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INVITED REVIEW

Anti–myelin-associated glycoprotein neuropathy: Where do we stand?

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Abstract

Myelin-associated glycoprotein (MAG) is a transmembrane glycoprotein concentrated in periaxonal Schwann cell and oligodendroglial membranes of myelin sheaths that serves as an antigen for immunoglobulin M (IgM) monoclonal antibodies. Individuals who harbor anti-MAG antibodies classically develop a progressive autoimmune peripheral neuropathy characterized clinically by ataxia, distal sensory loss, and gait instability, and electrophysiologically by distally accentuated conduction velocity slowing. Although off-label immunotherapy is common, there are currently no proven effective disease-modifying therapeutics, and most patients experience slow accumulation of disability over years and decades. The typically slowly progressive nature of this neuropathy presents unique challenges when trying to find effective anti-MAG therapeutic agents. Drug development has also been hampered by the lack of validated outcome measures that can detect clinically meaningful changes in a reasonable amount of time as well as by the lack of disease activity biomarkers. In this invited review, we provide an update on the state of clinicometric outcome measures and disease activity biomarkers in anti-MAG neuropathy. We highlight the insensitivity of widely used existing clinicometric outcome measures such as the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score as well as the INCAT sensory subscore in anti-MAG neuropathy, referencing the two previous negative randomized controlled clinical trials evaluating rituximab. We then discuss newly emerging candidate therapeutic agents, including tyrosine kinase inhibitors and enhanced B-cell–depleting agents, among others. We conclude with a practical approach to the evaluation and management of anti-MAG neuropathy patients.

KEYWORDS
anti-MAG neuropathy, biomarker, immunotherapy, outcome measure, rituximab

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BAFF, B-cell–activating factors; BCL-2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; BTU, Buhlmann titer units; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; ELISA, enzyme-linked immunosorbent assay; HNK-1, human natural killer-1; IgM, immunoglobulin M; IL-6, interleukin-6; IL-10, interleukin-10; IMAGiNe, Immunoglobulin M (IgM)-Anti-myelin-associated-glycoprotein (MAG) Peripheral Neuropathy study; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; ISS, INCAT sensory score; IVIg, intravenous immunoglobulin; MAG, myelin-associated glycoprotein; NLF, neurofilament light chain; NPSI, neuropathic pain symptom inventory; ONLS, Overall Neuropathy Limitations Scale; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-spike, and skin changes; SGPG, sulfate-3-glucuronyl paragloboside; WM, Waldenstrom macroglobulinemia.

1 | INTRODUCTION

Anti–myelin-associated glycoprotein (MAG) neuropathy is a rare acquired immune-mediated demyelinating polyneuropathy with a prevalence of 1 per 100 000.[1,2] Symptoms typically begin in the sixth or seventh decade of life, most commonly affecting men, with a male:female ratio of nearly 3:1.[3] Most patients develop a distal, sensory-predominant, ataxic neuropathy that evolves slowly over years. Although weakness may be absent early, many eventually develop motor dysfunction in the distal lower limbs. On examination, muscle stretch reflexes are invariably absent at the ankles, and usually absent or attenuated in more proximal areas.[4]

MAG is a transmembrane glycoprotein that plays a key role during myelin sheath formation and maintenance.[5] Pathogenic immunoglobulin M (IgM) monoclonal antibodies target the MAG protein, which leads to the characteristic histopathological findings that include widely spaced myelin lamellae and deposits of IgM and complement on the myelin sheath. Electrophysiological studies tend to show abnormalities that are accentuated in the distal portions of peripheral nerves.[6,7] On nerve conduction studies, markedly prolonged distal motor distal latencies are commonly observed. Lesser degrees of motor nerve conduction velocity slowing are present in proximal nerve segments. Conduction block and temporal dispersion are usually absent.

Despite having a well-characterized pathogenic antibody, anti-MAG neuropathy still has no proven effective therapies.[8] Although antibody removal with plasma exchange has been reported to be beneficial in some anti-MAG patients,[9] including those with acute neurological deterioration and IgM flare,[10] these benefits are typically modest and temporary.[11,12] The literature on intravenous immunoglobulin (IVIg) is also mixed. One randomized, double-blind, crossover trial showed improvement after 4 weeks[13] and an open-label study demonstrated efficacy at 6 months,[12] whereas others showed only modest or no benefit from IVIg.[14,15] The use of cytotoxic agents (cyclophosphamide, fludarabine, chlorambucil) to reduce antibody synthesis may be beneficial in some patients, but there is a lack of clinical trial data supporting efficacy and these agents have substantial toxicity.[3] Of all therapies studied, rituximab (a monoclonal antibody to CD20) shows the greatest promise and is frequently used off label despite two negative randomized controlled trials.[16,17]

There is a need for clinicometric, biomarker, and therapeutic advances in anti-MAG neuropathy. It has been 35 years since anti-MAG neuropathy was first described,[18] yet its therapeutic landscape remains remarkably limited. In this review we aim to: (1) explore the status of anti-MAG clinicometrics and biomarkers; (2) present the existing evidence on anti-MAG treatment and identify candidate therapeutics that may be of interest in future trials; and (3) offer commentary on how biomarkers, outcome measures, and existing trial data may be adopted into current clinical practice.

2 | DIAGNOSIS AND NATURAL HISTORY

In the typical anti-MAG patient, disability begins insidiously and slowly, but it progressively accumulates over time. About 80% of patients manifest a distal sensory-predominant neuropathy with functional impairment and disability developing secondary to hand tremor and gait ataxia. In one retrospective study of anti-MAG neuropathy patients, 24% were considered disabled at 10 years and 50% at 15 years.[11] Ten- and 15-year mortality figures from the same study were 6% and 33%, respectively. An anti-MAG antibody titer cutoff of 7500 Buhlmann titer units (BTU) is generally considered diagnostic in the proper clinical context.[19] Electrodiagnostic features supportive of anti-MAG neuropathy consist of a distally predominant demyelinating polyneuropathy, with disproportionate distal latency prolongation relative to conduction velocity slowing, manifest in the form of a terminal latency index of less than 0.26.[7] The preferential distal demyelinative electrodiagnostic pattern of anti-MAG neuropathy has been corroborated on autopsy findings of an anti-MAG neuropathy patient showing preferential distal nerve involvement.[20] A minority of patients with elevated MAG antibodies present with chronic sensorimotor polyradiculoneuropathy, small-fiber neuropathy, rapidly progressive proximal and distal weakness,[21] or multifocal neuropathy.[12] A causal relationship between the MAG antibody and the neuropathy is not certain in these atypical cases, especially when the anti-MAG titer is less than 10 000 BTU.

3 | OUTCOME MEASURES AND CLINICOMETRICS

No validated outcome measures exist for anti-MAG neuropathy. Numerous clinicometric outcome measures have been used in anti-MAG neuropathy clinical trials, with some proving more valuable than others (Table S1).[8] Nearly all measures, however, suffer from problems of sensitivity and/or lack of clinical meaningfulness. In the two largest anti-MAG trials, both of which explored the efficacy of rituximab, the lower limb portion of the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score[16] or the INCAT sensory sum score[17] was used as the primary outcome measures. Although the INCAT disability score is a validated outcome measure in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), it lacks sensitivity as a tool to capture clinically meaningful changes in anti-MAG neuropathy.[16,22] The INCAT sensory sum score also proved to lack sensitivity and was found to correlate poorly with quality of life.[22,23] The absence of an outcome measure that can reliably detect small but meaningful changes over a relatively short period of time was a limitation of both rituximab trials and may be one reason why neither trial showed treatment efficacy. Inflammatory Rasch-built Overall Disability Scale (I-RODS) is a disability scale that was developed specifically for patients with inflammatory neuropathy. I-RODS correlates well with quality of life[23] and may be an alternative to INCAT for anti-MAG neuropathy, but it needs further longitudinal data to understand the sensitivity and specificity to detect clinical change over time.

Considering the frequency with which anti-MAG neuropathy affects gait and balance, an ambulation assessment may be well suited to capture changes in clinical status. A 2018 study from Italy showed the 6-minute walk distance test to be the most reliable predictor of the physical component of overall function.[24] Both earlier rituximab

randomized clinical trials collected 10-meter walk time as a secondary outcome measure. Although one study showed statistically significant improvements in walk time for rituximab-treated patients,[16] these findings were not reproduced in the second study.[17] Nonetheless, it was notable that the 10-meter timed walk assessment may be able to capture gait balance, walking speed, and likelihood of fall in a way the INCAT (and probably also I-RODS) disability assessment cannot.[16]

Other outcome measures that have been employed in clinical trials include the Medical Research Council (MRC) sum score, neuropathy impairment score, ataxia score, and visual analog scale for pain. Not surprisingly, the MRC score correlates poorly with quality of life in anti-MAG neuropathy.[23] Pain, as captured via the neuropathic pain symptom inventory (NPSI), correlates with the physical component score of the 36-item Short-Form Quality-of-Life questionnaire, but is too nonspecific to have a prominent role in treatment trials.[23] With regard to ataxia, a subjective ataxia rating score (0 = normal, 1 = slight oscillations, 2 = marked oscillations, 3 = severe ataxia) was assessed in one of the rituximab trials.[17] Although difficult to quantify, considering that ataxia and tremor correlate with quality of life,[23] demonstrating improvement is an important goal of treatment. In the clinical trial, treatment with rituximab did not result in improvement in the group of patients with moderate or severe ataxia when compared with the placebo group.

Although clearly important during the anti-MAG diagnostic process, the roles of electrodiagnosis and neuroimaging as outcome measures in clinical trials or as tools to follow disease progression during clinical practice are less certain. Case series[9] and clinical trials[16] have failed to demonstrate clinically meaningful changes on nerve conduction studies. Ultrasonographic and magnetic resonance imaging data are even more limited. One ultrasonography study of eight anti-MAG neuropathy patients showed that all those with nerve hypertrophy were refractory to rituximab therapy.[25] A separate study of 28 anti-MAG neuropathy subjects showed no correlation between ultrasonographic findings (echotexture, nerve cross-sectional area, and intra- and internerve cross-sectional area variability) and INCAT disability score or disease duration.[26]

The ongoing Immunoglobulin M (IgM) Anti-myelin-associated-glycoprotein (MAG) Peripheral Neuropathy (IMAGiNe) study is a prospective, international, collaborative registry that aims to fill these clinicometric needs by identifying the best outcome measures in anti-MAG neuropathy.[5,27] As of 2022, 236 subjects from Europe and the United States were enrolled. Among the objectives of IMAGiNe are to improve outcome measures that can capture impairment, activity and participation, and quality of life in both clinical trials and day-to-day clinical practice, and to understand the minimum clinically important difference (MCID) of each outcome for anti-MAG patients. The study is currently enrolling participants.[27]

4 | IS SERIAL ANTI-MAG TITER TESTING A USEFUL DISEASE ACTIVITY BIOMARKER?

Pathologically, anti-MAG neuropathy involves the overproduction of pathogenic IgM antibodies that target the human natural killer 1 (HNK1) epitope on the MAG protein (and to a lesser extent the sulfate-3-glucuronyl paragloboside [SGPG] protein), leading to "unzipping" or detachment of the terminal myelin loop from the node of Ranvier. The evidence is strong in support of a causal pathogenic role of anti-MAG antibodies. Patients that harbor the anti-MAG antibody show IgM and complement depositions that colocalize with MAG on the characteristically widened myelin lamellae seen on electron microscopy,[4,22,28] and experiments using serum from diseased individuals recapitulate characteristic electrophysiological and histopathological changes when transferred to a healthy animal, similar to what is observed in the pathological human state.[29,30] Duration of exposure to the MAG complex also appears to contribute to irreversible demyelination and resultant axonal injury, which may in turn impact therapeutic responsiveness to agents such as rituximab.[31]

The most common commercial assay to detect anti-MAG antibodies is the anti-MAG IgM enzyme-linked immunosorbent assay (ELISA) from Buhlmann (Schönenbuch, Switzerland), with results expressed as Buhlmann titer units (BTU). Although Buhlmann testing allows for enhanced quantitated intra- and interpatient comparisons, it is criticized for its lack of clearly defined cutoffs.[32] With the generally utilized MAG antibody titer threshold of over 1000 BTU, one group demonstrated frequent false positive results among patients with CIDP, and an overall specificity of only 94%. Proposed cutoffs of 1500 BTU[33] or 7500 BTU have better specificity.[19] Interpretation of the result in clinical practice should consider the pretest probability of the patient, keeping in mind that not all "abnormal" anti-MAG results by Buhlmann testing are diagnostic of anti-MAG neuropathy if the characteristic clinical features are absent. "Atypical" phenotypes have been reported in 17% of patients with elevated anti-MAG titers, including those with acute or chronic sensorimotor polyneuropathies and multifocal neuropathies. Others have reported a "CIDP-like" phenotype in a third of patients. Unlike the typical anti-MAG presentations, these CIDP-like patients have proximal segment slowing on nerve conduction studies, no widened lamellae on nerve biopsy, and generally low-level anti-MAG titers.[21] Although pathogenicity of the anti-MAG antibody in the typical distally accentuated phenotype is well established, the degree to which the same can be said for "atypical" patients with elevated anti-MAG titer is unknown.

Although the diagnostic value of MAG antibodies in the appropriate clinical context is well established, its value as an outcome measure of disease activity or treatment response is uncertain.[32] Individual clinical trial data have shown inconsistent correlations between MAG titers and treatment response. This observation is difficult to reconcile. If one accepts that anti-MAG antibodies are indeed pathogenic and that higher titers more consistently correlate with the typical anti-MAG phenotype, then it would follow that lowering of the antibody level would correlate with treatment response. In contradistinction to the several individual trials that failed to show titer–clinical correlations, a meta-analysis of 50 anti-MAG clinical trials showed a strong association between anti-MAG IgM antibody reduction and clinical improvement.[34] Overall, treatment responders showed a 57.5% decline in MAG titer compared with only a 11.3% reduction in the nonresponding group. Also demonstrated was a titer/response

gradient where a 50% reduction was appreciated in 77.7% of responding patients. In nonresponding patients, only 6% of patients showed reductions of 20% or more, and in patients with acute deteriorations an increase of 204% titer by was observed. In addition, higher baseline MAG titer has been shown by some,[12] but not all,[35] to predict a favorable therapeutic response.

These findings have major implications for clinical practice and clinical trials. First, although the low-level cutoff for anti-MAG is controversial, evidence is mounting that higher levels are more likely to be diagnostic and pathogenic than lower levels. Second, phenotype matters. Patients with the clinical and electrophysiological characteristics of CIDP may be more appropriately classified (and treated) as CIDP, especially in the context of low-level anti-MAG antibodies. Third, although the value of indiscriminately following anti-MAG titers is uncertain, in patients with well-defined clinical characteristics and unequivocal titer elevations, serial anti-MAG monitoring may be a helpful biomarker of treatment response (provided testing methods are consistent), with a target reduction in anti-MAG level of 50%. Fourth, expectations for changes in anti-MAG antibody levels as a treatment response indicator should be balanced. Even if the titer correlates with disease activity, patients with long-standing disease and extensive axonal damage may not improve, even if disease activity is attenuated.

5 | WHAT OTHER BIOMARKERS HAVE BEEN EXPLORED IN ANTI-MAG NEUROPATHY?

Unlike anti-MAG levels that are expressed as a titer, monoclonal IgM paraprotein levels are measured as an absolute amount and typically recorded in grams per liter. Although this property may make it a more attractive surrogate for hematological response, it is a less direct assessment of changes in the pathogenic anti-MAG antibody. Most studies have demonstrated total serum IgM changes that correlate with therapeutic response and parallel anti-MAG titers. The 2009 rituximab trial,[16] the lenalidomide trial (NCT03701711), and the tyrosine kinase inhibition study[36] showed consistent reductions in total IgM levels relative to pretreatment status. Similar to anti-MAG reduction, posttreatment total IgM reductions of 52.3% were observed in patients who responded to treatment, compared with a 26.8% increase in the nonresponder group.[34] Nevertheless, the specificity of total IgM level as a therapeutic biomarker for anti-MAG neuropathy remains to be further elucidated.

Antibodies reactive to MAG also recognize the glycolipid SGPG. Although MAG is restricted to periaxonal Schwann-cell membranes, SGPG is widely distributed in myelin, axolemma, and neural endothelial cells. Because of the anti-MAG and SGPG cross-reactivity, an assay using SGPG (instead of MAG) has been proposed.[37] Considering that IgM monoclonal anti-MAG antibody binding to MAG is 10 to 100 times stronger than to the SGPG antigen, it is preferable to use MAG as the target antigen. Not only can low-affinity anti-MAG antibodies be missed if SGPG is used, but SGPG positivity with a negative MAG antibody has poor sensitivity. SGPG antibodies have been recognized in the context of other neuropathic conditions, including multifocal motor neuropathy and motor neuron disease.[38,39]

The antigenic region of MAG is an epitope called HNK1. In classic MAG testing, the ELISA evaluates the entire MAG protein, but anti-HNK1 antibody testing involves selective targeting of the HNK1 epitope (Table 1). HNK1 antibody testing demonstrates good sensitivity (98%) and specificity (99%), but it is not currently available commercially. Unlike anti-MAG titers, in one study HNK1 correlated with sensory deficits (INCAT sensory sum score), disability (I-RODS score and Overall Neuropathy Limitations Scale [ONLS]), and treatment response (decreased after rituximab therapy).[40] These results require confirmation before they can be adopted in clinical trials and in clinical practice.

B-cell–activating factors (BAFF) are cytokines that support B-cell survival and differentiation and, by doing so, play a role in innate and adaptive immune responses. Although not a reflection of nerve tissue status per se, BAFF may give prognostic insight into the likelihood of a positive treatment response in anti-MAG patients.[41] Patients with lower pre-rituximab BAFF levels have shown a greater likelihood to improve after rituximab, especially when the BAFF concentration increases 1 month after treatment. The observation that return of BAFF to pretreatment levels heralds clinical relapse also supports the potential role of BAFF as a treatment response biomarker and predictor of relapse. Other B-cell–stimulating cytokines that are elevated in anti-MAG neuropathy include interleukin-6 (IL-6) and interleukin-10 (IL-10).[42] The role that IL-6, IL-10, and BAFF play in the interchange between anti-MAG producing B cells and active T cells remains to be fully understood but may provide new opportunities to identify and follow treatment response and predict patients at risk for relapse.

Neurofilament light chain (NFL), a neuronal cytoplasmic protein highly expressed in myelinated axons, has been shown to reflect axonal injury in a number of central and peripheral nervous system disorders. In one study of 24 treatment-naive anti-MAG patients, serum NFL levels were similar to those of non-neuropathy controls.[43] Levels of contactin-1 protein, a potential marker of paranodal damage, were also similar to those of control patients. The findings suggest that NFL and contactin-1 protein may not be useful disease activity biomarkers in anti-MAG neuropathy. The authors of that study also measured complement activation products. Histopathological studies demonstrated complement components C3d and C5 within myelin sheets, suggesting that demyelination after anti-MAG binding is complement mediated. Despite evidence supporting the role of complement activation, in the study of 24 treatment-naive anti-MAG patients, complement activation components C3 b/c and C4 b/c were usually within normal ranges and not different from those of control patients. Although further studies with larger numbers of patients and greater diversity of disease durations and severity are needed, measurement of complement components currently does not appear to provide useful disease activity or prognostic information.

The *MYD88* gene mediates tumor-cell survival through activation of Bruton tyrosine kinase (BTK) and enhanced B-cell signaling.[44] *CXCR4* is a gene that activates signaling pathways responsible for cell

TABLE 1 Role of select biomarkers in anti-MAG neuropathy

Biomarker	Diagnostic role	Prognostic role	Outcome measure role	Phenotypic role
IgM	50% of IgM neuropathy patients do not have MAG antibodies	IgM titer is greater in WM than IgM MGUS, but WM patients do not necessarily have more axon loss[61]	77% of responders show paraprotein IgM titer reduction of >50% 93.3% of nonresponders show <20% reduction in IgM paraprotein[34]	IgM presents with a distal acquired (typically) demyelinating, even in absence of MAG antibodies[62]
MAG (ELISA)	Titer >1000 BTU has high sensitivity (100%) but undesirable specificity (94%)[19] Titer >7000 BTU has best specificity (100%), with sensitivity of 92.5%	No association between MAG titer and disease severity,[12] but higher baseline MAG titer >10 000 BTU correlates with favorable response (mRS or ONLS) to rituximab	77% of responders show MAG titer reduction of >50% 90% of nonresponders show reductions <20%[34]	Distally accentuated demyelinating polyneuropathy[62]
HNK-1 (EIA)	Sensitivity = 98%, specificity = 99%[40]	Unknown	Titer correlates with INCAT sensory subscore, I-RODS, and ONLS Titer does not correlate with anti-MAG antibody titer Titer decreases after rituximab therapy (*preliminary finding*)[40]	MAG + HNK1 antibody positive = distal demyelinating MAG neuropathy phenotype MAG + PNM antibody positive = axonal MAG neuropathy phenotype MAG antibody-positive alone = CIDP phenotype[63]
BAFF (ELISA)	Unknown	BAFF baseline titer highest in nonresponders to rituximab (cutoff 1665 pg/mL; sensitivity 71.4%; specificity 93.7%; likelihood ratio 11.4)[41]	Relapses occur in responders when BAFF levels return to baseline values	Unknown

Abbreviations: BAFF, B-cell activating factor; BTU, Buhlmann titer unit; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EIA, enzyme immunosorbent assay; ELISA, enzyme-linked immunosorbent assay; HNK-1, human natural killer-1; IgM, immunoglobulin M; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MAG, myelin-associated glycoprotein; mRS, modified Rankin scale; ONLS, Overall Neuropathy Limitations Scale; PNM, peripheral nerve myelin.

growth and proliferation. Up to 60% of patients with anti-MAG neuropathy and 90% of Waldenstrom macroglobulinemia (WM) carry a somatic point mutation in *MYD88*^{L265P}.[44,45] Mutations in *CXCR4* are present in 10% of MAG neuropathy and 25% to 50% of WM patients, and portend a more severe disease and poorer prognosis.[45] The combined presence of an *MYD88* and *CXCR4* mutation may provide some predictive value to novel therapeutic interventions such as tyrosine kinase inhibition.[46] Although genetic testing is not currently standard clinical practice for anti-MAG neuropathy patients, *MYD88* testing is recommended for those with WM,[47] and *CXCR4* testing may have prognostic value for those being considered for tyrosine kinase inhibition therapy.

6 | LESSONS LEARNED FROM THE 2009 AND 2013 RITUXIMAB RANDOMIZED CONTROLLED TRIALS

Despite failing to fulfill primary outcome measures, both the 2009[16] and 2013[17] randomized controlled trials of rituximab in anti-MAG neuropathy represent pivotal advances in anti-MAG neuropathy clinical trial research (Table 2). In the 2009 study conducted by Dalakas and colleagues, the intention-to-treat analysis did not reach significance ($P = .096$). However, it was noted that the mean baseline INCAT score in the placebo and treatment groups was 1.45 and 1.46, respectively, and one patient in the treatment group was incorrectly classified with a score of 1 at entry when the actual value was 0. At 8 months, the treatment group improved to 1.0 and the placebo group had a modest worsening to 1.54. When the patient with a normal INCAT score at entry was excluded from the analysis, the difference between the placebo and rituximab groups was significant ($P = .036$). Changes in 10-meter walk results also showed statistically significant changes (favoring the rituximab group), whereas no such statistical significance was observed for MRC sum scores, sensory sum scores, or nerve conduction studies.

In the 2013 study conducted by Leger and colleagues, the absolute change in INCAT sensory score (ISS) was essentially identical in both groups at 12 months. Although patients in the treatment group more often had INCAT disability score improvements of more than 1 point, the overall change in INCAT disability score was the same, and, unlike the 2008 study, there were no group differences in 10-meter walk scores.

What lessons were learned from these two anti-MAG neuropathy trials of rituximab? Considering that the natural history of anti-MAG

TABLE 2 Select outcome measures from the 2009 and 2013 randomized controlled clinical trials of rituximab in anti-MAG neuropathy

	Dalakas, 2009 [over 8 months][16]		RiMAG, 2013 [over 12 months][17]	
	Treatment (N = 13), 4 weekly infusions of 375 mg/m^2 rituximab	Placebo (N = 13)	Treatment (N = 26), 4 weekly infusions of 375 mg/m^2 rituximab	Placebo (N = 28)
INCAT, mean change (points)	(*Leg score only*) Improved[a] 0.46 (1.46→1.00)	(*Leg score only*) Worsened[a] 0.09 (1.45→1.54)	(*Total score*) No change (3.0→3.0)	(*Total score*) No change (3.0→3.0)
INCAT sensory subscore, mean change (points)	NA	NA	Improved[a] 1.0	Improved[a] 1.0
Timed 10-m walk, mean change (seconds)	Improved 0.9 (8.3→7.4)	Improved 0.2 (9.5→9.3)	Improved 0.1	Improved 0.3
Total IgM, mean change (mg/dL)	Decreased 254.4 (599→344.6)	Increased 33 (698.5→731.2)	NA	NA
MAG titer, mean change (units or g/L)	Decreased 21.4 units (38.8→17.4)	Increased 11.8 units (31.7→43.5)	Decreased 13 700 g/L	No change

Abbreviations: INCAT, Inflammatory Neuropathy Cause and Treatment; MAG, myelin-associated glycoprotein; RiMAG, Randomized Trial of Rituximab Versus Placebo in Polyneuropathy Associated with Anti-MAG IgM Monoclonal Gammopathy.
[a]Primary outcome.

neuropathy is typically slow progression and that short disease duration and preservation of nerve fiber density portend a favorable outcome after treatment,[31] inclusion of patients with intermediate ranges of disability, shorter disease durations, and preserved axonal integrity may be ideal as these patients are more likely to show improvement over a relatively short time of 6 to 12 months. These factors also speak to the importance of retreatment during the study period, as it provides patients with a longer window for clinical improvement to be possible. Neither of the rituximab clinical trials retreated patients after rituximab induction. Especially if the study population is too mild or too severe, there may be minimal opportunity for treatment groups to separate from placebo when benefit is assessed at 8 or 12 months after one rituximab induction course, even if there is some protective benefit that is difficult to prove.

The previous anti-MAG trial experience may be informative when considering future study design. Anti-MAG clinical trials may benefit from: (1) more sensitive outcome measures that include a quantitative gait assessment component; (2) inclusion of patients with greater than mild disease severity; and (3) exclusion of patients with long-standing disease or severe axonal loss. It is also desirable to have a sustained period of immunotherapy that adequately achieves a biological effect that is long enough for nerve regeneration and clinical improvement to occur, or long enough for disability accumulation as part of the natural untreated history of the disease to diverge from stable disease in treated patients. One cycle of rituximab with outcomes collected at 1 year may be insufficient to capture improvement in treated patients or worsening in placebo patients. For rheumatological diseases such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis[48] and rheumatoid arthritis,[49] repeat rituximab dosing at month 6 is generally advised as part of the treatment schedule. Some physicians advocate repeat dosing at month 6 for anti-MAG neuropathy only in the setting of clinical relapse,[50] but it may be more appropriate to retreat at month 6, regardless of clinical status, and to ascertain clinical responsiveness at month 12.

7 | CURRENT STATE OF IMMUNOTHERAPEUTIC RESEARCH

There is a dearth of data that support immunotherapy intervention for anti-MAG neuropathy. Even so, and despite two randomized controlled trials failing to meet primary endpoints,[16,17] rituximab remains the preferred treatment option for many practitioners. Uncontrolled study findings suggest that 30% to 50% of patients may experience some benefit, and it has also been suggested that the rituximab trials failed to capture benefit because the primary endpoints and method of rituximab administration (no retreatment) limited the sensitivity to detect benefit. An ongoing randomized clinical trial (not yet recruiting) in France (THERAMAG) seeks to re-evaluate the efficacy of rituximab in an enriched population of anti-MAG neuropathy patients with favorable treatment response characteristics, namely those with less than 2-year disease duration and with MAG titers of over 10 000 BTU (NCT05136976). Unlike the earlier rituximab trials, which used the INCAT disability score and INCAT sensory sum score as the primary outcome measures, the THERAMAG trial selected the I-RODS disability score as the primary efficacy determinant. Although selection of an enriched group of patients enhances the likelihood of detecting a treatment response, as in previous studies, the primary outcome will be recorded at month 12 and rituximab is being administered only at study onset without mid-study retreatment. This study is anticipated to be completed at the end of 2025.

Ibrutinib, a tyrosine kinase inhibitor, has been used in WM patients with the *MYD88* mutation and wild-type *CXCR4*, with some of these patients also having anti-MAG neuropathy. Although not

designed to assess for neuropathic changes, in one prospective WM trial that included 9 patients with IgM-associated polyneuropathy (3 of whom also had anti-MAG antibodies), all reported either stable or improved neuropathy.[46] In a separate series of three patients with WM and anti-MAG antibody neuropathy (*MYD88*^{L265P} mutation and wild-type *CXCR4* gene), treatment with ibrutinib led to improvements in INCAT disability and ISS scores within 9 months of treatment.[36] A second-line tyrosine kinase inhibitor, acalabrutinib, more versatile in binding and capable of overcoming treatment resistance, is currently being explored in a phase 2 trial (ACALA-R, NCT05065554) aimed to identify the efficacy and safety of tyrosine inhibition with B-cell–depleting therapy (rituximab) in patients with IgM MGUS or WM-associated polyneuropathy. The primary outcome is hematologic response, defined as a reduction in serum IgM level of 25% by year 6 relative to baseline. Investigators will also look at the proportion of patients with improvement or stability in neuropathy as assessed by INCAT, ISS, I-RODS, and 10-meter timed walk test. MAGNAZ is another planned phase 2 trial aimed to address the BTK inhibitor zanubrutinib in anti-MAG neuropathy, with the primary endpoint being change from baseline in I-RODS compared with cycle 12.[51] Only patients with a MAG titer of over 10 000 BTU will be included. In addition, successful use of tirabrutinib, a third BTK inhibitor, has been demonstrated in a case of rituximab-refractory anti-MAG neuropathy.[52] No tirabrutinib trials are currently underway or planned.

A desirable and novel approach to anti-MAG neuropathy treatment is direct and targeted therapy against the pathogenic antibody. In animal models, glycopolymer therapy (PPSGG)[53] demonstrated selective binding and neutralization of anti-MAG IgM autoantibodies. Despite encouraging animal data, a phase 1/2a, first-in-human trial in anti-MAG patients was terminated early because the collected data did not support further development (NCT04568174) and also due to concerns about complement activation–related pseudoallergy.[54]

Lenalidomide is an agent that exhibits a number of immunomodulatory effects, including T-cell and natural killer–cell activation as well as inhibition of proinflammatory cytokines. It has been approved by the United States Food and Drug Administration for the treatment of multiple myeloma and has demonstrated efficacy in treating neuropathy in polyneuropathy, organomegaly, endocrinopathy, M-spike, and skin changes (POEMS) syndrome. A phase 1b dose-finding clinical trial in anti-MAG neuropathy was recently completed (NCT03701711).

There is interest in exploring next-generation B-cell–depleting therapies, as suggested by the mixed observations from the rituximab literature. Ofatumumab and obinituzumab are two candidate therapeutic agents. Both are humanized anti-CD20 monoclonal antibodies with a more powerful B-cell depletion capacity than rituximab.[55,56] In addition, one study showed clinical improvement in four of eight anti-MAG neuropathy patients receiving higher dose rituximab (750 mg/m^2) rather than the standard 375 mg/m^2.[57] This higher dose was well tolerated, improved electrodiagnostic parameters, and reduced anti-MAG antibody titers. However, no prospective clinical trials in anti-MAG neuropathy exploring more powerful B-cell–depleting agents or higher dose rituximab are currently enrolling participants. Successful anti-MAG neuropathy treatment has also been reported in a patient treated with venetoclax in combination with rituximab. Venetoclax is a B-cell lymphoma 2 (BCL-2) inhibitor that combats tumor-cell apoptotic resistance and cell proliferation and it may facilitate IgM and anti-MAG antibody attenuation, even in those who are *CXCR4*-positive and refractory to tyrosine kinase inhibition.[58,59] The role of complement in anti-MAG neuropathy remains to be fully elucidated, but does not appear, at present, to be the focus of therapeutic targeting.[59] Likewise, neonatal Fc receptor inhibition, which preferentially targets IgG disorders, does not appear likely to impact an IgM-mediated disease such as anti-MAG neuropathy. Preliminary phase 1 and phase 2 data with rozanolixizumab and RVT-1401 in myasthenia have shown no impact on IgM level.[60]

8 | MANAGEMENT OF ANTI-MAG NEUROPATHY IN CLINICAL PRACTICE

No definitive guideline exists on the optimal management of anti-MAG neuropathy, so treatment varies widely. Diagnostically, we encourage focused attention to the characteristic clinical and electrophysiological features, as well as a critical interpretation of the anti-MAG level. Patients who do not have a distally accentuated pattern of clinical and electrophysiological abnormalities may warrant diagnostic re-exploration, as do patients with low-level MAG titers (<7500 BTU). The combination of unusual clinical features and anti-MAG titers less than 7500 BTU should draw especially heightened diagnostic scrutiny. Considering the poor sensitivity and specificity of anti-SGPG antibodies, we do not use SGPG antibodies to make a diagnosis of anti-MAG neuropathy. We are careful to quantify IgM levels and encourage close interdisciplinary collaboration with hematology–oncology in all patients with IgM monoclonal gammopathy for WM or other plasma-cell dyscrasia surveillance. We also encourage supportive care with physical and occupational therapy for most patients with anti-MAG neuropathy as well as referrals to orthotics for gait and ambulation support devices as needed to improve functionality.

We quantify disability in all patients by collection of scores from the I-RODS disability scale. Although the INCAT disability scale may also be used, we prefer I-RODS as it appears to be more sensitive than INCAT to capture changes in functionality over time. Gait assessments that are feasible in a small clinical environment include a 10-meter walk test or timed-up-and-go assessment. To capture changes in sensation we prefer the INCAT sensory sum score, although vibration thresholds using a quantitative Rydel–Seiffer tuning fork may provide useful data as well. We have found these tools invaluable when assessing disability and impairment changes over time, a measure that may be helpful when determining the appropriateness of immunotherapy.

Patients with mild disease and minimal disability may be managed supportively without immunotherapy. The rituximab clinical trials tell us that, if there is benefit from rituximab, it is at most modest. For some patients the rewards (which may take 1 year or more to be appreciated) may not be worth the risk of long-term B-cell depletion. We typically evaluate disability and impairment in mildly affected

patients every 6 months. When disability becomes more than mild or is clearly progressive on disability, gait impairment, or motor impairment scores, then the risk/benefit calculus of immunotherapy may change. In such patients we favor rituximab as first-line immunotherapy, dosed as either 375 mg/m^2 × four weekly doses (one cycle) or as 1 g × two doses, 2 weeks apart (one cycle). We evaluate patients at 3 months and 6 months after the first rituximab infusions to assess for improvement, each time collecting I-RODS, grip strength, ISS, and gait scores. As was learned from the rituximab clinical trials, repeat dosing is likely important before determining benefit (or lack of benefit) after rituximab initiation. We typically repeat rituximab dosing at month 6 so that a more accurate efficacy determination can be made between months 9 and 12. Pending the patient's tolerability, side effects, and evidence of benefit, subsequent dosing beyond 12 months can be made in a more informed way. We believe that 12 months is an appropriate cutoff to ascertain rituximab responsiveness, provided retreatment occurs at month 6. If there is no conclusive evidence of benefit by month 12, then we discourage continued use of rituximab. Although the role of serial anti-MAG monitoring in individual patients is yet to be well defined, when reductions of 50% or more are appreciated in patients with stable or improved clinical outcomes we are reassured that the clinical observations can be attributed to a biological effect.

Considering the available data, we do not favor long-term management with plasma exchange or IVIg in most patients, although, in some patients, a short-term benefit may be appreciated. Cytotoxic agents (cyclophosphamide, fludarabine, chlorambucil) may potentially reduce antibody synthesis and may be considered for severely affected patients who fail to respond to rituximab and continue to worsen. However, use of such agents is limited by toxicity and poor-quality clinical data. Each has unproven efficacy and requires the risks to be carefully balanced against the unknown benefits. Although there is encouraging data emerging for newer therapeutics, including tyrosine kinase inhibitors, new-generation B-cell–depleting agents, and lenalidomide, outside of clinical trials we do not advise use of these interventions.

9 | CONCLUSIONS AND THE ROAD AHEAD

There is an urgent need for improved clinicometrics, biomarkers, and therapeutics in anti-MAG neuropathy. Clearly, tools with greater sensitivity and specificity are needed to follow disease progression in clinical practice and in clinic trials. The I-RODS disability scale may be a step forward, but improved tools that can more closely follow disability, sensory impairment, and gait dysfunction are needed. Biomarkers that supplement these outcome measures are also desirable. Anti-MAG antibody titers are unequivocally helpful for diagnosis, but they are less informative as a surrogate of disease activity in individual patients. Candidate biomarkers that may enhance our understanding of tissue status, immunological activity, or treatment response include anti-HNK1 antibody, BAFF, cytokine profiles, complement profiles, NFL, and *MYD88/CXCR4* genetic testing, but none are ready for routine clinical practice. From a treatment perspective, rituximab remains the treatment of choice for many with anti-MAG neuropathy, although it is reasonable to manage patients with mild and stable disease with supportive care alone. We are optimistic that the enriched THERAMAG study population can provide stronger evidence supporting the use of rituximab for anti-MAG neuropathy, but, based on the earlier rituximab studies, the response is likely to be modest even in the most favorable scenario. Next-generation B-cell–depleting therapeutic agents, tyrosine kinase inhibitors, and lenalidomide are of interest and warrant further study in clinical trials. The ongoing IMAGiNe study aims to fill many of these clinometric and biomarker unmet needs and, by doing so, we anticipate enhancing the way these promising therapeutic agents are studied in clinical trials and used in clinical practice.

AUTHOR CONTRIBUTIONS

Amro Maher Stino: Writing – original draft; writing – review and editing. **Bakri Elsheikh:** Supervision; writing – review and editing. **Jeffrey A. Allen:** Supervision; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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