Extending the half-life of therapeutics

The FcRn pathway has already been targeted by some therapeutics to extend the half-life of antibodies and is being tested in a variety of diseases. Binding to FcRn can be enhanced by exchanging amino acids in the specific binding pocket via biomolecular engineering techniques. In this approach, the antibody binds to its antigen and is subsequently taken up by cells and enters the cellular degradation pathway (Fig. 1b). Then, the antigen is dissociated from the antibody in a manner dependent on the acidic environment or low calcium concentration present in endosomal vesicles and is degraded, whereas the antibody is recycled to the plasma membrane and released into the extracellular environment. Etanercept, which is approved for the treatment of rheumatoid arthritis (RA) and other autoimmune diseases, is a good example of biomolecular engineering. This biologic comprises a receptor for tumour necrosis factor (TNF) and the Fc region of IgG1. Thus, etanercept can bind freely available TNFα and β, thus reducing the levels of these inflammatory factors [83]. During degradation, TNF can be broken down after detachment, whereas the Fc fragment can be recycled via the FcRn pathway. This results in a reduction in the levels of proinflammatory cytokines, whereas the half-life of the therapeutic agent is extended. In addition to etanercept, dulaglutide and albiglutide, which were developed for the treatment of diabetes, and coagulation factors were fused with Fc of IgG1 or with albumin, increasing the half-life of therapeutics in the treatment of haemophilia by three–fivefold. The same result was possible via the fusion of coagulation factors to albumin, which also led to an extension of the half-life and to regulatory approval [75].

Excursus: Additional applications

In addition to its role in extending the half-life of therapeutics, the role of FcRn in viral diseases is being further investigated. One such antibody is currently being tested in patients with positivity for HIV: vrc-hivmab091-00-ab. In addition to decreasing the level of pathological IgGs and extending the half-life of therapeutics, these agents might also alter viral replication (see earlier). The N6LS antibody binds to the CD4 binding site on the HIV-1 gp120 protein and contains methionine (M) to leucine (L) and asparagine (N) to serine (S) (M428L/N434S, referred to as LS) substitutions within the C terminus of the H chain C region to increase its binding affinity for FcRn [84]. Positive safety and tolerability results of using the FcRn pathway to target envelope proteins have been published [85].

Biomolecular engineering: Satralizumab

Biomolecular engineering of the C regions of mAbs will impact many FcRs. Thus, specifically increasing the binding to FcRn is necessary. Binding and dissociation are determined not only by the pH value, but also by covalent bonding, the hinge region, and the identities of amino acids. Therefore, during the development of different biologicals, effects on different receptors must be considered [86]. Antibody recycling aims to protect IgGs from degradation by binding to FcRn. IgGs are taken up by cells and concentrated in early or sorting endosomes. Endosomes have a lower pH level than the extracellular environment, which abolishes the interaction between the antibody and antigen and strengthens the binding of IgG to FcRn. Thus, these IgG molecules are then recycled to the plasma membrane with FcRn [87]. The more basic pH of the extracellular environment leads to a sudden decrease in the binding affinity; thus, IgG is released again. All other endocytosed serum proteins contained in endosomes, as well as all IgG molecules that are not tightly bound to FcRn, are directed to lysosomes and undergo proteolytic degradation [87,88]. Thus, binding of IgG to FcRn can significantly extend the half-life of circulating IgGs [88]. In addition, the establishment of a mouse model with a humanized FcRn supported the development of such an approach, confirmed the basic hypothesis [89] (Fig. 1b).

The antibody recycling strategy was used to further propel the development of satralizumab via genetic modification of the tocilizumab scaffold to support enhanced antibody recycling. To this end, the amino acid sequence of the Fc region was altered [90,91]: a tyrosine residue was mutated to a histidine residue to improve the repulsive action in the acidic environment of endosomes. The effect can be directly measured by plasmon surface resonance and resulted in a significant increase in the plasma half-life in mice expressing the humanized FcRn. Thus, the change in the Fc region of the antibody introduced a decisive change in its pharmacokinetic (PK) profile that can also be assessed by the isoelectric point. This change enables the recycling antibody to participate in further cycles of activity, binding to its antigen and inhibiting or neutralizing it, which ultimately explains the extended duration of action and simultaneously emphasizes the different treatment regimen: subcutaneous administration of 120 mg monthly for satralizumab compared with subcutaneous administration of 162 mg weekly for tocilizumab.

Pharmacological interference with IL-6 in NMOSD

IL-6 has been explored as a therapeutic target in NMOSD and the utility of IL-6 blockade in NMOSD has been proven conceptually for tocilizumab, whereas the efficacy of satralizumab has been proven in two Phase III trials.

Tocilizumab

The first marketed drug against IL-6 signaling was tocilizumab, a humanized mAb that binds to the cytokine-binding module (CBM) of the IL-6R located in its D2 and D3 domains. The antibody is approved for the treatment of Castleman's disease [92], RA [93], systemic juvenile idiopathic arthritis [94], cytokine release syndrome, and giant cell arteritis [95,96].

Mechanistically, tocilizumab binds to both the soluble and membrane-bound forms of IL-6R and inhibits both the classical and alternative pathways of IL-6 activity [28]. Binding of tocilizumab to IL-6R prevents gp130 dimerization and, thus, signal transduction [97]. Furthermore, treatment with tocilizumab decreased the levels of circulating myeloid dendritic cells and monocytes [98]. In addition, the level of serum macrophage migration inhibitor factor and the number of Th17 cells were reduced, whereas the number of regulatory T cells was increased [99,100].

PK properties were primarily assessed in a large population PK study [101]. In this study, adequate plasma levels were achieved every 4 weeks with an intravenous dose because of a correspondingly long half-life. Tocilizumab is eliminated in a biphasic manner, whereby the total clearance is concentration dependent and represents the sum of the linear and the nonlinear clearance. Its clearance is not affected by concomitant administration of methotrexate, nonsteroidal anti-inflammatory drugs, or corticosteroids.

A meta-analysis of the efficacy of Il-6r blockade with tocilizumab included five clinical trials with a total of 89 patients and showed a significant benefit of tocilizumab-treated patients in terms of relapse rate and proportion of relapse-free patients [102,103].

Phase II evidence for tocilizumab in NMOSD: The TANGO trial

The TANGO trial (NCT03350633) was an open-label, multicenter, randomized, Phase II trial that was conducted at six hospitals in China [104]. A total of 112 adult patients (aged $\geq$ 18 years) with highly relapsing NMOSD diagnosed according to the 2015 International Panel for Neuromyelitis Optica Diagnosis criteria were recruited. The inclusion criteria were an Expanded Disability Status Scale (EDSS) score of 7.5 or lower and a history of at least two clinical relapses during the previous 12 months or three relapses during the previous 24 months with at least one relapse within the previous 12 months. Patients were randomly assigned (1:1) to receive intravenous tocilizumab (8 mg/kg every 4 weeks) or oral azathioprine (2–3 mg/kg per day). The minimum planned duration of treatment was 60 weeks. Regarding the primary outcome, the median time to first relapse was longer in the tocilizumab group than in the azathioprine group (78.9 weeks [interquartile range (IQR), 58.3–90.6] versus 56.7 [32.9–81.7] weeks; $P = 0.0026$). In the per-protocol analysis, 50 of the 56 patients (89%) in the tocilizumab group were relapse-free, compared with 29 of the 52 patients (56%) in the azathioprine group at the end of the study [Hazard ratio (HR), 0.188 95% confidence interval (CI), 0.076–0.463; $P < 0.0001$); the median time to first relapse was also longer in the tocilizumab group than in the azathioprine group [67.2 weeks (IQR, 47.9–77.9) versus 38.0 (23.6–64.9); $P < 0.0001$). Treatment-associated adverse events occurred in 36 of 59 tocilizumab-treated patients (61%) and 49 of 59 azathioprine-treated patients (83%). One death occurred in the tocilizumab group (2%) and one in the azathioprine group (2%), but neither of the deaths were treatment related. Thus, this study provided evidence for the superior efficacy of tocilizumab compared with azathioprine.

Satralizumab

Satralizumab is a humanized mAb that targets IL-6R and exploits the novel 'antibody recycling technology'. Compared with conventional technology, antibody recycling technology allows a longer duration of antibody circulation and, consequently, a lower frequency of application.

Satralizumab is subcutaneously administered and binds to both the membrane-bound and soluble forms of IL-6R. The safety and efficacy of satralizumab in NMOSD were evaluated in two randomized, double-blind, placebo-controlled trials. In the SAkuraSky study, satralizumab was administered as an adjuvant treatment to baseline immunosuppressive therapies that included oral corticosteroids, azathioprine, and mycophenolate mofetil [105]. By contrast, in the SAkuraStar study, satralizumab was evaluated as a monotherapy [106].

Research evidence for satralizumab in NMOSD

Satralizumab as a monotherapy was studied in the SAkuraStar trial (NCT02073279), a Phase III, double-blind, placebo-controlled, parallel-group trial [106]. The primary endpoint was time to first protocol-defined relapse based on the intention-to-treat population and analyzed with stratification for two randomization factors (previous therapy for prevention of attacks and the nature of the most recent attack). Eligible participants were adults aged 18–74 years with AQP4-Ab-seropositive or AQP4-Ab-seronegative NMOSD who had experienced at least one documented NMOSD attack or relapse in the past 12 months and had an EDSS score of 6.5 or less, at 44 investigational sites in 13 countries. Participants were randomly assigned (2:1) to receive 120 mg satralizumab or visually matched placebo subcutaneously at weeks 0, 2, and 4 and every 4 weeks thereafter. The double-blind phase was intended to last until 44 protocol-defined relapses occurred or 1.5 years after random assignment of the last patient enrolled, whichever occurred first. A total of 95 patients were enrolled (63 treated with satralizumab and 32 with placebo).

Protocol-defined relapses occurred in 19 patients receiving satralizumab (30%) and 16 receiving placebo (50%; HR, 0.45; 95% CI, 0.23–0.89; $P = 0{\cdot}018$). Thus, a 55% reduction in the risk of relapse was shown for satralizumab versus placebo. In the satralizumab group, 76.1% and 72.1% of the patients were relapse free at 48 and 96 weeks, respectively, compared with 61.9% and 51.2% in the placebo group. In particular, the reduction rate was 74% in patients with AQP4-Ab-seropositive NMOSD. At 48 and 96 weeks, 82.9% and 76.5% of the patients taking satralizumab were relapse free, respectively, compared with 55.4% and 41.1% in the placebo group, respectively.

The rate of adverse events was 473.9 events per 100 patient years in the satralizumab group and 495.2 events per 100 patient years in the placebo group, and the rate of serious adverse events was similar between the groups. The overall rates of infections and serious infections were similar between the satralizumab and placebo groups, and no opportunistic infections were reported in patients treated with satralizumab. Similar rates of injection-related reactions occurred in the satralizumab and placebo groups; these reactions included systemic injection-related reactions in four patients in the satralizumab group and one in the placebo group.

The Phase III SAkuraSky study evaluated the efficacy and safety of satralizumab (120 mg) in NMOSD as an adjuvant drug to oral immunosuppressive drugs, including azathioprine, mycophenolate mofetil, and/or corticosteroids [105]. The primary endpoint was the first protocol-defined relapse in a time-to-event analysis. Key secondary endpoints were the change from baseline to week 24 in the visual analog scale (VAS) pain score (range, 0–100; with higher scores indicating more severe pain) and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score (range, 0–52; with lower scores indicating more severe fatigue).

Satralizumab (120 mg; $N = 41$) or placebo ($N = 42$) was administered subcutaneously at weeks 0, 2, and 4 and every 4 weeks thereafter. In total, 83 patients were enrolled, with 41 assigned to the satralizumab group and 42 to the placebo group. The median duration of treatment with satralizumab in the double-blind period was 107.4 weeks. Relapse occurred in eight patients receiving satralizumab (20%) and 18 receiving placebo (43%; HR, 0.38; 95% CI, 0.16–0.88). Multiple imputation for censored data resulted in HRs ranging from 0.34 to 0.44 (with corresponding P values of 0.01–0.04). Among the 55 AQP4-IgG-seropositive patients, relapse occurred in 11% of those in the satralizumab group and 43% of those in the placebo group (HR, 0.21; 95% CI, 0.06–0.75); among the 28 AQP4-IgG-seronegative patients, relapse occurred in 36% and 43% of those in the respective groups (HR, 0.66; 95% CI, 0.20–2.24). The between-group difference in the change in the mean VAS pain score was 4.08 (95% CI, −8.44 to 16.61). The between-group difference in the change in the mean FACIT-F score was −3.10 (95% CI, −8.38 to 2.18). The rates of serious adverse events and infections did not differ between the groups.

Concluding remarks

Over the past 15 years, considerable progress has been made in our understanding of NMOSD. Most importantly, NMOSD can be differentiated from MS; moreover, because of the different pathophysiological backgrounds of these diseases, therapeutics approved for MS might even exacerbate the disease course in NMOSD. A deeper understanding of the immunological backgrounds of NMOSD, such as the importance of the complement system as well as the realization that IL-6 might act as a central cytokine, has paved the way for new therapeutic concepts.

The development of tocilizumab and now satralizumab fills a gap, because the IL-6 axis can be specifically influenced therapeutically for the first time. The difference between these two drugs is the short dosing interval of tocilizumab, which could be remedied by the antibody recycling strategy via FcRn and, thus, confer protection against the intracellular degradation machinery. This strategy enables a greatly extended dosing interval without the risk of increased occurrence of undesirable effects. However, unlike other therapeutic agents, the new therapeutic agent satralizumab was tested both as a monotherapy versus placebo and in combination with basic therapeutic agents; this diverse range of uses, the significant effect on preventing relapses within the framework of NMOSD, and the favorable profile of the adverse effects bring significant improvements for patients in the fight against NMOSD. Comparing the efficacy of tocilizumab and

TABLE 2

Overview of Phase II/III clinical trials for NMOSD and IL-6 inhibition.

Trial name (year)	Trial phase/ design	Patient number (*N*)	Diagnosis	Protocol	Treatment duration	Main efficacy outcomes	Adverse events and safety outcome
Tango (2019)	Phase II, comparative trial of TCZ versus AZA	118 (59 in each treatment arm)	AQP4-IgG$^+$ NMOSD ($N = 103$); seronegative NMOSD[a] ($N = 15$)	TCZ i.v. 8 mg/kg q4W or AZA 2–3 mg/kg/d	48 weeks	91.5% relapse-free in TCZ group versus 67.8% in AZA group; sustained reduction in disability more likely among patients treated with TCZ than with AZA; serum levels of AQP4-IgG reduced significantly (by 42%) with TCZ compared with 15% with AZA	Fatigue, skin rash, leukopenia or elevated liver enzymes in 20 patients (34%) receiving TCZ
SAkuraSky (2020)	Phase III randomized, double-blind, placebo-controlled STR monotherapy trial	95 (2:1 randomization to STR or placebo)	AQP4-IgG + NMOSD and seronegative NMOSD[b] (number of patients in each group not available)	STR SC 120 mg q4W	Double-blind treatment period ended 1.5 years after random assignment of last enrolled patient	Protocol-defined relapses occurred in 19 (30%) patients receiving STR and 16 (50%) receiving placebo (hazard ratio, 0.45, 95% CI 0.23–0.89; $P = 0.018$); compared with placebo, STR monotherapy reduced risk of relapse by 55%; percentages of relapse-free patients at weeks 48 and 96 were 76.1% and 72.1% in STR group versus 61.9% and 51.2% in placebo group, respectively	Incidence rates of serious adverse events and adverse events leading to withdrawal were similar between groups
SAkuraStar (2019)	Phase III randomized, double-blind, placebo-controlled adjuvant trial	83 (41 in STR group; 42 in placebo group)	AQP4-IgG$^+$ NMOSD ($N = 55$); seronegative NMOSD[a] ($N = 28$)	STR SC 120 mg q4W	Median 107.4 weeks in STR group and 32.5 weeks in placebo group	8 patients (20%) in STR group experienced relapse versus 18 patients (43%) in placebo group; 89% and 78% in STR group relapse-free at 48 and 96 weeks versus 66% and 59% in placebo group, respectively; ARR during double-blind period was 0.11 in STR group versus 0.32 in placebo group; no significant changes in pain and fatigue observed	Infections ($N = 28$), serious infections ($N = 2$), injection-related reactions ($N = 5$), benign thyroid neoplasm ($N = 1$), colon adenoma ($N = 1$), uterine leiomyoma ($N = 1$)

[a] Abbreviations: AQP4-IgG$^+$, seropositivity for antibodies against aquaporin-4; AZA, azathioprine; i.v., intravenous; q4W, every 4 weeks; s.c., subcutaneous; STR, satralizumab; TCZ, tocilizumab.

[b] MOG antibody status not reported.

satralizumab is not simple, because no head-to-head studies are available. However, both are efficacious in NMOSD. Regarding safety, no obvious concerns were observed in the trials (Table 2).

However, the mode of action via the FcRn pathway leaves open questions about safety. On the one hand, the total IgG level decreases not only because of IL-6 blockade, but also because of saturation of FcRn, and infections can result. However, IgG is not completely depleted by satralizumab, and the levels of IgA, IgM, and IgE are not altered. The native immune system appears to be unaffected at first examination. However, the immune system is not understood in detail and can be considered an alliance of many factors. A change in one factor can have indirect effects on others. Recently, the FcRn pathway was also shown to have an important role in antigen cross-presentation. Thus, cellular immunity, as well as humoral immunity, could be affected [107]. Patients with defective FcRns exhibit reduced IgG and albumin levels [108] and immune surveillance might be disturbed because of these low IgG levels [109]. In addition, results from animal studies suggest that a lack of FcRn affects antitumour immunity and natural killer cell development [110]. However, vigilant monitoring of adverse effects, including infections and malignancies, is mandatory for clinicians. The applications are increasing exponentially. Here, we close the loop and return to NMOSD. The first drug approved for the treatment of NMOSD was eculizumab, a C5 inhibitor [111–114]. Ravulizumab has a longer half-life than eculizumab; this increase is also achieved via the FcRn pathway, reducing the number of necessary yearly infusions from 26 to 6 and is being tested in a Phase III trial [115].

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Declaration of interests

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