

# IgG4-Mediated Neurologic Autoimmunities

## Understanding the Pathogenicity of IgG4, Ineffectiveness of IVIg, and Long-Lasting Benefits of Anti-B Cell Therapies

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### Abstract

#### Background and Objectives

Describe the unique functions of immunoglobulin G4 (IgG4) in IgG4-neurologic disorders (IgG4-ND) and explain why, in contrast to their IgG1-counterparts, they respond poorly to intravenous immune globulin (IVIg) but effectively to anti-B cell therapies.

#### Methods

The IgG4 structure and isotype switch, B cells and plasmablasts relevant to IgG4 production, and IgG4-induced disruption of the targeted antigens are reviewed and compared with IgG1-mediated autoimmune ND, where IVIg inhibits IgG1-triggered inflammatory effects.

#### Results

The main IgG4-ND include muscle-specific kinase myasthenia; nodal/paranodal chronic inflammatory demyelinating polyradiculoneuropathy with antibodies to neurofascin-155, contactin-1/caspr-1, or pan-neurofascins; antileucine-rich, glioma-inactivated-1 and contactin-associated protein-like 2 associated-limbic encephalitis, Morvan syndrome, or neuromyotonia; and anti-IgLON5 disorder. The IgG4, because of its unique structural features in the hinge region, has noninflammatory properties being functionally monovalent and bispecific, unable to engage in cross-linking and internalization of the targeted antigen. In contrast to IgG1 subclass which is bivalent and monospecific, IgG4 does not activate complement and cannot bind to inhibitory Fc $\gamma$  receptor (Fc $\gamma$ RIIb) to activate cellular and complement-mediated immune responses, the key functions inhibited by IVIg. Because IVIg contains only 0.7%–2.6% IgG4, its idiotypes are of IgG1 subclass and cannot effectively neutralize IgG4 or sufficiently enhance IgG4 catabolism by saturating FcRn. In contrast, rituximab, by targeting memory B cells and IgG4-producing CD20-positive short-lived plasma cells, induces long-lasting clinical benefits.

#### Discussion

Rituximab is the preferred treatment in IgG4-ND patients with severe disease by effectively targeting the production of pathogenic IgG-4 antibodies. In contrast, IVIG is ineffective because it inhibits immunoinflammatory functions irrelevant to the mechanistic effects of IgG4 and contains IgG-1 idiotypes that cannot sufficiently neutralize or possibly catabolize IgG4. Controlled studies with anti-CD19/20 monoclonals that also activate Fc $\gamma$ RIIb may be more promising in treating IgG4-ND.

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## Glossary

**AChR** = acetylcholine receptor; **CASPR2** = contactin-associated protein-like 2; **CIDP** = chronic inflammatory demyelinating polyradiculoneuropathy; **CTL** = cytotoxic T lymphocytes; **FcγR** = Fcγ receptor; **IgG4** = immunoglobulin G4; **IgG4-ND** = IgG4-neurologic disorder; **IgG4-RD** = IgG4-related disease; **IVIg** = intravenous immune globulin; **LGII** = leucine-rich, glioma-inactivated-1; **MAC** = membranolytic attack complex; **MG** = myasthenia gravis; **MuSK** = muscle-specific kinase; **PNS** = peripheral nervous system.

Several autoimmune, multisystemic, or fibroinflammatory disorders have been recently identified based on their association with immunoglobulin G4 (IgG4) subclass of autoantibodies, referred to as IgG4-related diseases (IgG4-RD).<sup>1-3</sup> In contrast, however, to a broad IgG4-RD spectrum with nondisease-specific pathogenic autoantibodies except for pemphigus vulgaris, membranous nephropathy, and thrombotic thrombocytopenic purpura, we are witnessing key IgG4-neurologic disorders (IgG4-ND) with pathogenic IgG4 antibodies targeting neural antigens highlighted by MuSK-myasthenia; nodal/paranodal chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with paranodal antibodies to neurofascin-155, contactin-1, contactin-associated protein-like 1 (CASPR1), and nodal/paranodal pan-neurofascins (NF140/NF186/NF155); leucine-rich, glioma-inactivated-1 (LGII) or the juxtapanodal CASPR2-associated autoimmune encephalitis, Morvan syndrome, neuromyotonia, or autoimmune pain syndromes; and the rare anti-IgLON5 disorder.<sup>4-10</sup> The unique feature of IgG4-ND is their significant disease severity that, in contrast to their IgG1 counterparts, exhibit poor response to intravenous immune globulin (IVIg) and inadequate response to steroids or plasmapheresis but excellent response to anti-B cell therapies, such as rituximab, that downregulate humoral immunity. Although some of these patients may have unique clinical phenotypes, most often present similarly to IgG1 counterparts and treated identically until recognized in retrospect that they are refractory to conventional immunotherapies. Their resistance to these therapies especially IVIg, which is the treatment of choice in their IgG1-counterparts based on controlled trials, is poorly understood, leading to therapeutic delays necessitating vigilance for proper therapy initiation.

Because IgG4-ND are now increasingly recognized, it has become imperative to understand the uniqueness of IgG4 pathogenicity and the rationale of the most effective immunotherapies. For the neurologists, the information is also relevant to IgG4-RD which, although present with autoimmune multisystemic, lymphoproliferative, or fibroinflammatory conditions, may also exhibit neurologic manifestations of meningeal and spinal cord disease, hypertrophic pachymeningitis, orbital myositis, or hypophysitis that may also need neurologic expertise.

The article addresses the uniqueness of IgG4 isotype; the role of regulatory B cells, cytokines, and plasmablasts in the IgG4 production; the mechanism by which IgG4 antibodies cause dysfunction of their targeted antigens; the reasoning of why IVIg, which is often the first-line therapy in their IgG1 counterparts, is

ineffective; the currently successful anti-B cell therapy with rituximab, including practical issues on repeated infusions or IgG4 biomarkers; and promising future anti-IgG4-immunotherapies.

### The Uniqueness of IgG4 Antibodies

IgG4 antibodies evolve as an anti-inflammatory response to chronic antigenic stimulation traditionally connected to peripheral tolerance because of high-dose allergen exposure, as occurring in beekeepers, cat owners, or helminth-infected subjects, alleviating allergic inflammation by interfering with the binding of allergen-specific IgE to the allergens.<sup>2</sup> In healthy adults, IgG4 is the least common IgG subclass, comprising only 5% of the total IgG with a concentration of 0.08–1.4 g/L.<sup>1-3</sup> Owing to its unique structural features in the hinge region, the IgG4 antibodies, although continuously undergo half antibody exchange with other IgG4 molecules, are considered immunologically inert and functionally monovalent because, in contrast to IgG1 which are bivalent and monospecific, they recognize the antigen essentially with only 1 Fab-arm of the IgG4; as a result, they are unable to engage in cross-linking and internalization of their target antigen or form immune complexes having noninflammatory properties.<sup>1,3,5,11</sup> IgG4 functions differently from the other IgG subclasses by 2 key characteristics: first, cannot bind the first C1q complement component to activate the complement cascade, and second, they bind uniquely to Fc receptors with markedly reduced binding capacity to inhibitory Fcγ receptor (FcγRIIb) but with enhanced binding to the activating FcγRI.<sup>1-3</sup> Collectively, IgG4-antibodies are inadequate in activating cellular or complement-mediated immune responses, which are directly targeted by IVIg and conventional immunotherapies; instead, they exert their pathogenicity by blocking protein-protein interactions and affecting signal transduction pathways. Whether genetic factors promote the development of IgG4 isotype as a response to certain antigens, as noted for certain paranodal antibodies mentioned later, is a possibility that needs to be further explored.

### Role of Cytokines, T Cells, and B Cells in IgG4 Production and Isotype Switch

The IgG4 production is augmented by IL-10, which in IgG4-RD is overexpressed in affected tissues playing a key role in the isotype switching of B cells to IgG4 subclass.<sup>1-3</sup> IL-10-expressing T-follicular regulatory cells and follicular helper T (Tfh) cells that produce IL-4, IL-10, and IL-21 are also involved in class switch, contributing to the pathogenesis of IgG4-RD.<sup>1,3,11-14</sup> CD4<sup>+</sup> cytotoxic T lymphocytes (CTLs) are

prominent in IgG4-RD and decline after B cell-targeted therapy, suggesting that B cells present antigen to activate CD4<sup>+</sup> CTLs.<sup>1</sup> Memory B cells and plasmablasts are also increased in the peripheral blood with the expansion of IgG4-producing CD19<sup>hi</sup>CD20<sup>+</sup>CD27<sup>hi</sup>CD38<sup>hi</sup> plasmablasts, especially during relapses or active disease.<sup>1-3</sup>

Insidious isotype switch can also occur late in the immune response because of maturation and hypermutation, as noted in nodal CIDP, from IgG3 against CNTN1/CASPR1 to IgG4 against CASPR1<sup>15</sup> and in MuSK-MG from IgG4 to IgG1.<sup>5</sup> Although overlooked, isotype switch can be clinically important in IgG4-ND when patients previously responding to IVIg become IVIg-unresponsive after isotyped to IgG4.

### **IgG4-Neurologic Autoimmunity: The Effect of IgG4 Antibodies on Targeted Antigens**

The IgG4 antibodies arise after chronic antigenic exposure late in the immune response and exhibit very high affinity for their antigen after undergoing several rounds of affinity maturation and somatic hypermutation.<sup>16</sup> In contrast to most IgG4-RD, however, where the immunopathogenicity of IgG4 is poorly understood and their clinicopathology is broad—defined by increased serum IgG4 and tumefactive lesions with IgG4+ plasma cell infiltrates in multiple organs<sup>1,2</sup>—the IgG4-neuroautoimmunity is distinct, characterized by antigen-specific disorders affecting only CNS or PNS. Most importantly, in IgG4-ND, the IgG4 antibodies exert a direct pathogenic effect by blocking enzymatic activity or disrupting protein-protein interactions of their target antigens affecting signal transduction pathways.<sup>5</sup> Among the IgG4-RD, the main ones with antigen-specific IgG4 that share immunologic similarities with IgG4-ND are pemphigus vulgaris with antidesmoglein antibodies, membranous nephropathy with M-type phospholipase A2 receptor 1 or thrombospondin type-1 antibodies, thrombotic thrombocytopenic purpura with antibodies to metalloprotease ADAMTS13, and possibly Goodpasture syndrome with antitype IV collagen antibodies. The IgG4-ND include

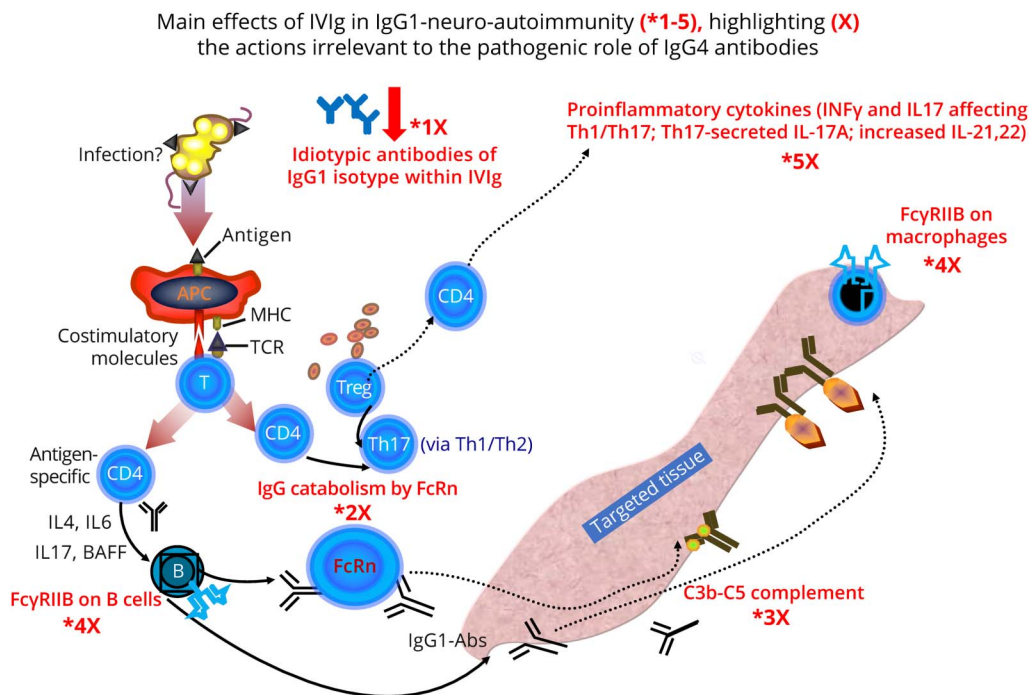
1. **Anti-MuSK-MG.** It comprises 7% of all patients with myasthenia gravis (MG) and is highlighted by IgG4 antibodies against muscle-specific kinase (MuSK), a transmembrane polypeptide expressed at the neuromuscular junction, that plays a fundamental role in acetylcholine receptor (AChR) clustering via interactions with agrin and rapsyn.<sup>4,5</sup> Although MuSK-MG may have a phenotype similar to AChR-MG, many times has unique presentation with selective weakness and atrophy of the neck, tongue, shoulder, and bulbar muscles.<sup>17,18</sup> MuSK-IgG4 antibodies are pathogenic, can passively transfer disease, and cause dysfunction of the neuromuscular junction by interfering with AChR clustering through the inhibition of Lrp4/MuSK signaling, but not by antigen cross-linking, internalization, or end-plate destruction as the IgG1-AChR antibodies do.<sup>4,19</sup>

2. **CIDP with nodal/paranodal antibodies.** This clinicopathologically distinct CIDP subset, identified in the last 10 years, comprises 10% of patients with CIDP and is caused by IgG4 antibodies to paranodal neurofascin-155, CASPR1, and CNTN1<sup>6,20,22</sup> and the nodal/paranodal pan-neurofascin (NF140/NF186/NF155 also called “nodal neurofascin”). These patients have distinct clinical phenotypes with distal weakness, tremor, and sensory (proprioceptive) ataxia. NF155 is a Schwann cell adhesion protein at the paranodal terminal myelin loops that binds to CNTN1, forming a complex critical for the maintenance of nodal structures ensuring rapid impulse propagation.<sup>23</sup> The antibodies are pathogenic, disrupting the NF155/CNTN1 complex by binding distinct epitopes associated with cell adhesion, resulting in the disadhesion of NF155/CNTN1 components by affecting glycosylation.<sup>6,20,22,23</sup> The IgG4 NF155 antibodies are specifically deposited at the axoglial junction causing dissection at the paranode perturbing conduction in the absence of demyelination.<sup>23,24</sup> These antibodies do not fix complement or internalize target antigens and do not cause inflammation; instead, they block protein-protein interaction leading to conduction failure.<sup>5,23</sup> Specific HLA-DRB1\*15 alleles show strong association in anti-NF155 patients implicating a constitutive genetic risk susceptibility factor.<sup>25</sup>
3. **LGI-1 and CASPR2-autoimmune syndromes** presenting with limbic encephalitis and seizures, Morvan syndrome and neuromyotonia, or severe neuropathic pain. These IgG4 antibodies are directed against the leucine-rich, glioma-inactivated-1 (LGI1) antigen or the juxtaparanodal contactin-associated protein-like 2 (CASPR2) that stabilize the voltage-gated potassium channel complex into the membrane.<sup>7,9</sup> The LGI1 plays a role in bridging the presynaptic voltage-gated potassium channel protein Kv1.1 with the postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor through interaction with synaptic anchor molecules ADAM22/23; the anti-LGI1 antibodies alter the binding of LGI1 with ADAM22, decreasing the postsynaptic levels of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.<sup>8</sup>

Although patients with anti-LGI-1 and CASPR2 antibodies may exhibit overlapping clinical symptomatology, the antibodies to LGI1 are most commonly associated with limbic encephalitis and epilepsy, whereas antibodies to CASPR2 with Morvan syndrome and neuromyotonia. Refractory epilepsy and mental and behavioral abnormalities are variably present. Pain, as seen in small fiber sensory neuropathy, and seizures involving ipsilateral face and limb dystonia-like seizures are also increasingly recognized.

4. **Anti-IgLON5 disorder** defines a complex syndrome of gait instability, craniofacial dyskinesias, sleep-disordered breathing, abnormal eye movements, and cognitive decline, characterized by antibodies, mostly of IgG4

**Figure** Immunopathogenic Network in IgG1-ND as Related to the Actions of IVIg (\*1-5), Highlighting (\*1-5 X) the Effects Irrelevant to IgG4-ND



In IgG1-ND, antigens presented via antigen presenting cells to CD4+T cells stimulate B cells to produce IgG1 antibodies which, by fixing complement at the target organ, lead to tissue damage. FcRn plays a role in catabolism of IgG1 antibodies, whereas the inhibitory FcγRIIB receptors on macrophages and B cells mediate inflammatory and immune effector functions. Induction of Tregs and proinflammatory cytokines sustain immune imbalance (adapted from 58). IVIg is effective in IgG1-ND collectively by supplying idiopathic antibodies of IgG1 subclass that exert neutralizing effects on circulating pathogenic IgG1 autoantibodies (\*1); this function is irrelevant to IgG4-ND because IVIg contains only IgG1 isotypes that cannot neutralize IgG4 (\*1-X); saturating the FcRn in endosomes resulting in increased catabolism of pathogenic IgG1(\*2); this function is probably irrelevant to IgG4-ND because IgG1 isotypes may not sufficiently affect IgG4 catabolism (\*2-X); binding to C3b, intercepting complement activation and the destructive effects of complement-fixing IgG1 antibodies (3\*); this function is irrelevant to IgG4-ND because IgG4 does not fix complement (3\*-X); upregulating FcγRIIB receptors on macrophages and B cells (\*4); this function is irrelevant to IgG4-ND because IgG4 cannot bind to FcγRIIB (\*4-X); and inhibiting proinflammatory cytokines (5\*); this is irrelevant to IgG4-ND because IgG4 has anti-inflammatory effects and does not sufficiently induce such cytokines (5\*-X). IgG1-ND = IgG1-neurologic disorder; FcγRIIB = Fcγ receptor; IVIg = intravenous immune globulin.

isotype, against IgLON5, a neural cell adhesion molecule.<sup>10</sup> IgLON5 antibodies disrupt the crosstalk between cell surface and cytoskeleton, leading to the abnormal accumulation of neurofilaments, providing a link between antibody-mediated autoimmunity and neurodegeneration.<sup>26</sup>

### Why IVIg Is Ineffective in IgG4-ND: Mechanisms of Actions of IVIg in Relevance to IgG4 Antibodies

In contrast to their autoimmune-ND counterparts that respond to IVIg in controlled studies, in IgG4-ND, there is no antigen cross-linking or immune complex formation, no recruitment of immune cells via Fc receptors, and no antigenic destruction via phagocytosis or antibody-dependent cellular cytotoxicity. Because these are the key functions inhibited by IVIg,<sup>27,28</sup> all the hallmark anti-inflammatory effects of IVIg that define its success in IgG1-ND are irrelevant to the pathogenicity of IgG4, explaining not only the ineffectiveness of IVIg but also the suboptimal benefit of steroids. The key

immunoregulatory actions of IVIg, contrasting with their irrelevance in IgG4-ND, include (Figure)

1. Supply idiopathic antibodies of IgG1 isotype capable of neutralizing pathogenic autoantibodies via  $F(\alpha\beta')_2$  binding. IVIg has more than 95% IgG of IgG1 subclass but minimal IgG4 (0.7%–2.6%). Derived from thousands of donors, IVIg contains anti-idiopathic IgG1 antibodies with a wide range of idiopathic and anti-idiopathic specificities, forming dimers connected by double-arm or single-arm binding between their  $F(\alpha\beta')_2$  domains that bind to and neutralize pathogenic autoantibodies.<sup>27,29,30</sup> The effect of idiotypes within the IVIg is highlighted in GBS and other demyelinating neuropathies with serum anti-GM1, anti-GQ1b, or other anti-glycolipid antibodies that block quantal release and impair neuromuscular transmission; the IgG1-idiopathic antibodies within the IVIg recognize these IgG glycoconjugates and inhibit or neutralize the blocking effects exerted by their sera, explaining the quick clinical benefits of IVIg.<sup>31,32</sup> Because IVIg does not contain idiotypes of IgG4 subclass, it

cannot exert similar and sufficiently enough neutralizing or blocking effects on the circulating IgG4 antibodies (#1, Figure).

2. Acceleration of IgG1 catabolism by saturating the FcRn transport receptors. Normally, IgG antibodies bind to FcRn to return via endocytotic vesicles intact back into the circulation, being protected from degradation by the lysosomes.<sup>33</sup> The supraphysiological levels of IgG derived from IVIg administration saturate the FcRn, so a portion of endogenously produced pathogenic IgG antibodies are not recycled back to the circulation but degraded<sup>33,34</sup>; as a result, the infused IVIg, by competing with pathogenic autoantibodies for FcRn binding, reduces the serum half-life of autoantibodies by approximately 40%, causing a reduction of the circulating IgG.<sup>33-35</sup> This effect, although not studied, may not be applicable to IgG4 antibodies because IVIg has no IgG4 to affect sufficiently enough IgG4 recycling, adding to its ineffectiveness (#2, Figure).
3. Inhibition of complement binding and prevention of membranolytic attack complex (MAC) formation. IVIg inhibits complement uptake, intercepting the formation and deposition of MAC on the targeted tissues by activated complement or complement-fixing antibodies.<sup>36,37</sup> On this basis, IVIg intercepts complement deposits on muscle or nerve fibers<sup>36-38</sup> and prevents the cytotoxicity induced by dermatomyositis or GBS sera.<sup>37,38</sup> These key anticomplement effects are not applicable to IgG4 antibodies because they do not mobilize or fix complement, as described earlier (#3, Figure).
4. Modulation of FcγR. The FcγRs transduce either activating signaling via the FcγRIA, FcγRIIA, and FcγRIIIA or inhibitory signals via the FcγRIIB, regulating immune cell activation.<sup>39,40</sup> IgG molecules bind through their Fc region to FcγR present on monocytes, macrophages, dendritic cells, and B cells and mediate inflammatory or immune effector functions by activating or inhibiting intracellular signaling, cellular activation, proliferation, and cytokine production.<sup>27,39,40</sup> IVIg selectively upregulates the inhibitory FcγRIIB, a negative regulator of lymphoid cell activation, inhibiting phagocytosis and cytokine production and intercepting antibody-dependent cell-mediated cytotoxicity.<sup>39-41</sup> Patients with CIDP have lower than normal FcγRIIB expression on naïve B cells and monocytes but, after IVIG, the FcγRIIB expression is upregulated, coinciding with clinical improvement.<sup>27,39,41,42</sup> This important effect, that also predicts response to IVIG in CIDP,<sup>39</sup> is not applicable to IgG4-ND because IgG4 antibodies cannot bind to inhibitory FcγRIIB receptor, as mentioned earlier (#4, Figure).
5. Suppression of pathogenic cytokines and immunoinflammatory molecules. IVIg effectively suppresses proinflammatory cytokines,<sup>27,28,41</sup> but such cytokines are irrelevant in IgG4-ND because of the overall anti-inflammatory effects of IgG4 that cannot recruit immune cells via Fc receptors or induce phagocytosis and trigger tissue inflammation (#5, Figure).

## Rituximab Is the Preferred Treatment in IgG4-ND

The expansion of activated B cells that correlate strongly with disease activity, the evidence of a pathogenic role for self-reactive B cells, and the clinical efficacy of B cell-depletion therapies<sup>1-3</sup> strongly support rituximab as the treatment of choice. Rituximab, a chimeric monoclonal antibody against CD20, a 297 AA membrane-associated phosphoprotein present on all B cells, except stem cells, pro-B cells, and plasma cells, depletes circulating B cells but not bone marrow and lymph node B cells.<sup>43</sup> Immunoglobulins are produced by long-lived plasma cells, but IgG4 are likely produced by CD20-positive short-lived plasma cells under the influence of IL-4 and IL-21.<sup>44</sup> Rituximab eliminates B cells before they differentiate into plasma cells having no effect on non-CD20-expressing plasma cells; it reduces, however, IgG4 levels by targeting IgG4-producing CD20-positive short-lived plasma cells and their related CD20<sup>+</sup> precursors, resulting in steep decline of plasmablast counts.<sup>45</sup> In several nonrandomized trials in IgG4-RD, rituximab rapidly reduced serum IgG4 levels compared with serum IgG1.<sup>1-3</sup>

In IgG4-ND, the success of rituximab is also impressive. In MuSK-MG, in a multicenter, blinded, prospective review, 58% (14/24) rituximab-receiving patients reached the primary outcome compared with 16% (5/31) of controls ( $p = 0.002$ ), after a median follow-up of 3.5 years; furthermore, 29% of rituximab-treated patients required a mean-prednisone dose of 4.5 mg/d compared with 13 mg/d required by 74% of controls ( $p = 0.005$ ).<sup>46</sup> IgG4-MuSK antibodies were markedly reduced 2–7 months after rituximab, being even undetectable within 2 years coinciding with clinical remission and sustained improvement for several years<sup>47,48</sup>; in 1 patient who did not respond, MuSK-IgG4 antibodies remained unchanged, supporting the view that short-lived antibody-secreting CD20<sup>+</sup> cells are the main producers of MuSK antibodies.<sup>47</sup>

In neurofascin-155 and CASPR1/CNTN1 CIDP, the evidence of IVIg unresponsiveness is overwhelming with less than 10% partially and transiently responding to IVIg but more than 80% responding to rituximab, as confirmed in a recent large patient collection.<sup>25</sup> Similar is the experience in LGI1 and CASPR2-associated encephalitis, where in a large series the patients with worse outcome were those more frequently treated with both IVIg and steroids; however, the noted increased LGI1-specific plasmablasts/plasma cells in these patients' CSF fully justifies anti-CD19-specific immunotherapies.<sup>49</sup>

### Rituximab Maintenance

In IgG4-RD, the risk of relapse tended to be lower with rituximab maintenance, compared with 1 rituximab induction therapy with elevated serum IgG4 considered a risk factor for relapse.<sup>1,3,50</sup> The value of circulating IgG4 as a biomarker in IgG4-RD is however unclear because IgG4 alone can non-specifically increase in chronic immune activation.<sup>1</sup> The IgG4

levels also seem irrelevant in IgG4-ND; in 39 patients with CIDP, including several with IgG4-nodal antibodies, the IgG4 concentration was normal (<1,350 mg/L, the limit for active IgG4-RD [Dalakas et al. unpublished observations]). In contrast, IgG4-ND antibody-specific titers seem to correlate with disease activity as shown in MuSK-MG<sup>47</sup> but also in LGI1-encephalitis, where high CSF IgG4 titers strongly correlate with worse outcome.<sup>49</sup> The need for follow-up rituximab infusions remains still empirical. Some prefer a repeated infusion when clinical relapse occurs; others use 2 g every 6 months or 1 g every 3 months to ensure stability.<sup>43,47,48,51</sup> The most promising marker remains the re-emergence of CD27 + memory B cells<sup>43,52,53</sup>; in 1 study, no MG relapses occurred when the CD27 + memory B cells were below the therapeutic target, whereas their resurgence was associated with clinical relapses.<sup>52</sup> Because reduction of IgG4-MuSK antibodies coincides with clinical remission,<sup>47</sup> the value of follow-up antibody titers as a disease activity biomarker needs to be assessed in all IgG-4 ND, as discussed below, along with the reappearance of memory B cells and IgG4-producing CD20-positive short-lived plasma cells.

### Future Therapies in IgG4-ND

Some of the novel therapeutic approaches targeting B cells or CD4<sup>+</sup> CTLs, currently evaluated in IgG4-RD, are also applicable to IgG4-ND and include (1) anti-CD19/20 including rituximab, inebilizumab—now approved for NMO-SD<sup>54</sup>—and obexelimab (XmAb5871) all in phase-3 trials in IgG4-RD. Obexelimab, targeting CD19/FcγRIIB, is especially promising because it binds simultaneously to CD19 and FcγRIIB, promoting internalization of CD19 in the lipid rafts<sup>55</sup>; obexelimab markedly enhances the inhibitory FcγRIIB and downregulates CD19, both effects tailored to IgG-4-ND by also activating FcγRIIB receptor; (2) dupilumab against IL-4Ra; (3) zanubrutinib and rilzabrutinib, both oral and well tolerated Bruton's tyrosine kinase inhibitors, now in phase 2 trials in pemphigus vulgaris and multiple sclerosis<sup>1,56</sup> Because Bruton tyrosine kinase is an enzyme expressed on B lymphocytes and myeloid cells, its irreversible inhibition by these agents suppresses B cell activation, relevant to IgG4-ND; and (4) elotuzumab, a monoclonal anti-SLAMF7 antibody ready to begin<sup>1</sup>; elotuzumab is a rational therapy for IgG-4 diseases because targets key cellular interactions between activated B cell subsets, plasmablasts, and CD4<sup>+</sup> CTLs that all express SLAMF7.<sup>1</sup>

### Conclusions on the Clinical Importance of IgG4-ND, the Functions of IgG4 as Related to Immunotherapies, and the Potential Role of IgG4-Antibody Titers as Disease Biomarkers

The purpose of this article is to increase awareness and highlight the progress made in our understanding of the unique function of IgG4-antibodies and their associations with specific neurologic diseases which, in contrast to their IgG1 counterparts, have a more severe clinical phenotype and distinct response to immunotherapies. Unlike the other IgG isotypes, the IgG4 antibodies do not activate cellular or

complement-mediated immune responses, which are directly targeted by IVIg and conventional immunotherapies, but they exert pathogenicity by blocking protein-protein interactions and signal transduction. As a result, IgG4-ND do not respond to IVIg like their IgG1 counterparts but respond impressively well to anti-B cell therapies which, if initiated early in the disease course, may ensure faster recovery preventing long-term disabilities. Importantly, there is convincing evidence that IgG-4 specific antibody titers are reduced in remissions and increased in exacerbations, having the potential to serve as reliable disease biomarkers not only in future controlled trials but also in current clinical practice. Because IgG4 antibody titers seem to correlate with the clinical status within the same patient,<sup>25</sup> it may serve as a monitoring tool not only in assessing disease activity and treatment response but also in guiding the need for the next anti-B cell infusion therapy. In some patients, IgG4 antibody titers decrease more than 90% or even become negative after rituximab, as noted in MuSK-MG<sup>47</sup> and in some autoimmune nodopathy patients,<sup>25</sup> suggesting that antibody reappearance or significant titer increase may precede a relapse and guide the need for retreatment. If proven in controlled studies that IgG4 antibody titers are a solid biomarker for long-term therapy, it will be a remarkably novel observation in autoimmune neurotherapeutics. Currently, in IgG-1 antibody-mediated chronic autoimmune neurologic diseases, antibody titers are not reliable biomarkers, as observed with anti-MAG and antiganglioside antibodies in neuropathies,<sup>53</sup> anti-AChR antibodies in MG, anti-HMGCR or SRP antibodies in inflammatory myopathies, or anti-GAD antibodies in stiff-person syndrome<sup>57</sup>; even anti-MOG and AQP-4 antibodies, although helpful, are not consistent predictors of disease relapse.

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## Appendix Author

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