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Report of Consensus Panel 1 from the 12th International Workshop on the management of patients with IgM and Waldenstrom's Macroglobulinemia related neuropathy

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ABSTRACT

The IgM-related peripheral neuropathies (IgM-PN) are a group of chronic disorders characterized by the presence of monoclonal IgM that may be associated with one of several diseases affecting the peripheral nerves. In many cases, there is a monoclonal IgM associated with activity against neural targets, leading to progressive peripheral nerve demyelination. Neurological symptoms in this setting can also result from direct invasion of the peripheral or central nervous system by lymphoplasmacytic cells (neurolymphomatosis and Bing-Neel syndrome respectively) or via other mechanisms (for example AL amyloid deposition or cryoglobulinemic vasculitis). There is an expanding array of treatment options, but high-quality data are sparse. Diagnostic accuracy is important and needs collaboration between hematologists and neuromuscular specialists to determine the sequence and intensity of investigations. Appropriate causal attribution to the IgM disorder is essential to enable the correct therapeutic intervention. The aims of treatment intervention should be clear and realistic. Consistent and clinically meaningful measures are needed to capture treatment success. Despite therapeutic advances, many patients experience persistent disability, highlighting the need for further research.

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Introduction

The IgM-related peripheral neuropathies (IgM-PN) are a group of chronic disorders characterized by the presence of monoclonal IgM that may be associated with one of several diseases affecting the peripheral nerves. Monoclonal IgM related demyelinating polyneuropathy (IgM-DMPN) is a chronic disorder characterized by the presence of monoclonal IgM associated with activity against neural targets, leading to progressive peripheral nerve demyelination. IgM-DMPN is typically a slowly progressive, length-dependent predominantly sensory neuropathy, with or without distal weakness and ataxia. It is mainly associated with IgM monoclonal gammopathy of undetermined significance (MGUS) or Waldenström's macroglobulinemia (WM), and occasionally other B-cell lymphomas. Neurological symptoms in association with monoclonal IgM can also result from direct invasion of the peripheral or central nervous system by lymphoplasmacytic cells (neurolymphomatosis and Bing-Neel syndrome (BNS) respectively) or via other mechanisms (for example AL amyloid deposition or cryoglobulinemic vasculitis).

The prevalence of the entirety of monoclonal IgM protein related neuropathies is unknown, but amongst those with IgM monoclonal gammopathies (including WM) approximately 30% experience symptoms of PN [1–4]. The diagnosis and management of IgM-PN poses challenges because of clinical overlap with other inflammatory neuropathies, their slow progression, and lack of standardized treatments. Electrophysiological studies, serum immunofixation and testing for anti-MAG and other antineuronal antibodies are important for accurate diagnosis but have limited utility in measuring response to treatment.

There is an expanding array of effective treatment options, but uncertainty persists due to limited high-quality data and the lack of robust neuro-hematology provision in healthcare settings.

Thus, many patients receive inappropriate treatment and experience persistent disability, highlighting the need for further research. Following the deliberations of the IWWM-12 in Prague in 2024, a panel of experts discussed common clinical problems in the diagnosis, evaluation and treatment of patients with IgM-PN. The consensus of the discussions is presented in the current manuscript.

How can we be sure that neuropathy in the presence of IgM MGUS or WM is causally related? When are invasive investigations indicated?

The causal relationship of IgM monoclonal gammopathies with PN is not straightforward**.** IgM MGUS and PN are both more prevalent with advancing age [5–7], but the close association between peripheral neuropathy and IgM paraprotein suggests a causal link. Experimental and clinical observations suggest that about half of IgM-associated demyelinating neuropathies are causally related to the targeted epitope of that paraprotein, most often myelin associated glycoprotein (MAG) [8–12] and that high serum antibody titers are more likely to be pathogenic than low titers. Antibodies targeting other epitopes such as gangliosides GM1 and GD1b and sulphatide are found in a smaller proportion of MGUS-associated neuropathy. In about 40% to 50% of patients with IgM and a demyelinating or 'conduction slowing' PN, neither anti-MAG nor other neuronal antibodies are found [13,14]. Table 1 summarizes the differential diagnoses.

A confirmed association between the gammopathy and the PN requires neurological, serological and hematological categorization of both. Close collaboration with peripheral nerve or neuromuscular specialists will define the requirement for invasive investigations (Table 2), optimization of supportive therapy and the need for clone-directed therapy, particularly in cases where clinical features are atypical. Alternative or additional causes of neuropathic symptoms (diabetes, nutritional deficiencies and alcohol, connective tissue disease, drugs or mechanical root irritation, or genetic) should be actively sought.

Typical features of IgM anti-MAG demyelinating PN include slowly progressive (at least 6-12 months) distal, symmetrical neuropathy, usually painless with frequent imbalance, ataxia and tremor. Usually there are no or few motor symptoms; if motor involvement occurs it is typically mild and distal, and later in the course of disease. Cranial nerve involvement is rare. Other phenotypes of neuropathy are recognizable and are summarized in Table 1.

Nerve conduction studies (NCS) / electromyography (EMG) is recommended whenever a neuropathy is identified by clinical history and examination as an extension of the clinical examination. These tests define the characteristics of neuropathy, its nature (conduction slowing/demyelinating vs axonal vs a mixed picture), and the pattern and extent of nerve damage (symmetrical, upper or lower limb, patchy mononeuropathy or confluent, and whether there is prominent denervation of axonal loss or a radiculopathy). Typical electrophysiological findings in the anti-MAG setting are symmetrical reduction or absence of sensory action potentials, reduced conduction velocities, and disproportionately prolonged distal motor latencies. An important distinction to be made is from chronic inflammatory demyelinating polyneuropathy (CIDP) which has differences on NCS [15–17] and clinical characteristics [14,18,19]. Neurophysiological findings in monoclonal IgM related demyelinating neuropathies are shown in Table 1.

Rarely, a nerve biopsy may be needed if the diagnosis remains unconfirmed despite appropriate assessments as above and if done should be undertaken by an experienced neurosurgeon and analyzed in specialized neuropathology laboratories [16,17].

CSF analysis is typically nonspecific in inflammatory neuropathies, but if malignant nerve root or CNS invasion is suspected, flow cytometry should be carried out within 2 to 4 hours of CSF sampling to minimize the chance of false-negative results. MRI should be done before lumbar puncture to avoid false positive leptomeningeal enhancement.

Table 2 summarizes some of the other invasive supportive tests that might be performed.

Does everyone with an IgM-associated neuropathy need treatment?

Treatment is only indicated in progressive neuropathy that impairs function and has a confirmed causal link to the monoclonal condition. A significant proportion of patients with a monoclonal IgM protein and neuropathy *do not have a causal link* and so the paraprotein and the neurology should be managed separately. Grey cases should be discussed in a specialist neurohematology panel if possible.

Many patients with a monoclonal IgM protein related demyelinating PN remain stable for years with minimal impact on their daily activities; in such cases, there is no indication to treat. Symptom management with walking aids, appropriate footwear and environmental advice is appropriate. Pain is not usually a feature of anti-MAG neuropathy, but may be present in protein deposition diseases, cryoglobulinemia, incidental nerve root compression or unrelated causes and pain can be managed as below.

Guidance for treatment of different disease scenarios and aspects of disease is presented in Table 3.

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Table 1
Features of IgM and non-IgM-related neuropathies.

	Anti-MAG	Multifocal motor neuropathy	Non-MAG PN	Cryoglobulinemia	AL Amyloidosis	CANOMAD	Neurolymphomatosis
Onset	Gradually and slowly progressive	Progressive or stepwise, asymmetric usually upper limb first	Gradually progressive	**Rapidly progressive <6 months**	**Usually Rapidly progressive <6 months**	Gradually progressive	Gradually progressive but can suddenly progress due to loss of function
Clinical features	Symmetrical Distal Sensory- predominant Mild-moderate distal muscle weakness	Motor weakness only	Symmetrical Distal, Sensory -predominant Mild-moderate distal muscle weakness Sometimes pain	Symmetrical Sensory May be painful Skin: Purpura Acrocyanosis Ulceration Swelling Kidney: Glomerulonephritis Other Myalgia Arthralgia	**Symmetrical Painful Length- dependent, Sensorimotor Autonomic Erectile dysfunction Diarrhea (sometimes nocturnal) Bladder dysfunction Postural hypotension Weight loss**	Paresthesia Hypoesthesia ataxia Double vision	Sensory and or motor symptoms Maybe painful
NCS/EMG	Sensory>motor with reduced or absent SNAP Motor conduction slowing without consistent block. Disparate DML prolongation (leading to Tli <0.25)	Patchy motor conduction slowing with conduction block. Normal SNAP	Various. Conduction slowing with variable amounts of axonal loss. May be heavy or light chain deposition, vasculitis or atypical – need nerve biopsy	Patchy multifocal mononeuropathies or motor and sensory nerves	Can be axonal or demyelinating, patchy or symmetrical and confluent. Usually early axonal loss.	Mixed picture with demyelination and axonal loss, predominantly sensory > motor	Patchy multiple mononeuropathy or confluent axonal or conduction slowing which may mimic CIDP, PDPN, vasculitis or amyloid
Demyelinating/ Axonal	Demyelinating	Demyelinating	Demyelinating or axonal or mixed	Axonal multiple mononeuropathies later confluent.	Axonal, ±sufficient conduction slowing to resemble demyelination	Mixed	Axonal multiple mononeuropathies or mixed
Supportive tests	High anti-MAG titer typical	Anti-GM1 antibodies, usually of very high titer compared to idiopathy MMNCB	Anti-MAG negative. Sensory nerve biopsy often required	Cryoglobulins, complement. Sensory nerve biopsy.	Autonomic function testing Involved organ tests (cardiac, renal, soft tissue, lymph node) May need biopsy. NT-ProBNP DPD scan SAP scan etc	Anti-disialosyl antibodies	PET scan **Central nervous system signs** CSF studies MRI head Nerve biopsy
Light chain type	IgMκ is nearly all	Not reported	Not reported	IgMκ 85% type I IgMκ 77% type II	IgMλ predominance	No κ/λ predominance	IgMκ 84%

DML = distal motor latency.
Bold flag features. Adapted from [20] SNAP- sensory nerve action potentials.

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Table 2
Role of invasive neurological testing and complex imaging.

Diagnostic Method	Recommendation	Key findings/indications
Neurophysiological testing (NCS and EMG) [16,17,21]	Routinely required for IgM-PN diagnosis	To characterize neuropathy (demyelinating, axonal, or mixed) and pattern (confluent, symmetrical multiple mononeuropathies) and assess extent of irreversible nerve damage Typical electrophysiological findings in anti-MAG IgM-PN: - Symmetrical reduction in conduction velocities—Predominant sensory involvement - Disproportionately prolonged distal motor latency—Absent sural nerve potentials Important to differentiate IgM-PN from CIDP associated with an incidental IgM paraprotein Advanced cases may require assessment in a specialist neuromuscular clinic
Sensory nerve biopsy [11,22–25]	Not routinely required or performed	Consider when rapid progression, mixed/axonal neuropathy, neuropathic pain, or autonomic dysfunction suggest alternative diagnoses (e.g., AL amyloidosis, cryoglobulinemia, or other IgM-related axonal neuropathies) Patients with intermediate or low anti-MAG titers (<10,000) may need a sural nerve biopsy to confirm IgM myelin deposits, widely spaced myelin or/and differentiate from CIDP Small fiber neuropathy is not generally associated with IgM-PN
Skin biopsy for small fiber neuropathy	Not recommended	While skin punch biopsy may show deposition of monoclonal protein or amyloidosis, the panel do not regard measurement of small fiber density to be of value in IgM-related neuropathy
Other tissue biopsy	Not routinely required	AL amyloidosis: Requires tissue biopsy (abdominal fat, bone marrow, or target organ) for amyloid typing If other diagnostic findings are inconclusive, a nerve biopsy may be necessary Skin biopsy for AL deposits may help in amyloid diagnosis. Counting epidermal nerve fibres does not help identify IgM related problems
Cerebrospinal fluid (CSF) examination [15,17]	Not routinely required	Increased CSF protein in >70% of demyelinating neuropathies with monoclonal gammopathy (nonspecific finding). In IgM PDPN the cell count should be <10/mm3 Consider lumbar puncture if: - Malignant nerve root infiltration is suspected - Asymmetrical neuropathy or multiple mononeuropathies present - CNS symptoms suggestive of Bing-Neel syndrome, requiring immunophenotyping and molecular testing
Imaging studies (MRI and ultrasound of nerves)	Not routinely required	MRI of the neuraxis is primarily used to exclude alternative diagnoses and should be performed with Gadolinium. If needed, MRI should be performed before lumbar puncture to prevent reactive meningeal enhancement Consultation with a neuroradiologist is recommended for optimal imaging (sites, sequences, contrast, etc.) Ultrasound of nerves may provide additional information but requires specialist ultrasonographers and the changes are not specific to 1 diagnosis

Table 3
Treatment considerations.

Treatment considerations [26–30]	Key points
When to consider clone-directed treatment	Indicated in progressive neuropathy that impairs function and has a confirmed causal link to the monoclonal condition. Most likely to benefit: - Younger patients - Patients with rapidly changing symptoms and signs - Patients within ≤5 years from symptom onset Note: 1. IgM paraprotein levels and anti-MAG/antiganglioside antibody titer do not predict clinical benefit. 2 - Bühlmann anti-MAG ELISA values: - The lower the titer, i.e. below 70,000 BTU, the less likely it is to be causative.
Treatment principles for PN in (WM)	When PN is the only indication for treatment in WM, management follows the same principles as in WM, though proteasome inhibitors such as bortezomib should be avoided because of potential for neurotoxicity.
When not to treat	Many IgM-PN patients remain stable for years with minimal impact on daily activities. - In such cases, no treatment is indicated beyond supportive care.
Symptom management	
Pain Tremor Physical/occupational therapy	Pain management: Though anti-MAG neuropathy is typically not painful, pain can occur in monoclonal IgM deposition diseases, radiculopathy, or unrelated causes: Gabapentin, pregabalin, tricyclic antidepressants, or newer antidepressants might be used, with tricyclic antidepressants favored for radicular pain. Tremor management in anti-MAG neuropathy: Propranolol, clonazepam, topiramate, gabapentin, barbiturates, botulinum toxin, or deep brain stimulation (response varies between patients). Falls prevention, physical therapy, rehabilitation, and customized ankle-foot orthoses are essential supportive measures. Mobility aids, appropriate footwear, and environmental modifications are recommended.

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What are the primary treatment options for these patients? What is the role of rituximab monotherapy, chemoimmunotherapy, targeted therapies and plasmapheresis?

Principals of therapy

The aim of therapy in the setting of IgM-related PN is improvement in symptoms and disability due to neuropathy. The speed and depth of the hematological response needed for a successful outcome remain unknown. Thus, the aim should be to achieve an appropriate clinical improvement in disability for any given patient whilst provoking the least toxicity.

A few prospective studies and small retrospective case-series exist in IgM-PN. There is significant heterogeneity in the data, and several include patients with and without anti-MAG antibodies. The interpretation of these studies [28,30–45], supported by an older meta-analysis [29], indicates that a subset of patients with IgM-related PN can derive significant clinical benefit from anti-CD20 B-cell directed therapy such as rituximab. A temporary worsening of PN symptoms following rituximab therapy has been reported and linked to the IgM-flare [32,39,46–50]. Shorter disease duration (<2-5 years), younger age, active progression at time of treatment and preservation of nerve density in biopsies might predict response to therapy [1,21,26,51–53].

The optimal dosing regimen for rituximab is uncertain; however standard hematological dosing is commonly prescribed (375mg/m^2 weekly x4) with clinical evaluation at 4-6 months and consideration of retreatment at 6 months. Alternative agents may be considered, preferably in the context of a clinical trial.

It is important to note that this benefit is associated with IgM reduction, rather than reduction in the titer of the anti-neuronal antibody, and the benefit is usually evident at later points of evaluation (often 6-8 months or more from start of therapy). Elimination of the clonal IgM is not achievable with rituximab alone and is only very rarely achieved with low intensity rituximab-based combinations such as dexamethasone, rituximab and cyclophosphamide (DRC) or BTKis.

Nevertheless, R-chemotherapy combinations are likely more cytoreductive, and improvement could be more rapid (although still slow) [38,42] and have relatively low toxicity. Cyclophosphamide may be considered appropriate if there is an inflammatory/vasculitic component of neuropathy, in consultation with peripheral nerve or neuromuscular specialist. In such cases it may be appropriate to apply the dose and duration of cyclophosphamide as per the CYCLOPS protocol [54]: IV Cyclophosphamide 15 mg/kg (max 1.2 g per dose) every 2 weeks for the first 3 doses, then every 3 weeks for a total of 6 to 10 doses.

More intensive combinations may achieve higher rates of complete IgM response (CR/VGPR) but are less favored outside the setting of systemic AL amyloidosis because of their greater toxicity. Data on bendamustine and rituximab (BR) show that hematologic responses are impressive and prolonged, but limited data exist about the clinical effect on the symptoms of PN and electrophysiology and neurologic assessment scales [41]. As BR has greater toxicity than DRC it is not a commonly selected approach. It may be appropriate for relapse following prior R-chemotherapy or when there is substantial systemic disease load to reduce.

There are limited data and availability of combinations of rituximab with non-neurotoxic proteasome inhibitors (carfilzomib or ixazomib) [55–57].

Data on BTKi in IgM-PN are being accrued in prospective studies in IgM-PN. Case reports suggest efficacy and relatively swift improvement by ibrutinib in IgM-PN [58]. Symptomatic improvement in WM-associated PN that progressed after rituximab has also been seen [59].

Regarding zanubrutinib, an *ad hoc* analysis of the ASPEN trial in 49 WM patients with PN symptoms (zanubrutinib, 27; ibrutinib, 22) showed resolution of PN symptoms in 35 (71.4%) at a median time of 10 months. A significant relationship of PN symptom resolution with major response and with lower baseline anti-MAG antibody levels was seen [43]. A case report indicates that tirabrutinib may also be effective [60]. Data on pirtobrutinib are currently lacking. The potential benefits of BTKi should be weighed against the need for indefinite use and possible accrual of toxicity or resistance over time. New combinations of chemoimmunotherapy with BTKi inhibitors (BR + acalabrutinib) may be associated with high rates of deep IgM responses but there are no data for patients with neuropathy.

Limited data indicate that venetoclax (with or without rituximab) may be an option for patients with IgM anti-MAG neuropathy, after failure of other options [51,61].

For patients with anti-MAG antibody-associated PN, IVIG or plasmapheresis have limited, if any effect and are not recommended; corticosteroids alone are ineffective [27,29,53,62]. Patients with an IgM paraprotein and a demyelinating neuropathy not consistent with either CIDP or anti-MAG neuropathy may respond to plasma exchange, steroids, IVIG or clonal depletion but responses are less reliable and frequent and there may be no response at all.

How does the bone marrow disease burden influence treatment? Should MYD88 and CXCR4 mutation status affect management of IgM-related neuropathy?

The degree of bone marrow infiltration by LPL plays a modulating role in IgM-PN treatment decisions. Whilst the severity and evolution of the neuropathy dictates *whether* treatment is needed, marrow infiltration influences *what and how* systemic therapy should be applied. In all cases, an individualized approach is critical, integrating both hematological and neurological considerations. Other important concerns include patient fitness, organ function, duration and pace of disability or impairment.

As LPL cells drive production of pathogenic IgM, a greater burden of clonal disease could have a greater impact on nerve damage. However, the volume of LPL cells does not necessarily correlate with the IgM level, and neither influences the avidity of monoclonal IgM for its neural target antigen. Thus, a deep cellular response will not necessarily translate into neural recovery.

If neuropathy is predominantly axonal and rapidly progressive, amyloidosis or cryoglobulinemia (both more common in high LPL burden cases) could be instrumental and may require more aggressive therapies despite the level of marrow disease. IgM myeloma should be ruled out in the event AL amyloidosis is detected. For the treatment of AL amyloidosis refer to the Report of Consensus Panel 6 from the 11th International Workshop on Waldenström's Macroglobulinemia on Management of Waldenström's Macroglobulinemia Related Amyloidosis [63]. Axonal neuropathies are less likely to demonstrate recovery although these may stabilize if progressive.

It is recommended that all patients deemed in need of treatment for their IgM-related PN undergo a bone marrow examination to include molecular analysis prior to treatment. This, in parallel with the nature and rate of progression of the neuropathy will guide the selection and delivery of therapy.

The molecular profile of WM has an increasing impact on treatment decisions, particularly in the context of BTKi and rituximab-based therapies [51]. MYD88^{WT} patients have a lower likelihood of responding to BTKi, making rituximab monotherapy the preferred first-line option. These data will not necessarily be applicable to response in treatment of IgM-PN. The presence of MYD88^{L265P}, while

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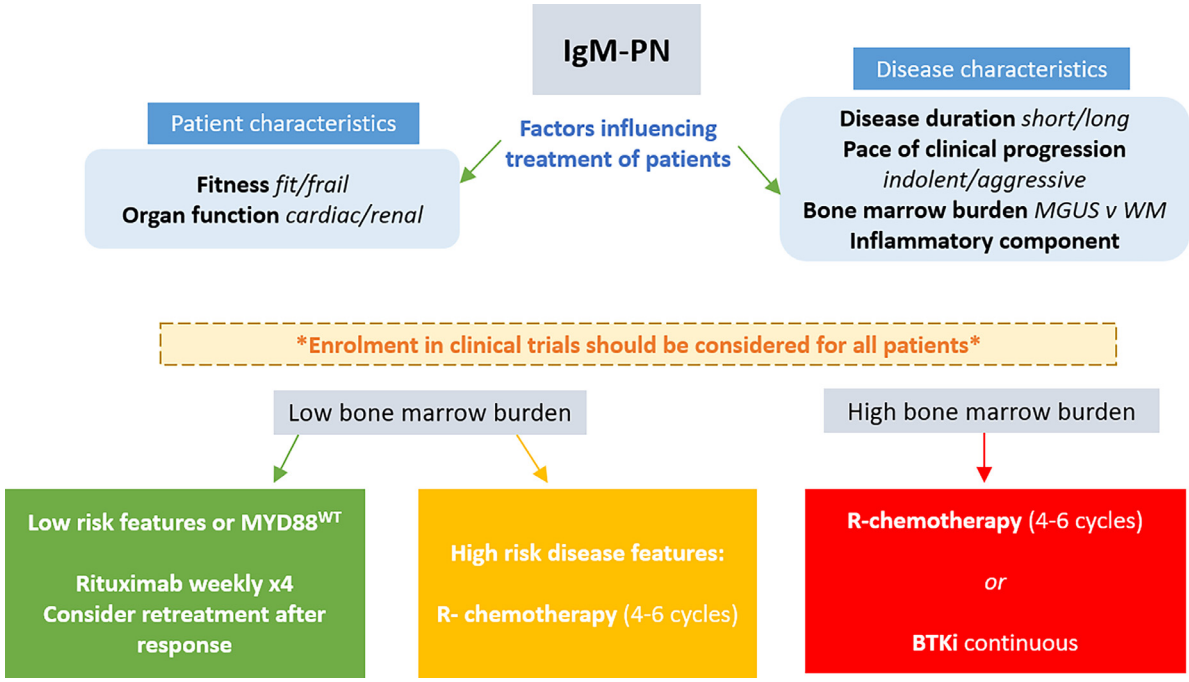

Fig. 1. Factors influencing management of patients and suggested treatment approach. Notes: High risk features include AL amyloidosis, cryoglobulinemic vasculitis or other inflammatory features on nerve biopsy, neurolymphomatosis. Regarding CXCR4 mutations or TP53 disruptions, there is currently insufficient data to recommend treatment selection in the setting of IgM PN.

Table 4
Considerations regarding bone marrow infiltration by LPL on IgM-PN treatment decisions.

Category	High bone marrow infiltration (>20%-30%)	Low bone marrow infiltration (<10%-20%)
Direct influence on clone-directed therapy decisions	- May predict a more aggressive disease course. - There may be concurrent hematological reasons to treat. - Higher IgM levels increase risk of hyperviscosity and systemic complications.	- The rate of progression of the neuropathy may still be rapid but the target monoclonal population is smaller and could be mitigated by less intensive treatment.
Impact on treatment selection	- Rituximab alone may exacerbate IgM levels ("IgM flare"), temporarily worsening neuropathy. - Plasmapheresis or Combination therapy with chemotherapy (cyclophosphamide or bendamustine) may help mitigate neurosymptomatic rituximab driven IgM flares. - Combination therapy targeting the malignant clone (rituximab, BTK inhibitors, alkylating agents) may be more appropriate in keeping with the principles of treating WM for hematological reasons (depth and duration of response).	- Systemic therapy may still be considered, but lower treatment intensity may be sufficient. - May avoid chemotherapy if neuropathy is stable or slowly progressing. - Monotherapy with rituximab or BTK inhibitors may be an option.
Consideration of alternative mechanisms of neuropathy	- Higher risk of additional neuropathic mechanisms (e.g., amyloidosis, cryoglobulinemia). - More likely to require potent anti-clonal therapies.	- Aggressive pathogenic mechanisms e.g. amyloidosis, cryoglobulinemia can occur in the setting of a lower disease burden
Treatment tolerability and risk-benefit consideration	- Older patients or those with significant marrow infiltration are more susceptible to myelosuppression from systemic therapy. - BTK inhibitors (ibrutinib, zanubrutinib) show good tolerability and may be preferred in frail patients who cannot tolerate rituximab or chemotherapy.	- Better overall tolerance to treatment. - Systemic therapy may still be required, but careful assessment of functional impairment and progression guides decisions.

not associated with more severe neuropathy, may guide the use of WM-directed regimens. As data on MYD88 mutational status is further advanced, it is felt to be appropriate to include it in the treatment algorithm for IgM-PN (Fig. 1).

CXCR4 mutations, particularly S338X, are associated with slower responses and higher treatment failure rates with BTKi, though zanubrutinib appears to be less impacted than ibrutinib. Although del17p and TP53 mutations have not been extensively studied in IgM-PN, their known impact in hematologic malignancies suggests that BTKi may be a more appropriate frontline option over rituximab-based therapy in affected patients. However, at this time, specific recommendations cannot be made based on current data.

Moving forward, personalized treatment approaches integrating molecular profiling may further optimize outcomes in patients with IgM-PN and WM-associated neuropathies.

What is the relevance of antineuronal antibodies such as anti-MAG, or anti-ganglioside etc., and should we follow the titers in response to treatment?

All patients with demyelinating PN and monoclonal IgM should be tested for IgM anti-MAG antibodies. IgM antibodies are too large to penetrate a normally functional blood-nerve barrier; thus, in vivo IgM anti-MAG pathogenesis may depend on factors (local or systemic) that increase penetration of IgM into the endoneurium

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Table 5
Relevance of anti-MAG titers [13,14,66–68].

Anti-MAG titer (Bühlmann assay)	Dilutional endpoint assay	Designation	Clinical relevance
≤1000 BTU	≤800	Negative	Not associated with MAG neuropathy.
1000-7000 BTU	N/A	Weak Positive	Not clinically relevant in neuropathies.
≥10,000 BTU	≥1:25,600	Positive	More likely associated with typical MAG neuropathy.
>70,000 BTU	N/A	Strongly Positive	Highly associated with typical MAG neuropathy.

Notes:
There is no correlation between anti-MAG titers and severity of the neuropathy.
There is no utility to measuring changes in titer to predict worsening or improvement of a neuropathy.
There is no correlation between IgM levels and anti-MAG titers.
Although the titer of anti-MAG may alter following treatment, they are not useful to determine therapeutic efficacy of any treatment.
Making treatment modifications based on serial anti-MAG evaluations is not recommended
IgM levels usually decline with successful treatment, but this may not impact on the neuropathology.
On the other hand, lack of an IgM response or steady increase of IgM level could be a factor in deciding to escalate treatment in case of progression of PN.

Table 6
Relevant non-MAG antibody testing in IgM-PN.

Antibody	Associated syndrome	Clinical features	Considerations
Anti-GM1	Multifocal Motor Neuropathy (MMN)	- Asymmetric, slowly progressive motor neuropathy- Predominantly affects upper limbs- No significant sensory involvement	- IVIG is first-line treatment- Steroids are ineffective or may worsen symptoms
Anti-GD1b	Multifocal Motor Neuropathy (MMN)	- Overlaps with anti-GM1 MMN phenotype- Pure motor neuropathy	- Similar treatment to MMN
IgM disialosyl	CANOMAD Syndrome (Chronic Ataxic Neuropathy with Ophthalmoplegia, M-protein, Agglutination, and Disialosyl antibodies)	- Chronic ataxic neuropathy- Ophthalmoplegia- Cold agglutinin hemolysis may be present	- Treatment may include IVIG, rituximab, or plasma exchange

[9,64]. Anti-MAG antibodies are most commonly tested by ELISA [65]. The 2 ELISA assays are the Bühlmann assay (commercially available and commonly used) and a dilutional endpoint assay. Locally validated ELISAs, Western blot or immunohistochemistry assays may also be useful [17]. Anti-MAG antibodies can be found incidentally in CIDP or neuropathy from many causes.

In patients with a monoclonal IgM protein, a demyelinating peripheral neuropathy and absent anti-MAG antibodies, testing for IgM antibodies against other neural antigens (gangliosides GM1, GD1a, GD1b, GT1b, GM2 and GM3 and the paraglobosides, sulphate-3-glucuronyl para-globoside (SPGP) or SGLPG (Table 4), should be discussed with a peripheral nerve or neuromuscular specialist [14,65]. Anti-GM1 and anti-GD1b antibodies have been associated with a multifocal motor neuropathy; IgM disialosyl antibodies with CANOMAD; however, these syndromes have a different clinical presentation to anti-MAG PN and warrant often different types of treatment [69,70] (Tables 5 and 6).

How should clinical response to treatment be assessed?

Given that the indication to treat patients with IgM-PN is progressive neuropathy, the evaluation of clinical improvement following treatment is the priority. Neurological clinical improvement may occur late and continue beyond the hematologic response.

Whatever treatment is used, there is a weak correlation between IgM response and clinical improvement of PN and the only purpose of evaluating the IgM level is to demonstrate the effectiveness of clonal B-cell depletion. A pretreatment bone marrow biopsy is recommended to guide treatment decisions as above, but the need to examine the bone marrow after treatment is based on the pretreatment levels. If the clone is WM-sized, then post treatment evaluation should proceed as per IWWM6 response criteria. If the pretreatment clone was less than 10%, the usefulness of a repeat marrow is debatable, unless clinical response is inadequate, and a different treatment is under consideration.

Stability rather than improvement is the most likely outcome of treatment although some improvement is reported by a significant minority of patients. Cases of dramatic improvement are rare. The rate and degree of neurological response depends on the pretreatment status of the patient, the presence of axonal loss (which accumulates over years) and timing of assessments after treatment [21,26]. Due to the slow pace of improvement, it is advisable that clinical and neurologic responses should be assessed after a minimum of 6 months, and preferably at 1 and 2 years, provided no significant deterioration occurs. The neurologic assessment should include clinical assessments.

The evaluation of the clinical response is not standardized and has not been studied extensively in IgM-PN but there are multiple published and effective measures that can be used. The assessment of impairment and disability at the patient-reported and clinician-measured levels is meaningfully important [14,32] Frequently used thresholds for change in demyelinating neuropathies can be found in Table 7, but as previously stated, primary goal of treatment is to keep patients stable. Lack of deterioration in these outcome measures or contemporaneous improvement on 2 or more outcome measures e.g. walking, muscle and grip strength, or disability (e.g. i-RODS, the adjusted INCAT) indicates a clinical response. The role of NCS/EMG in the evaluation of the response to treatment in IgM-PN remained controversial among panel members.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SD: BeiGene- honoraria, speaker fees, congress expenses; grant funding Sanius Health Ltd; Cellectar- advisory board; Ouro Medicines- advisor; Janssen- honoraria for Preceptorship. MAD: Honoraria from participation in advisory boards and satellite symposia from Amgen, Sanofi, Regeneron, Menarini, Takeda, GSK, BMS, Janssen, BeiGene, Swixx and Astrazeneca. RH: Reports a consultant or advisory relationship with Janssen, Amgen, Celgene, AbbVie, BMS, Novartis, PharmaMar, and Takeda; has received honoraria from Janssen, Amgen, Celgene, BMS, PharmaMar, and Takeda; has received research funding from Janssen, Amgen, Celgene, BMS, Novartis, and Takeda; is member of Advisory Boards: BMS, Takeda, Amgen, Oncopeptides, Sanofi, Janssen, GSK; has received support for attending meetings and/or travel from Amgen, Celgene, Takeda, Janssen. JL: Reports honoraria from Takeda, BMS, Janssen; Confer-

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Table 7
Clinical and functional assessment tools with significant change criteria.

Assessment tool	Description	Clinically significant change
Adjusted INCAT disability score	Evaluates disability in arms and legs, frequently used in clinical trials.	≥1-point change in adjusted INCAT score is considered meaningful.
i-R-ODS	Patient-reported outcome scale for daily activities.	≥4-point (centile) change in R-ODS indicates meaningful functional change.
Modified Rankin Scale (mRS)	Global disability scale often used in neuropathy studies.	Decrease of ≥1 point in mRS score reflects improved disability status.
MRC sum score	Measures muscle strength in key muscle groups.	≥4-point change in the MRC sum score is considered clinically significant.
Smaller changes (1–3 points) may still be relevant in patients with severe weakness.		
Martin vigorimeter	Measures grip strength	Increase/decrease of 8 kPA

ence and travel support; BMS, Amgen, Takeda, BeiGene, Ad Board: Amgen, Pfizer, Janssen, and Bristol Myers Squibb. PM: Honoraria from Janssen, Astra Zenecca and Incyte; consultancy or advisory role for Janssen and Beigene; and travel support from Abbvie. AT: Received honoraria from AbbVie, J&J, Beigene, Lilly, Astrazeneca. SPT: Received research funding and/or consulting fees from Abbvie/Pharmacyclics, Janssen, Beigene, Lilly, BMS, and Ono Pharmaceuticals. CB: Reports consultancy, honoraria, advisory board, and travel expenses from Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead, Celltrion, MorphoSys, Regeneron, Sobi, and Lilly. JVM: Received consulting fees from Beigene. MV: Received research funding, and/or consulting fees from AbbVie, Astrazeneca, BeiGene, Janssen. JMIV: received honoraria from Amgen, Beigene, BMS, Janssen, and Sanofi, and research funds from AbbVie/Genmab, and BeiGene. FE: Received funding in grants from CSL Behring, Grifols, Terumo BCT, Takeda, Kendion and the GBS/CIDP foundation. He has also received consultation fees (paid to institution) from Takeda, Dianthus, Sanofi and Argenx. MPL: Reports consulting fees and or travel expenses from ad hoc advisory boards to Roche, Annexon, AstraZeneca, Sanofi, UCB, Sanofi, Takeda, Polyneuron and BeiGene. Research funding associated with trials with CSL Behring, Novartis and UCB Pharma, Optic, Perinoms and IMAGiNe. DSMB for Octapharma trial and Investigator led IoC trial. Unrestricted conference expenses have also been received from Beigene and CSL Behring. EK: Honoraria from GSK, Janssen, Pfizer, and Prothena, and research funds from GSK, Janssen, and Pfizer. CC: Advisory board and/or Consultant and/or speaker for Abbvie, AMGEN, Astellas, Beigene, BMS, Curis, Glycomimetics, GSK, Immunogen, Janssen, Jazz, Karyopharm, Menarini - Stemline, Oncopeptides, Pfizer, Sanofi, Servier, Skyline DX, Stemline, Takeda. JK, SC, ID:, MG, GM, CJP, ML: No disclosures to report.

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References

[1] Treon SP, Hanzis CA, Ioakimidis LI, et al. Clinical characteristics and treatment outcome of disease-related peripheral neuropathy in Waldenstrom's macroglobulinemia (WM). J Clin Oncol 2010;28:8114.
[2] Zis P, Hadjivassiliou M, Sarrigiannis, et al. Prevalence of peripheral neuropathy (PN) among patients with asymptomatic monoclonal gammopathies: a clinical & electrophysiological study. Blood 2023;142:529.
[3] Nobile-Orazio E, Marmiroli P, Baldini L, et al. Peripheral neuropathy in macroglobulinemia: incidence and antigen-specificity of M proteins. Neurology 1987;37:1506–14.
[4] Baldini L, Nobile-Orazio E, Guffanti A, et al. Peripheral neuropathy in IgM monoclonal gammopathy and Wäldenstrom's macroglobulinemia: a frequent complication in elderly males with low MAG-reactive serum monoclonal component. Am J Hematol 1994;45:25–31.
[5] GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol 2024;23:344–81.
[6] Taams NE, Drenthen J, Hanewinckel R, Ikram MA, van Doorn PA. Age-related changes in neurologic examination and sensory nerve amplitude in the general population: aging of the peripheral nervous system. Neurology 2023;101:e1351–8.
[7] Hanewinckel R, Drenthen J, van Oijen M, et al. Prevalence of polyneuropathy in the general middle-aged and elderly population. Neurology 2016;87:1892–8.
[8] 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;37:242–56.
[9] McGinnis S, Kohriyama T, Yu RK, Pesce MA, Latov N. Antibodies to sulfated glucuronic acid containing glycosphingolipids in neuropathy associated with anti-MAG antibodies and in normal subjects. J Neuroimmunol 1988;17:119–26.
[10] Willison HJ, Trapp BD, Bacher JD, et al. Demyelination induced by intraneural injection of human antimyelin-associated glycoprotein antibodies. Muscle Nerve 1988;11:1169–76.
[11] Jacobs JM, Scadding JW. Morphological changes in IgM paraproteinaemic neuropathy. Acta Neuropathol 1990;80:77–84.
[12] 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;54:96–104.
[13] Nobile-Orazio E, Vietorisz T, Messito MJ, Sherman WH, Latov N. Anti-MAG IgM antibodies in patients with neuropathy and IgM M proteins: detection by ELISA. Neurology 1983;33:939–42.
[14] Klein CJ, Triplett JD, Murray DL, et al. Optimizing anti-myelin-associated glycoprotein and IgM-gammopathy testing for neuropathy treatment evaluation. Neurology 2024;103:e210000.

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[15] Notermans NC, Franssen H, Eurelings M, Van der Graaf Y, Wokke JH. Diagnostic criteria for demyelinating polyneuropathy associated with monoclonal gammopathy. Muscle Nerve 2000;23:73–9.
[16] Van den Bergh PYK, Hadden RDM, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. Eur J Neurol 2010;17:356–63.
[17] Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force-second revision. Eur J Neurol 2021;28:3556–83.
[18] Matà S, Ambrosini S, Saccomanno D, et al. Anti-MAG IgM: differences in antibody tests and correlation with clinical findings. Neurol Sci 2020;41:365–72.
[19] Swart G, Skolka MP, Shelly S, et al. Distinguishing chronic inflammatory demyelinating polyneuropathy from mimic disorders: the role of statistical modeling. J Peripher Nerv Syst 2025;30:e12682.
[20] Khwaja J, D'Sa S, Minnema MC, et al. IgM monoclonal gammopathies of clinical significance: diagnosis and management. Haematologica 2022;107:2037–50.
[21] Niermeijer JM, Eurelings M, van der Linden MW, et al. Prognosis of polyneuropathy due to IgM monoclonal gammopathy: a prospective cohort study. Neurology 2010;74:406–12.
[22] Di Troia A, Carpo M, Meucci N, et al. Clinical features and anti-neural reactivity in neuropathy associated with IgG monoclonal gammopathy of undetermined significance. J Neurol Sci 1999;164:64–71.
[23] Takatsu M, Hays AP, Latov N, et al. Immunofluorescence study of patients with neuropathy and IgM M proteins. Ann Neurol 1985;18:173–81.
[24] Ritz MF, Erne B, Ferracin F, et al. Anti-MAG IgM penetration into myelinated fibers correlates with the extent of myelin widening. Muscle Nerve 1999;22:1030–7.
[25] 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;95:540–546.
[26] Galassi G, Tondelli M, Ariatti A, et al. Long-term disability and prognostic factors in polyneuropathy associated with anti-myelin-associated glycoprotein (MAG) antibodies. Int J Neurosci 2017;127:439–47.
[27] Latov N, Brannagan TH 3rd, Sander HW, Gondim FA A. Anti-MAG neuropathy: historical aspects, clinical-pathological correlations, and considerations for future therapeutical trials. Arq Neuropsiquiatr 2024;82:1–7.
[28] 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;29:3611–22.
[29] Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev 2016;10:Cd002827.
[30] Ferfoglia R Iancu, Guimarães-Costa R, Viala K, et al. Long-term efficacy of rituximab in IgM anti-myelin-associated glycoprotein neuropathy: RIMAG follow-up study. J Peripher Nerv Syst 2016;21:10–14.
[31] Levine TD, Pestronk A. IgM antibody-related polyneuropathies: b-cell depletion chemotherapy using Rituximab. Neurology 1999;52:1701–4.
[32] Kilidireas C, Anagnostopoulos A, Karandreas N, Mouselimi L, Dimopoulos MA. Rituximab therapy in monoclonal IgM-related neuropathies. Leuk lymphoma 2006;47:859–64.
[33] Benedetti L, Briani C, Franciotta D, et al. Predictors of response to rituximab in patients with neuropathy and anti-myelin-associated glycoprotein immunoglobulin M. J Peripher Nerv Syst 2007;12(2):102–7.
[34] Benedetti L, Briani C, Franciotta D, et al. Long-term effect of rituximab in anti-MAG polyneuropathy. Neurology 2008;71(21):1742–4.
[35] 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(3):286–93.
[36] Gruson B, Ghomari K, Viala K, et al. Long-term response to rituximab and fludarabine combination in IgM anti-myelin-associated glycoprotein neuropathy. J Peripher Nerv Syst 2011;16(3):180–5.
[37] Léger JM, Viala K, Nicolas G, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. Neurology 2013;80(24):2217–25.
[38] Hospital MA, Viala K, Dragomir S, et al. Immunotherapy-based regimen in anti-MAG neuropathy: results in 45 patients. Haematologica 2013;98(12):e155–7.
[39] Stork ACJ, van Schaik IN, Notermans NC, et al. Fcγ receptor IIIA genotype is associated with rituximab response in antimyelin-associated glycoprotein neuropathy. J Neurol Neurosurg Psychiatry 2014;85(8):918–20.
[40] 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):1094–7.
[41] Massa F, Zuppa A, Pesce G, et al. Bendamustine-rituximab (BR) combined therapy for treatment of immuno-mediated neuropathies associated with hematologic malignancy. J Neurol Sci 2020;413:116777.
[42] 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(1):302–5.
[43] Heyman BM, Opat SS, Wahlin BE, et al. Peripheral neuropathy in the phase 3 ASPEN study of Bruton tyrosine kinase inhibitors for WaldenstrÃ¶m macroglobulinemia. Blood Advances 2024;9(4):722–32.
[44] Renaud S, Gregor M, Fuhr P, et al. Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. Muscle & Nerve 2003;27(5):611–15.
[45] Renaud S, Fuhr P, Gregor M, et al. High-dose rituximab and anti-MAG-associated polyneuropathy. Neurology 2006;66(5):742–4.
[46] Sala E, Robert-Varvat F, Paul S, Camdessanché JP, Antoine JC. Acute neurological worsening after Rituximab treatment in patients with anti-MAG neuropathy. J Neurol Sci 2014;345:224–7.
[47] Noronha V, Fynan TM, Duffy T. Flare in neuropathy following rituximab therapy for Waldenstrom's macroglobulinemia. J Clin Oncol 2006;24:e3.
[48] Siconolfi G, Vitali F, Sciarrone MA, et al. IgM flare in anti-MAG neuropathy post rituximab treatment: A clinical case and a systematic review of the literature. Brain Sciences 2024;14(12):1294.
[49] Gironi M, Saresella M, Ceresa L, et al. Clinical and immunological worsening in a patient affected with Waldenstrom macroglobulinemia and anti–MAG neuropathy after treatment with rituximab. Haematologica 2006;91(6 Suppl):ECR17.
[50] Broglio L, Lauria G. Worsening after rituximab treatment in anti-mag neuropathy. Muscle Nerve 2005;32:378–9.
[51] 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.
[52] Matsui T, Hamada Y, Kuwahara M, et al. Association of variability in antibody binding affinity with a clinical course of anti-MAG neuropathy. J Neuroimmunol 2020;339:577127.
[53] 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):710–17.
[54] Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis 2012;71:955–60.
[55] Castillo JJ, Meid K, Flynn CA, et al. Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenstrom macroglobulinemia: long-term follow-up. Blood Adv 2020;4:3952–9.
[56] Kersten MJ, Amaador K, Minnema MC, et al. Combining Ixazomib with subcutaneous Rituximab and Dexamethasone in relapsed or refractory Waldenstrom's macroglobulinemia: final analysis of the phase I/II HOVON124/ECWM-R2 study. J Clin Oncol 2022;40:40–51.
[57] Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenstrom's macroglobulinemia. Blood 2014;124:503–10.
[58] Castellani F, Visentin A, Campagnolo M, et al. The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy. Neurol Neuroimmunol Neuroinflamm 2020 Apr 13;7(4):e720.
[59] Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med 2015;372:1430–40.
[60] Yasuda H, Tomizawa Y, Harada S, et al. Anti-myelin-associated-glycoprotein neuropathy successfully treated with tirabrutinib. Heliyon 2022;8:e10928.
[61] Briani C, Visentin A, Castellani F, et al. The BCL2 Inhibitor Venetoclax Plus Rituximab Is Active in MYD88 Wild-Type Polyneuropathy With Anti-MAG Antibodies. Neurol Neuroimmunol Neuroinflamm 2022;9(4):e001181.
[62] Comi G, Roveri L, Swan AV, et al. A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. J Neurol 2002;249:1370–7.
[63] Merlini G, Sarosiek S, Benevolo G, et al. Report of Consensus Panel 6 from the 11 th International Workshop on Waldenström's Macroglobulinemia on Management of Waldenström's macroglobulinemia related amyloidosis. Semin Hematol 2023;60(2):113–17.
[64] Kanda T, Usui S, Beppu H, et al. Blood-nerve barrier in IgM paraproteinemic neuropathy: a clinicopathologic assessment. Acta Neuropathol 1998;95:184–92.
[65] Latov N. Antibody testing in neuropathy associated with anti-myelin-associated glycoprotein antibodies: where we are after 40 years. Curr Opin Neurol 2021;34:625–30.
[66] Magy L, Kaboré R, Mathis S, et al. Heterogeneity of polyneuropathy associated with anti-MAG antibodies. J Immunol Res 2015;2015:450391.
[67] 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.
[68] Nobile-Orazio E, Francomano E, Daverio R, et al. Anti-myelin-associated glycoprotein IgM antibody titers in neuropathy associated with macroglobulinemia. Ann Neurol 1989;26:543–50.
[69] Le Cann M, Bouhour F, Viala K, et al. CANOMAD: a neurological monoclonal gammopathy of clinical significance that benefits from B-cell-targeted therapies. Blood 2020;136:2428–36.
[70] Pascual-Goñi E, Martín-Aguilar L, Martínez-Martínez L, et al. Excellent response to anti-CD38 therapy with daratumumab in a patient with severe refractory CANOMAD. J Neurol Neurosurg Psychiatry 2024;95:609–11.

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