



Anti-MAG neuropathy: historical aspects, clinical-pathological correlations, and considerations for future therapeutical trials

Neuropatia anti-MAG: aspectos históricos, correlações clínico-patológicas e considerações para ensaios terapêuticos futuros

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Abstract

Background Patients with anti-MAG neuropathy present with distal demyelinating polyneuropathy, IgM monoclonal gammopathy, and elevated titers of anti-MAG antibodies.

Objective This paper reviews what is known about the clinical presentation, course, pathophysiology, and treatment of anti-MAG neuropathy, with considerations for the design of therapeutic trials.

Methods A literature review of the medical and scientific literature related to anti-MAG neuropathy, and the design of therapeutic clinical trials in peripheral neuropathy.

Results Anti-MAG neuropathy can remain indolent for many years but then enter a progressive phase. Highly elevated antibody titers are diagnostic, but intermediate titers can also occur in chronic inflammatory demyelinating polyneuropathy (CIDP). The peripheral nerves can become inexcitable, thereby masking the demyelinating abnormalities. There is good evidence that the anti-MAG antibodies cause neuropathy. Reduction of the autoantibody concentration by agents that target B-cells was reported to result in clinical improvement in case series and uncontrolled trials, but not in controlled clinical trials, probably due to inadequate trial design.

Conclusion We propose that therapeutic trials for anti-MAG neuropathy include patients with the typical presentation, some degree of weakness, highly elevated anti-

Keywords

- ▶ Demyelinating Diseases
- ▶ Anti-MAG
- ▶ Neuropathy

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MAG antibody titers, and at least one nerve exhibiting demyelinating range abnormalities. Treatment with one or a combination of anti-B-cell agents would aim at reducing the autoantibody concentration by at least 60%. A trial duration of 2 years may be required to show efficacy. The neuropathy impairment score of the lower extremities (NIS-LL) plus the Lower Limb Function (LLF) score would be a suitable primary outcome measure.

Resumo

Antecedentes Pacientes com neuropatia anti-MAG apresentam polineuropatia desmielinizante distal, gamopatia monoclonal IgM e títulos elevados de anticorpos anti-MAG.

Objetivo Este artigo revisa o que se sabe sobre a apresentação clínica, curso, fisiopatologia e tratamento da neuropatia anti-MAG, com considerações para o desenho de ensaios terapêuticos.

Métodos Revisão bibliográfica da literatura médica e científica relacionada à neuropatia anti-MAG e desenho de ensaios clínicos terapêuticos em neuropatia periférica.

Resultados A neuropatia anti-MAG pode permanecer indolente durante muitos anos, mas depois entra numa fase progressiva. Títulos de anticorpos altamente elevados são diagnósticos, mas títulos intermediários também podem ocorrer na polineuropatia desmielinizante inflamatória crônica (CIDP). Os nervos periféricos podem tornar-se inexcitáveis, mascarando, assim, as anomalias desmielinizantes. Há boas evidências de que os anticorpos anti-MAG causam a neuropatia. Foi relatado que a redução da concentração de autoanticorpos por agentes direcionados às células B resultou em melhora clínica em séries de casos e ensaios não controlados, mas não em ensaios clínicos controlados, provavelmente devido ao desenho inadequado dos ensaios.

Conclusão Propomos que os ensaios terapêuticos para neuropatia anti-MAG incluam pacientes com apresentação típica, algum grau de fraqueza, títulos de anticorpos anti-MAG altamente elevados e pelo menos um nervo exibindo anormalidades na faixa desmielinizante. O tratamento com um ou uma combinação de agentes anticélulas B teria como objetivo reduzir a concentração de autoanticorpos em pelo menos 60%. Pode ser necessária uma duração de ensaio de 2 anos para demonstrar eficácia. A pontuação de comprometimento da neuropatia das extremidades inferiores (NIS-LL) mais a pontuação da função dos membros inferiores (LLF) seria uma medida de resultado primário adequada.

Palavras-chave

- ▶ Doenças Desmielinizantes
- ▶ Anti-MAG
- ▶ Neuropatia

INTRODUCTION

Historical aspects, epidemiology, and pathophysiology

The association of IgM monoclonal gammopathy with demyelinating neuropathy and anti-MAG antibodies was first reported by Latov and colleagues in 1980,¹⁻³ and subsequently confirmed by other investigators.⁴⁻⁶

The prevalence of anti-MAG neuropathy is estimated to be between 0.45 and 1.2 per 100,000, with the lower number based on a survey in Southern England,⁷ and the latter from epidemiologic studies reporting a prevalence of IgM monoclonal gammopathy of 51 per 100,000,⁸ with 5.4% of Waldenström's patients experiencing neuropathy,⁹ and approximately 50% of IgM proteins of patients with neuropathy exhibiting anti-MAG antibody activity.¹⁰ In a large study of 202 patients, the male-to-female

ratio was 1.9 to 1, with a mean age of symptom onset of 62.6 years (range 25-91).¹¹

There is considerable evidence that the neuropathy is caused by the monoclonal IgM anti-MAG antibodies.^{12,13} The target antigen, MAG, is a component of peripheral nerve myelin. Anti-MAG antibodies immunostain myelin.¹⁴ Sural nerve biopsies from affected patients show demyelination, widened myelin lamellae or unraveling of compact myelin at the minor dense line, and deposits of the monoclonal IgM and complement on the myelin sheaths, and in particular at the paranodes, Schmidt-Lanterman clefts, and widened myelin lamellae, consistent with the known distribution of MAG.¹⁵⁻¹⁸ Intraneural injection of anti-MAG antibodies induces demyelination in experimental nerves.¹⁹⁻²¹ Passive transfer of anti-MAG IgM into experimental chicks induced demyelination, widening of the myelin lamellae, with deposits of IgM concentrated at the nodes of Ranvier, and

Schmidt-Lanterman incisures, similar to that seen in affected human nerves.²² The demyelination in the intraneural injection studies was complement-dependent, but the role of complement in the passive transfer chick studies was not investigated. It is likely that anti-MAG antibodies exert their effects via both complement-dependent and independent mechanisms. Other factors, such as permeability of the blood-nerve barrier, cytokines, macrophage activation, or complement regulatory molecules such as CD59 may also play a role in the development of neuropathy.^{23–26} Such factors might explain the acute exacerbations that are sometimes seen following rituximab treatments, in the absence of an increase in antibody concentrations, presumably due to cytokine release,²⁷ or the transient improvement that can occur following therapy with IVIG.²⁸

Clinical presentation and course

Patients with MAG neuropathy typically present with a chronic and slowly progressive distal demyelinating neuropathy, beginning with distal paresthesias or large fiber sensory loss and ataxia that spreads proximally with weakness and sensory loss. In a large study of 202 patients, 83% presented with the typical phenotype, but 17% had atypical presentations that included acute or chronic sensorimotor polyradiculopathies, and asymmetric or multifocal neuropathies, and 30% had a tremor.¹¹ Magy and colleagues²⁹ reported that 28% of patients presented with distal paresthesias only, whereas 53% had some level of weakness. Other studies also reported weakness in approximately half of the patients.^{30,31} The tremor in anti-MAG neuropathy appears to be neurogenic,³² is often unrelated to the severity of the underlying neuropathy, and often non-responsive to treatment,³³ as has also been described in CIDP.³⁴

Atypical presentations can result from other properties of the monoclonal gammopathies. Amyloid deposition of the monoclonal light chains has been associated with painful, autonomic,³⁵ asymmetric,³⁶ or cranial neuropathies.³⁷ Cryoglobulin deposition of the M-protein can be associated with multifocal vasculitic neuropathy.^{38,39} Infiltration by B-cell lymphoma cells can be associated with mononeuritis multiplex.^{40,41}

The neuropathy can remain stable or be slowly progressive for many years, but then enter a more rapidly progressive course that can lead to disability, resulting from cumulative nerve damage with secondary axonal degeneration.^{42–45} The disability rate is 16% at 5 years, 24% after 10 years, and 50% after 15 years.⁴⁶ There is no correlation between antibody titers and the severity of the neuropathy, although increasing antibody titers are probably indicative of expansion of the monoclonal B-cell population.

In the study by Svahn and colleagues,¹¹ approximately 68% had monoclonal gammopathy of unknown significance (MGUS), 29% had Waldenström's macroglobulinemia, and 3% had chronic lymphocytic leukemia or B-CLL. Castellani and colleagues reported that 66.7% of 75 patients tested had a mutation in MYD88, more often in macroglobulinemia^{47,48} making them susceptible to treatment with Bruton tyrosine kinase inhibitors.

Serological studies

Anti-MAG antibodies are routinely tested for by Enzyme-Linked Immunosorbent Assays (ELISA).¹² The two most commonly used assays are 1) The Buhlmann assay (Buhlmann Laboratories AG, Switzerland), a commercially available kit that compares the binding of the tested sera to a standard curve, and 2) a dilutional endpoint assay the results of which are given as the highest dilution at which binding above background is observed. In general, highly elevated anti-MAG antibody titers are more likely to be specific or diagnostic than mild or intermediate elevations that are higher than normal, but not necessarily pathogenic. Normal titers are ≤ 800 in the dilutional endpoint assay and ≤ 1000 in the Buhlmann assay, but titers of $\geq 1:25,600$ in the dilutional endpoint assay⁴⁹ or $\geq 7,500$ to 10,000 in the Buhlmann assay, are more likely to be associated with typical MAG neuropathy.^{29,50} In patients with intermediate titers, the distinction from chronic inflammatory demyelinating polyneuropathy (CIDP) can be problematic given the overlapping clinical and electrophysiological features, and lack of a diagnostic test for CIDP,⁵¹ although the presence of IgM myelin deposits on sural nerve biopsy would be diagnostic of anti-MAG neuropathy.

For B-cell-depleting therapies, the change in serum IgM concentration can be used to monitor the antibody response as it generally parallels the change in the concentration of the anti-MAG IgM. The Buhlmann assay can also be used to follow antibody titers, but the sera would have to be tested on the same ELISA plate at the same time for comparison, due to potential differences between kits, test conditions, or standards. The dilutional endpoint assay is less sensitive to change, as it is exponential rather than linear, so that a change of at least 50% would be required to detect a change in titer.¹²

Electrodiagnostic studies

Electrophysiologic studies in anti-MAG neuropathy typically show demyelinating abnormalities, consistent with the known pathophysiology. Nerve conduction velocities can be severely slowed early on, including in patients with relatively mild clinical deficits, likely resulting from chronic subclinical disease activity. Disability is more closely correlated with a reduction of CMAP amplitudes indicative of axonal loss.⁴³ The lower limb motor and sensory potentials show a marked trend to become unexcitable over time,⁴⁵ so that the studies may not meet EFNS/PNS demyelinating criteria, with the percentage of patients meeting the criteria reported as ranging from 20.9 to 91%.^{29,30,42,45} In the study reporting 20.9% however, at least 1 nerve in all patients showed demyelinating range abnormalities.⁴² Distal accentuation of conduction velocity slowing has also been described in a variable number of patients.^{29,30,42,49,52–56}

Therapy

Therapy of anti-MAG neuropathy is directed at reducing the concentration of the monoclonal IgM autoantibody concentrations using chemotherapeutic agents, such as chlorambucil, cyclophosphamide, or fludarabine, or with rituximab, a therapeutic monoclonal antibody that targets CD20 on B-cells, with the latter being the preferred therapy, due to

the need for chronic treatment and cumulative toxicities of the chemotherapeutic agents.²⁸ More recently, treatment with the anti-Bruton's tyrosine kinase (BTK) agents ibrutinib⁵⁷ or tirabrutinib,⁵⁸ or with venetoclax, an anti-B-cell lymphoma-2 (BCL2) agent that promotes apoptosis,⁵⁹ have also been reported to be of benefit. A retrospective analysis of 50, mostly uncontrolled studies with 410 patients found that a relative reduction in the serum IgM anti-MAG antibody level is associated with a clinical response.⁶⁰ IgM MGUS and Waldenström's associated anti-MAG neuropathies displayed similar responses.⁶¹

A series of 25 patients treated with a combination of rituximab/cyclophosphamide/prednisolone every 21 days for 6 cycles showed improvement in the overall neurological limitations scale (ONLS), a derivation of the INCAT scale which improved from a median of 3 to 2 at year 1 and 2 to 1 at year 2. Among the patients with weakness, there was an improvement of 69% in the MRS sum scale. The ISS improved by 50%. Electrophysiologic studies showed improvement in the mean distal motor latency score and the sensory nerve action potential (SNAP) amplitude sum score.⁶²

Two placebo-controlled studies of IVIG in IgM-associated neuropathy did not meet their primary endpoint. In a placebo-controlled crossover study, 11 patients were randomized to 2gm/kg IVIG or placebo monthly for three months followed by the other treatment.⁶³ No significant differences were seen in the endpoints other than improved strength in 2 of 11 patients and an improved sensory score in one patient. In a double-blind crossover study, 22 patients (50% of whom had anti-MAG antibodies) were randomized to 2gm/kg IVIG or placebo followed by the other treatment. There was no difference between the two groups in the primary outcome of INCAT disability score at two weeks although there was improvement at four weeks (secondary outcome) in the IVIG group.⁶⁴ Two small controlled clinical trials of rituximab in anti-MAG neuropathy failed to show a therapeutic benefit,^{65,66} although a meta-analysis concluded that there is low-quality evidence of a benefit from this treatment.²⁸ The Dalakas study⁶⁵ included 26 patients, with the treatment group given a single course of rituximab and followed for 8 months, using the INCAT score as the primary outcome measure. This study showed a statistically significant change (favoring the rituximab group) in the 10-meter walk test, which was a secondary outcome. The Leger study⁶⁶ included 54 patients, with the treatment group given a single course of rituximab and followed for 12 months, using the INCAT Sensory Score (ISS) as the primary outcome measure. Possible reasons for the studies' failures include size, patient selection, regimen, duration, or choice of outcome measures.^{67,68}

CONSIDERATIONS FOR FUTURE CLINICAL TRIALS

Patient selection

Given the potential overlap with CIDP, it would be prudent to include patients with the typical phenotype, with at least 1 nerve exhibiting demyelinating range abnormalities, with an IgM monoclonal gammopathy (MGUS or Waldenström's

macroglobulinemia), and highly elevated anti-MAG antibodies of $\geq 7,500$ using the Buhlmann assay or $\geq 1:25,600$ in the dilutional assay, as previously discussed.

Due to the indolent course of the disease, more likely progression in patients with weakness, and relative insensitivity of outcome measures assessing mild gait instability, it would be preferable to include patients with some degree of weakness, even if it is only at the toes, or difficulty rising on the heels or toes. Such patients are more likely to be in a progressive phase, and changes in strength are more readily detected and quantified than changes in sensation or gait alone.

A longer trial duration of 2 years with rituximab or another anti-CD20 agent,⁶⁹ and continued treatment would increase the likelihood of detecting a difference between treated and non-treated patients. Continued treatment may be required to sufficiently lower the antibody concentration or prevent a rebound, and subjects in the placebo group are more likely to worsen and less likely to exhibit a placebo response over the longer time period. In the Dalakas study, as an example, a single course of treatment with rituximab reduced IgM levels at 8 months by only 34%.⁶⁵ Addition of BTK inhibitors in those with the MYD88 mutation or with venetoclax which targets BCL2 could also be considered in cases where the IgM levels are insufficiently responsive to therapeutic anti-CD20 antibodies at the 6-month time period.

With regards to the primary outcome measure, the neuropathy impairment score (NIS) of the lower extremities (NIS-LL) plus Lower Limb Function (LLF)⁷⁰ is likely to be more suitable for anti-MAG neuropathy trials than previously used measures. The NIS-LL measures both manual muscle strength and sensory functions including at the toes and ankles, and the LLF also measures functional strength at the ankles, whereas the INCAT score of the lower extremities only assesses gait. The NIS score has been used in clinical trials of hereditary amyloidosis which also presents with distal weakness and sensory loss,⁷¹ whereas the INCAT score has mostly been used in trials of CIDP which typically presents with both proximal and distal weakness.⁷² The MRC score can also be used for grading muscle strength but is best suited for patients with more severe weakness.⁷³ Walking speed, or the 10-meter walk test, which demonstrated a significant improvement in the treatment vs control groups in the Dalakas but not Leger study, would also be of interest, especially with the inclusion of more sensitive gait parameters that can be electronically measured.²⁷ Given that many of the patients in both arms of the trial may not show a change given the indolent nature of the disease, the use of two independent measures such as the number improving or worsening, or a combination of outcome measures might show a greater treatment effect.⁷⁴ These issues could be best addressed in collaborative multicenter studies such as the ongoing IMAGiNe study.⁷⁵

Authors' Contributions:

NL: is the main author and he reviewed the literature, planned the manuscript and selected the review topic, did selection of articles and data extraction, evaluated the quality of selected articles and wrote the first draft and the final version for the first submission; THBIII: did literature revision, selection of

articles and data extraction, evaluated the quality of selected articles, helped with critical review and group discussion and wrote the final version for the first submission; HWS: did literature revision, selection of articles and data extraction, evaluated the quality of selected articles, helped with critical review and group discussion and wrote the final version for the first submission; FAAG: planned the manuscript and selected the review topic, did literature revision, selection of articles and data extraction, evaluated the quality of selected articles, helped with critical review and group discussion and wrote the final version for the first submission.

Conflict of Interest

NL: is a consultant for Grifols Biologicals, Inc., Ipsen Pharma S.A.S, Pfizer, Inc. Takeda Pharmaceutical Company Limited; THBIII: has received honorarium for speaking from CSL Behring; HWS: is an employee of Grifols, a manufacturer of IVIg products. Dr. Sander contributed to this article in his personal capacity. The views expressed are his own and do not necessarily reflect the views of Grifols; FAAG: received travel grants and speaker honoraria from Takeda and CSL Behring.

References

- Latov N, Sherman WH, Nemni R, et al. Plasma-cell dyscrasia and peripheral neuropathy with a monoclonal antibody to peripheral-nerve myelin. *N Engl J Med* 1980;303(11):618–621. Doi: 10.1056/NEJM198009113031105
- Latov N, Braun PE, Gross RB, Sherman WH, Penn AS, Chess L. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. *Proc Natl Acad Sci U S A* 1981;78(11):7139–7142. Doi: 10.1073/pnas.78.11.7139
- Braun PE, Frail DE, Latov N. Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. *J Neurochem* 1982;39(05):1261–1265. Doi: 10.1111/j.1471-4159.1982.tb12563.x
- Gregson NA, Leibowitz S. IgM paraproteinaemia, polyneuropathy and myelin-associated glycoprotein (MAG). *Neuropathol Appl Neurobiol* 1985;11(05):329–347. Doi: 10.1111/j.1365-2990.1985.tb00030.x
- Ilyas AA, Quarles RH, MacIntosh TD, et al. IgM in a human neuropathy related to paraproteinemia binds to a carbohydrate determinant in the myelin-associated glycoprotein and to a ganglioside. *Proc Natl Acad Sci U S A* 1984;81(04):1225–1229. Doi: 10.1073/pnas.81.4.1225
- Steck AJ, Murray N, Meier C, Page N, Perruisseau G. Demyelinating neuropathy and monoclonal IgM antibody to myelin-associated glycoprotein. *Neurology* 1983;33(01):19–23. Doi: 10.1212/wnl.33.1.19
- Mahdi-Rogers M, Hughes RA. Epidemiology of chronic inflammatory neuropathies in southeast England. *Eur J Neurol* 2014;21(01):28–33. Doi: 10.1111/ene.12190
- Kyle RA, Larson DR, Therneau TM, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med* 2018;378(03):241–249. Doi: 10.1056/NEJMoa1709974
- Olszewski AJ, Treon SP, Castillo JJ. Evolution of Management and Outcomes in Waldenström Macroglobulinemia: A Population-Based Analysis. *Oncologist* 2016;21(11):1377–1386. Doi: 10.1634/theoncologist.2016-0126
- Nobile-Orazio E, Bianco M, Nozza A. Advances in the Treatment of Paraproteinemic Neuropathy. *Curr Treat Options Neurol* 2017;19(12):43. Doi: 10.1007/s11940-017-0479-9
- Svahn J, Petiot P, Antoine JC, et al; Francophone anti-MAG cohort Group. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. *J Neurol Neurosurg Psychiatry* 2018;89(05):499–505. Doi: 10.1136/jnnp-2017-316715
- Latov N. Antibody testing in neuropathy associated with anti-Myelin-Associated Glycoprotein antibodies: where we are after 40 years. *Curr Opin Neurol* 2021;34(05):625–630. Doi: 10.1097/WCO.0000000000000975
- Steck AJ. Anti-MAG neuropathy: From biology to clinical management. *J Neuroimmunol* 2021;361:577725. Doi: 10.1016/j.jneuroim.2021.577725
- Takatsu M, Hays AP, Latov N, et al. Immunofluorescence study of patients with neuropathy and IgM M proteins. *Ann Neurol* 1985;18(02):173–181. Doi: 10.1002/ana.410180203
- Hays AP, Lee SS, Latov N. Immune reactive C3d on the surface of myelin sheaths in neuropathy. *J Neuroimmunol* 1988;18(03):231–244. Doi: 10.1016/0165-5728(88)90101-4
- Monaco S, Bonetti B, Ferrari S, et al. Complement-mediated demyelination in patients with IgM monoclonal gammopathy and polyneuropathy. *N Engl J Med* 1990;322(10):649–652. Doi: 10.1056/NEJM199003083221002
- Gabriel JM, Erne B, Bernasconi L, et al. Confocal microscopic localization of anti-myelin-associated glycoprotein autoantibodies in a patient with peripheral neuropathy initially lacking a detectable IgM gammopathy. *Acta Neuropathol* 1998;95(05):540–546. Doi: 10.1007/s004010050835
- Kawagashira Y, Koike H, Tomita M, et al. Morphological progression of myelin abnormalities in IgM-monoclonal gammopathy of undetermined significance anti-myelin-associated glycoprotein neuropathy. *J Neuropathol Exp Neurol* 2010;69(11):1143–1157. Doi: 10.1097/NEN.0b013e3181fa44af
- Hays AP, Latov N, Takatsu M, Sherman WH. Experimental demyelination of nerve induced by serum of patients with neuropathy and an anti-MAG IgM M-protein. *Neurology* 1987;37(02):242–256. Doi: 10.1212/wnl.37.2.242
- Willison HJ, Trapp BD, Bacher JD, Dalakas MC, Griffin JW, Quarles RH. Demyelination induced by intraneural injection of human antimyelin-associated glycoprotein antibodies. *Muscle Nerve* 1988;11(11):1169–1176. Doi: 10.1002/mus.880111111
- Monaco S, Ferrari S, Bonetti B, et al. Experimental induction of myelin changes by anti-MAG antibodies and terminal complement complex. *J Neuropathol Exp Neurol* 1995;54(01):96–104. Doi: 10.1097/00005072-199501000-00012
- Tatum AH. Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM anti-myelin-associated glycoprotein. *Ann Neurol* 1993;33(05):502–506. Doi: 10.1002/ana.410330514
- Koski CL, Estep AE, Sawant-Mane S, Shin ML, Highbarger L, Hansch GM. Complement regulatory molecules on human myelin and glial cells: differential expression affects the deposition of activated complement proteins. *J Neurochem* 1996;66(01):303–312. Doi: 10.1046/j.1471-4159.1996.66010303.x
- Wanschitz J, Maier H, Lassmann H, Budka H, Berger T. Distinct time pattern of complement activation and cytotoxic T cell response in Guillain-Barré syndrome. *Brain* 2003;126(Pt 9):2034–2042. Doi: 10.1093/brain/awg207
- Latov N, Renaud S. Effector mechanisms in anti-MAG antibody-mediated and other demyelinating neuropathies. *J Neurol Sci* 2004;220(1-2):127–129. Doi: 10.1016/j.jns.2004.03.012
- Sato R, Shimizu F, Kuwahara M, et al. Autocrine TNF- α Increases Penetration of Myelin-Associated Glycoprotein Antibodies Across the Blood-Nerve Barrier in Anti-MAG Neuropathy. *Neurol Neuroimmunol Neuroinflamm* 2023;10(03):e200086. Doi: 10.1212/NXI.0000000000200086
- Vo ML, Martin P, Latov N. Correlation of Changes in Gait Parameters, With Phenotype, Outcome Measures, and Electrodiagnostic Abnormalities in a Patient With Anti-MAG Neuropathy After Exacerbation and Improvement. *J Clin Neuromuscul Dis* 2015;17(01):22–26. Doi: 10.1097/CND.0000000000000087
- Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database Syst Rev* 2016;10(10):CD002827. Doi: 10.1002/14651858.CD002827.pub4

- 29 Magy L, Kaboré R, Mathis S, et al. Heterogeneity of Polyneuropathy Associated with Anti-MAG Antibodies. *J Immunol Res* 2015; 2015:450391. Doi: 10.1155/2015/450391
- 30 Lozeron P, Ribrag V, Adams D, et al. Is distal motor and/or sensory demyelination a distinctive feature of anti-MAG neuropathy? *J Neurol* 2016;263(09):1761–1770. Doi: 10.1007/s00415-016-8187-z
- 31 Gazzola S, Delmont E, Franques J, et al. Predictive factors of efficacy of rituximab in patients with anti-MAG neuropathy. *J Neurol Sci* 2017;377:144–148. Doi: 10.1016/j.jns.2017.04.015
- 32 Pedersen SF, Pullman SL, Latov N, Brannagan TH III. Physiological tremor analysis of patients with anti-myelin-associated glycoprotein associated neuropathy and tremor. *Muscle Nerve* 1997;20(01):38–44. Doi: 10.1002/(sici)1097-4598(199701)20:1<38:aid-mus5>3.0.co;2-i
- 33 Canepa C. Waldenstrom-associated anti-MAG paraprotein polyneuropathy with neurogenic tremor. *BMJ Case Rep* 2019;12(03):e228376. Doi: 10.1136/bcr-2018-228376
- 34 van Veen R, Pallada G, Wieske L, et al. The effect of tremor on disability assessment in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2023;28(01):58–68. Doi: 10.1111/jns.12528
- 35 Garces-Sanchez M, Dycck PJ, Kyle RA, et al. Antibodies to myelin-associated glycoprotein (anti-Mag) in IgM amyloidosis may influence expression of neuropathy in rare patients. *Muscle Nerve* 2008;37(04):490–495. Doi: 10.1002/mus.20955
- 36 Briani C, Ferrari S, Berno T, et al. Peripheral neuropathy as clinical onset of monoclonal IgM/k-related amyloidosis. *J Peripher Nerv Syst* 2023;28(02):262–265. Doi: 10.1111/jns.12540
- 37 Yoshida T, Yazaki M, Gono T, et al. Severe cranial nerve involvement in a patient with monoclonal anti-MAG/SGPG IgM antibody and localized hard palate amyloidosis. *J Neurol Sci* 2006;244(1-2):167–171. Doi: 10.1016/j.jns.2006.01.018
- 38 Thomas FP, Lovelace RE, Ding XS, et al. Vasculitic neuropathy in a patient with cryoglobulinemia and anti-MAG IGM monoclonal gammopathy. *Muscle Nerve* 1992;15(08):891–898. Doi: 10.1002/mus.880150805
- 39 Vital A, Favereaux A, Martin-Dupont P, et al. Anti-myelin-associated glycoprotein antibodies and endoneurial cryoglobulin deposits responsible for a severe neuropathy. *Acta Neuropathol* 2001;102(04):409–412. Doi: 10.1007/s004010100381
- 40 Maillot F, Gelot A, Diot E, Larmande P, Guilmot JL. Neuropathie à IgM anti-MAG avec atteinte des nerfs crâniens révélant un lymphome B. [IgM anti-MAG neuropathy with involvement of the cranial nerves disclosing B-cell lymphoma] *Ann Med Interne (Paris)* 1996;147(05):373–374
- 41 Daher A, Kamiya-Matsuoka C, Woodman K. Patient With 2 Hematologic Malignancies Presenting as Neurolymphomatosis. *J Clin Neuromuscul Dis* 2018;19(03):124–130. Doi: 10.1097/CND.000000000000183
- 42 Galassi G, Tondelli M, Ariatti A, Benuzzi F, Nichelli P, Valzania F. Long-term disability and prognostic factors in polyneuropathy associated with anti-myelin-associated glycoprotein (MAG) antibodies. *Int J Neurosci* 2017;127(05):439–447. Doi: 10.1080/00207454.2016.1191013
- 43 Gesquière-Dando A, Delmont E, Launay M, Boucraut J, Attarian S. Are electrophysiological features related to disability in patients with anti-MAG neuropathy? *Neurophysiol Clin* 2017;47(01):75–81. Doi: 10.1016/j.neucli.2017.01.002
- 44 Falzone YM, Campagnolo M, Bianco M, et al. Functioning and quality of life in patients with neuropathy associated with anti-MAG antibodies. *J Neurol* 2018;265(12):2927–2933. Doi: 10.1007/s00415-018-9081-7
- 45 Bourque PR, Masson-Roy J, Warman-Chardon J, et al. Temporal evolution of nerve conduction study abnormalities in anti-myelin-associated glycoprotein neuropathy. *Muscle Nerve* 2021;63(03):401–404. Doi: 10.1002/mus.27134
- 46 Nobile-Orazio E, Meucci N, Baldini L, Di Troia A, Scarlato G. Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies. *Brain* 2000;123(Pt 4):710–717. Doi: 10.1093/brain/123.4.710
- 47 Vos JM, Notermans NC, D'Sa S, et al. High prevalence of the *MYD88 L265P* mutation in IgM anti-MAG paraprotein-associated peripheral neuropathy. *J Neurol Neurosurg Psychiatry* 2018;89(09):1007–1009. Doi: 10.1136/jnnp-2017-316689
- 48 Castellani F, Visentin A, Schirinzi E, et al. Mutational Profile in 75 Patients With Anti-Myelin-Associated Glycoprotein Neuropathy: Clinical and Hematologic Therapy Response and Hints on New Therapeutic Targets. *Neurol Neuroimmunol Neuroinflamm* 2023;10(04):e200122. Doi: 10.1212/NXI.000000000000200122
- 49 Trojaborg W, Hays AP, van den Berg L, Younger DS, Latov N. Motor conduction parameters in neuropathies associated with anti-MAG antibodies and other types of demyelinating and axonal neuropathies. *Muscle Nerve* 1995;18(07):730–735. Doi: 10.1002/mus.880180709
- 50 Liberatore G, Giannotta C, Sajeev BP, et al. Sensitivity and specificity of a commercial ELISA test for anti-MAG antibodies in patients with neuropathy. *J Neuroimmunol* 2020;345:577288. Doi: 10.1016/j.jneuroim.2020.577288
- 51 Doneddu PE, Ruiz M, Bianchi E, et al. A diagnostic score for anti-myelin-associated-glycoprotein neuropathy or chronic inflammatory demyelinating polyradiculoneuropathy in patients with anti-myelin-associated-glycoprotein antibody. *Eur J Neurol* 2023;30(02):501–510. Doi: 10.1111/ene.15296
- 52 Kaku DA, England JD, Sumner AJ. Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronyl paralogoside. *Brain* 1994;117(Pt 5):941–947. Doi: 10.1093/brain/117.5.941
- 53 Attarian S, Azulay JP, Boucraut J, Escande N, Pouget J. Terminal latency index and modified F ratio in distinction of chronic demyelinating neuropathies. *Clin Neurophysiol* 2001;112(03):457–463. Doi: 10.1016/s1388-2457(01)00469-2
- 54 Gondim FA, De Sousa EA, Latov N, Sander HW, Chin RL, Brannagan TH. Anti-MAG/SGPG associated neuropathy does not commonly cause distal nerve temporal dispersion. *J Neurol Neurosurg Psychiatry* 2007;78(08):902–904. Doi: 10.1136/jnnp.2006.111930
- 55 Lupu VD, Mora CA, Dambrosia J, Meer J, Dalakas M, Floeter MK. Terminal latency index in neuropathy with antibodies against myelin-associated glycoproteins. *Muscle Nerve* 2007;35(02):196–202. Doi: 10.1002/mus.20678
- 56 Ohara M, Sanjo N, Kanouchi T, Yokota T. Entrapment partly participates in the longitudinal progression of neuropathy with anti-MAG antibodies. *Rev Neurol (Paris)* 2023;179(1-2):118–122. Doi: 10.1016/j.neuro.2022.07.009
- 57 Castellani F, Visentin A, Campagnolo M, et al. The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy. *Neurol Neuroimmunol Neuroinflamm* 2020;7(04):e720. Doi: 10.1212/NXI.0000000000000720
- 58 Yasuda H, Tomizawa Y, Harada S, et al. Anti-myelin-associated-glycoprotein neuropathy successfully treated with tirabrutinib. *Heliyon* 2022;8(10):e10928. Doi: 10.1016/j.heliyon.2022.e10928
- 59 Briani C, Visentin A, Castellani F, Cacciavillani M, Trentin L. The BCL2 Inhibitor Venetoclax Plus Rituximab Is Active in MYD88 Wild-Type Polyneuropathy With Anti-MAG Antibodies. *Neurol Neuroimmunol Neuroinflamm* 2022;9(04):e1181. Doi: 10.1212/NXI.0000000000001181
- 60 Hänggi P, Aliu B, Martin K, Herrendorff R, Steck AJ. Decrease in Serum Anti-MAG Autoantibodies Is Associated With Therapy Response in Patients With Anti-MAG Neuropathy: Retrospective Study. *Neurol Neuroimmunol Neuroinflamm* 2021;9(01):e1109. Doi: 10.1212/NXI.0000000000001109
- 61 Campagnolo M, Zambello R, Nobile-Orazio E, et al. IgM MGUS and Waldenstrom-associated anti-MAG neuropathies display similar

- response to rituximab therapy. *J Neurol Neurosurg Psychiatry* 2017;88(12):1094–1097. Doi: 10.1136/jnnp-2017-315736
- 62 Colchester NTH, Allen D, Katifi HA, et al. Chemoimmunotherapy with rituximab, cyclophosphamide and prednisolone in IgM paraproteinaemic neuropathy: evidence of sustained improvement in electrophysiological, serological and functional outcomes. *Haematologica* 2021;106(01):302–305. Doi: 10.3324/haematol.2019.243139
- 63 Dalakas MC, Quarles RH, Farrer RG, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. *Ann Neurol* 1996;40(05):792–795. Doi: 10.1002/ana.410400516
- 64 Comi G, Roveri L, Swan A, et al; Inflammatory Neuropathy Cause and Treatment Group. A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. *J Neurol* 2002;249(10):1370–1377
- 65 Dalakas MC, Rakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol* 2009;65(03):286–293. Doi: 10.1002/ana.21577
- 66 Léger JM, Viala K, Nicolas G, et al; RIMAG Study Group (France and Switzerland) Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology* 2013;80(24):2217–2225. Doi: 10.1212/WNL.0b013e318296e92b
- 67 Pruppers MH, Merkies IS, Notermans NC. Recent advances in outcome measures in IgM-anti-MAG⁺ neuropathies. *Curr Opin Neurol* 2015;28(05):486–493. Doi: 10.1097/WCO.0000000000000236
- 68 Stino AM, Elsheikh B, Allen JA. Anti-myelin-associated glycoprotein neuropathy: Where do we stand? *Muscle Nerve* 2023;68(06):823–832. Doi: 10.1002/mus.27954
- 69 Parisi M, Dogliotti I, Clerico M, et al. Efficacy of rituximab in anti-myelin-associated glycoprotein demyelinating polyneuropathy: Clinical, hematological and neurophysiological correlations during 2 years of follow-up. *Eur J Neurol* 2022;29(12):3611–3622. Doi: 10.1111/ene.15553
- 70 Dyck PJB, Kincaid JC, Wiesman JF, et al. mNIS+7 and lower limb function in inotersen treatment of hereditary transthyretin-mediated amyloidosis. *Muscle Nerve* 2020;62(04):502–508. Doi: 10.1002/mus.27022
- 71 Brannagan TH, Coelho T, Wang AK, et al; NEURO-T. T. R. Open-Label Extension Investigators. Long-term efficacy and safety of inotersen for hereditary transthyretin amyloidosis: NEURO-TTR open-label extension 3-year update. *J Neurol* 2022;269(12):6416–6427. Doi: 10.1007/s00415-022-11276-8
- 72 Latov N, Deng C, Dalakas MC, et al; IGIV-C CIDP Efficacy (ICE) Study Group. Timing and course of clinical response to intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Arch Neurol* 2010;67(07):802–807. Doi: 10.1001/archneurol.2010.105
- 73 John J Medical Research Council. Grading of muscle power: comparison of MRC and analogue scales by physiotherapists. *Int J Rehabil Res* 1984;7(02):173–181
- 74 Teixeira-Pinto A, Siddique J, Gibbons R, Normand SL. Statistical Approaches to Modeling Multiple Outcomes In Psychiatric Studies. *Psychiatr Ann* 2009;39(07):729–735. Doi: 10.3928/00485713-20090625-08
- 75 Hamadeh T, van Doormaal PTC, Pruppers MHJ, et al; IMAGiNe Consortium. IgM anti-MAG[±] peripheral neuropathy (IMAGiNe) study protocol: An international, observational, prospective registry of patients with IgM M-protein peripheral neuropathies. *J Peripher Nerv Syst* 2023;28(02):269–275. Doi: 10.1111/jns.12547