

Investigation and management of IgM and Waldenström's associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel

Shirley D'Sa MD FRCP FRCPath¹, Marie José Kersten MD PhD², Jorge J. Castillo MD³, Meletios Dimopoulos MD⁴, Efstathios Kastritis MD⁴, Edward Laane MD PhD⁵, Véronique Leblond MD⁶, Giampaolo Merlini MD⁷, Steven P Treon MD PhD³, Josephine M Vos MD^{2,8}, and Michael P Lunn MA FRCP PhD⁹

1. Waldenström's Clinic, Cancer Division, University College London Hospitals NHS Foundation Trust, London, United Kingdom
2. Department of Haematology, Academic Medical Center, Amsterdam, The Netherlands
3. Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA
4. Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece
5. Department of Hematology, North Estonia Medical Center, Tallinn, Estonia.
6. AP-HP Hôpital Pitié Salpêtrière, UPMC Univ. Paris 6 GRC-11, Grechy, Paris France
7. Centre for Research and Treatment of Systemic Amyloidosis, University of Pavia, Italy
8. Cancer Center, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands
9. Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London, United Kingdom

Abstract

Paraproteinaemic neuropathies are a heterogeneous group of disorders most frequently associated with IgM monoclonal gammopathies including Waldenström macroglobulinaemia (WM). Their consequences are significant and challenging for affected patients and identification and treatment not straightforward for their physicians. The variability of clinical presentation and progression as well as the attribution of causality hamper classification and management. The indications for invasive investigations such as CSF analysis, nerve conduction tests and sensory nerve biopsies remain unclear, as does the optimal way to measure clinical response to therapeutic interventions. When to intervene and in whom also present challenges to physicians. As part of its latest deliberations (International Workshops on WM, London, UK, August 2014), the IWWM8 panel have proposed a consensus approach to the diagnosis and management of peripheral neuropathies associated with IgM monoclonal gammopathies, including WM. Importantly, a consensus regarding the use of clinical outcome measures and recommended models of care for this group of patients is discussed, as well as appropriate treatment interventions.

Introduction

IgM paraprotein-associated neuropathies are a heterogeneous group of disorders whose exact prevalence is unknown. Their consequences are significant and challenging for patients and physicians alike with no consensus regarding clinical evaluation and optimal baseline assessment.

The International Workshops on Waldenström's Macroglobulinaemia (IWWM) have proposed criteria for diagnosis and therapy in WM patients (Owen, *et al* 2003), response (Owen, *et al* 2013), and treatment (Dimopoulos, *et al* 2014). As part of its latest consensus deliberations (IWWM8, London 2014), the panel reviewed the management of peripheral neuropathies (PN) associated with IgM monoclonal gammopathies, including WM.

The prevalence of peripheral neuropathy (PN) in persons with MGUS is approximately 5% in IgG, 15% in IgA and possibly up to 30-50% in IgM MGUS (Gosselin, *et al* 1991, Kissel and Mendell 1996, Nobile-Orazio, *et al* 1984, Yeung, *et al* 1991), although this high prevalence rate probably reflects patient selection bias in specialist settings and sensitive identification of sub-clinical cases (Dispenzieri and Kyle 2005). Monoclonal gammopathies are common with a prevalence of 1% of the general population aged 50 and increasing to 8-9% by the age of 90 (Kyle, *et al* 2006). Peripheral neuropathy affects 2.4% of the general population, increasing to 8.0% with advancing age (Martyn and Hughes 1997). A frequent challenge when 2 such common conditions coexist, is to relate the causality of the MGUS versus coincidental association.

High quality evidence links at least 50% of the demyelinating neuropathies to a causal IgM paraprotein, including antibody transfer models (Tatum 1993, Willison, *et al* 1993), high titre IgM antibodies with a neural target (myelin associated glycoprotein (MAG)), site specific binding studies by light and immunoelectron microscopy, a unique pathological substrate (widely spaced myelin) and a response to treatment to reduce paraprotein levels. Other antibody targets have been proposed and identified in a small number of cases (for example gangliosides GM1 and GD1b, and sulphatide), and more are postulated.

The presence of a neuropathy alone is not a justification for treatment, but steady progression with accumulating disability should prompt action. There is little evidence to recommend specific therapies (Rajabally 2011); outcomes of clinical trials are hampered by few appropriate participants for trial inclusion, their heterogeneity and use of ordinal multi-item composite outcome measures that lack reliability, validity and responsiveness (DeVellis 2006, Merkies, *et al* 2012).

Diagnostic Evaluation

General Work-up

As with any diagnostic evaluation, items of diagnostic or therapeutic usefulness appear through the assessment and together assist a final decision. We first present the broad concepts of diagnostic evaluation, before discussing specifics relating to each diagnosis below.

Neurological evaluation of a PN accompanied by a paraprotein is best achieved with parallel investigation to establish the nature of the IgM monoclonal gammopathy as MGUS, asymptomatic or symptomatic WM (**Table 1**). In this document, the use of the terms IgM MGUS, asymptomatic WM and symptomatic WM are based on the clinicopathological definition of WM according to the consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia (Owen, *et al* 2003). A history and examination will delineate the important clinical features of the PN and are key to further appropriate testing and management (**Table 2**). It is important to identify alternative causes of neuropathy such as diabetes, nutritional deficiencies and alcohol, connective tissue disease, drugs (the majority are axonal, rather than demyelinating) or pre-existent hereditary neuropathy. The nature of the PN symptoms, including speed of onset, clinical course, rate of change and effect on functional abilities, as well as the involvement of motor, sensory and autonomic systems assists the differential diagnosis and subsequent decision making. The conclusions from these investigations, based on a discussion between a haematologist and neurologist provides a foundation to establish whether the PN is likely related to the monoclonal gammopathy and whether there is a need for treatment.

Nerve conduction tests and electromyography

Electrical tests including nerve conduction studies (NCS) and electromyography (EMG) are an extension of the clinical examination and characterise the nature, pattern and extent of nerve damage. Evidence for demyelination and/or axonal damage should be determined by standard criteria (1991). Features indicative of axonal and demyelinating neuropathy are shown in **Table 3**.

Electrophysiological features associated with IgM-associated PN include uniform symmetrical reduction of conduction velocities; more severe sensory than motor involvement; disproportionately prolonged distal motor latency (DML) and absent sural potentials. Partial motor conduction block and marked distal CMAP dispersion are very rare (Joint Task Force of the and the 2006). Specific features of the different paraprotein associated neuropathies are delineated below in each section.

It is important to pose a specific question or have a discussion with the neurophysiologist when requesting NCS to permit modification of the examination for maximal yield. The implantation of some cardiac pacemakers may contraindicate NCS, as life threatening events can be triggered by an external voltage applied in close proximity to an implantable cardioverter/defibrillator device. Anticoagulants are associated with a risk of intramuscular haematoma with EMG needling; anticoagulants might need to be suspended prior to an examination.

Recommendations:

- Neurophysiological testing is recommended where a neuropathy is identified on clinical examination to clarify the nature of the neuropathy and expand or curtail investigation.
- Specific clinical questions should be included in the request for neurophysiological studies to allow for appropriate modifications by the neurophysiologist.
- The results of neurophysiological testing should be assessed in conjunction with the clinical picture and the haematological context (MGUS, asymptomatic, symptomatic WM) in order for meaningful and practical conclusions to be drawn, and how this influences the management of the patient,
- Relevant steps should be taken to minimise the risk to the patient on anticoagulants or with a pacemaker or implantable defibrillator.

CSF Examination

CSF protein (normal range usually 0.15-0.45g/l) is significantly elevated (>1.0 g/L) in up to 80% of demyelinating paraproteinaemic neuropathies (Notermans, *et al* 2000); in these cases, the effect of the IgM antibody is most likely to be humoral attack. In other cases, the clinical picture is of painful patchy nerve dysfunction or progressive involvement of nerve roots suggestive of infiltration. Where relevant symptomatology is present, such as an asymmetrical or mononeuritis multiplex pattern, infiltration of the peripheral nerves may be the cause, as humoral mechanisms typically result in a symmetrical length-dependent neuropathy. If neurolymphomatosis is suspected, biopsy of possibly affected nerves is often not feasible, so in this situation, the judicious use of lumbar puncture for CSF examination combined with appropriate imaging (PET-CT and/or gadolinium-enhanced MRI) may help to confirm the diagnosis (Shaikh, *et al* 2015). If the clinical examination is in keeping with CNS disease, then the presence of malignant cells in the CSF should be sought by immunocytology and/or flow cytometry. A single large volume (10 ml) CSF sample will have a 50% chance of identifying pathological cells; three consecutive 10 ml samples increases the pick-up rate to about 90%.

Recommendations:

- In cases of demyelinating neuropathy, although not mandatory, examination of the CSF supports the diagnosis if the protein is raised and other biochemical constituents are normal.
- When the clinical work up is unrevealing or inconclusive, and a malignant meningitis or invasion of the CNS is suspected, (repeated) examination of the CSF is indicated for cellular constituents.
- If cellular material is identified, then cytological examination and/or immunophenotyping is indicated to characterize the cellular population.

Nerve Biopsy

The indications for nerve biopsy are limited. Sensory nerve biopsies are invasive and associated with

a permanent sensory deficit and a 10-20% risk of post biopsy pain. There are limited sensory nerves available for biopsy because of anatomy, normal control specimens or affectation.

However, if a comprehensive clinical work up fails to identify a cause in the presence of a progressive and debilitating PN, and/or amyloidosis, vasculitis or direct nervous system invasion is suspected, a sensory nerve biopsy is recommended, if possible in a centre with experience in procuring and analysing the biopsy. In suspected amyloidosis, alternative sites for biopsy such as bone marrow, abdominal fat or rectum should be explored first. Where histological evidence for amyloid has been found in other tissues and the clinical and neurophysiological characteristics of the PN are compatible with amyloidosis, a nerve biopsy is usually not required.

Congo red staining identifies amyloid, which can be further sub classified by immunohistochemistry (Thomas and King 1974) or mass spectrometry (Klein, *et al* 2011) where available to identify immunoglobulin light chain or familial types, for example transthyretin (the most common). In case of suspected lymphomatous infiltration, immunohistochemical staining for monoclonal B cell surface markers is mandatory, although the diagnostic yield is often low due to the small sample size.

Recommendations:

- Where a comprehensive systemic work up has failed to identify a cause and there remains a suspicion of amyloid, vasculitis or direct cellular invasion, in atypical cases unresponsive to treatment, or progressive, debilitating conditions, a sensory nerve biopsy may be indicated.
- The risk-benefit ratio of carrying out the biopsy needs to be carefully weighed, if the procedure is likely to alter the course of management, it should be performed.
- The need for a nerve biopsy should be ratified by a neurologist with a specialist interest in PN and carried out at a centre with relevant expertise.

Skin biopsies

Full thickness skin biopsy samples may be useful for histological confirmation of a small fibre neuropathy. Procedural risks of a punch biopsy are very low, and complications are rare. Epidermal nerve fibre density is abnormally decreased in only two-thirds of patients suspected of having small fibre neuropathy (Periquet, *et al* 1999). Dermal fibre analysis is developing in usefulness for demonstrating IgM deposits on myelinated nerve fibres (Lauria, *et al* 2006) , but this remains in development.

Recommendations:

- Skin biopsy is not routinely recommended. A normal skin biopsy does not rule out a small fibre neuropathy and the test rarely provides information that alters the management of the patient.

Imaging

MRI should ideally be performed *prior* to a diagnostic lumbar puncture (LP) for CSF analysis, as false-positive leptomeningeal enhancement may result from LP-related meningeal irritation.

Specific MR sequences with or without gadolinium enhancement of the neuraxis is indicated in cases of suspected neural compression, leptomeningeal or radicular infiltration (Keraliya, *et al* 2015) or where peripheral *and* central nervous system (CNS) features are present in the clinical examination. Focal neurological signs of motor, sensory or higher function are indicative of possible brain involvement visualised as parenchymal lesions on MRI images, the so called Bing-Neel syndrome (Castillo, *et al*). Progressive, sequential root or cranial nerve involvement, radicular pain or symptoms of meningism are indicative of meningeal involvement and may be identified with leptomeningeal, subependymal or dural enhancement, cranial nerve enlargement and enhancement. Spinal MRI can reveal enhancing intradural soft tissue, thickening and enhancement of nerve roots and leptomeningeal enhancement (Haldorsen, *et al* 2011). Lymphomatous infiltration of individual nerves, spinal roots, cranial nerves or plexi is characterised by nodular or diffuse thickening of nerves which usually enhance with contrast (Grisariu, *et al* 2010). Ultrasound scanning can identify focal and more extensive thickened nerves in the distal limbs, but has no other differentiating ability.

Recommendations:

- MRI of the neuraxis should be performed prior to lumbar puncture to avoid false positive meningeal enhancement.
- Prior discussion of likely sites of involvement with an experienced neuroradiologist will ensure that the correct sequences of the correct anatomical area are performed with appropriate Gadolinium enhancement.
- MRI, CT and Ultrasound have little ability to differentiate the nature of individual nerve lesions but can target diagnostic biopsies.

Clinical Phenotypes and their treatment

The paraprotein-associated neuropathies fall into a number of identifiable clinical groups, in which the paraprotein is considered causal. Where a causal association is suspected, the following statements can act as a useful guide:

- In the presence of an IgM MGUS or WM and high titres of anti-MAG antibodies, a causal relationship between the paraprotein and a demyelinating PN is highly probable (high quality evidence).
- An IgM paraprotein with high titres of IgM antibodies to other neural antigens (such as GD1a, GD1b, GM2) and a slowly progressive predominantly distal neuropathy may be causally associated (low quality evidence).
- An IgM paraprotein with a high titre of anti-GM1 associated with a multifocal motor neuropathy is likely to be causally linked (moderate quality evidence).
- An IgM paraprotein with a high titre of antibodies against disialyated gangliosides (GQ1b, GT1a, GT1b, GD1b, GD2 and GD3) and a neuropathy with ophthalmoplegia and ataxia (CANOMAD) is likely associated (high quality evidence).

A causal antibody relationship is *less likely* in IgM MGUS cases where:

- The neuropathy is axonal.
- Time to peak of PN <6 months; most antibody targeted paraprotein associated neuropathy is slowly progressive. Amyloid, vasculitis or other incidental neuropathy is more likely.
- The neuropathy has a relapsing and remitting course (spontaneous or to prednisolone/IVIG treatment) which is more suggestive of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- There is cranial nerve involvement (except CANOMAD) – more likely meningeal (cellular infiltration), amyloid (light chain infiltration), vasculitic, CIDP, infectious, idiopathic.
- Non-symmetrical distribution (consider vasculitis, infiltration, diabetes, pressure palsies)
- History of infection 10 days to 6 weeks preceding the onset (GBS, polio and other viral neuroinvasive diseases, HIV, diphtheria, Lyme disease, leprosy).
- A lambda light chain is present and systemic symptoms suggestive of possible POEMS syndrome are identified.

In the following section, the most common clinical entities will be addressed. A schematic decision tree is shown in **Figure 1**, which assists in clarifying the pathways to particular IgM-associated diagnoses.

IgM MGUS-associated peripheral neuropathy without antibodies (Distal acquired demyelinating sensorimotor neuropathy) PN

The typical clinical phenotype of antibody-negative PN seen in the setting of IgM MGUS is a predominantly distal, chronic (>6 months), symmetrical, painless neuropathy with a predominance of sensory symptoms, accompanied by imbalance or ataxia, tremor (up to 89% at onset, 15% disabling) and mild or minimal weakness and demyelination on electrophysiological studies (Nobile-Orazio, *et al* 2000, Smith 1994). This phenotype is so characteristic, that the acronym DADS (Distal, Acquired, Demyelinating, Sensory-neuropathy) has been coined to capture its features. While the DADS phenotype is most commonly associated with anti-MAG antibodies (Katz, *et al* 2000) (see below), some patients may have more prominent ataxia and others proximal weakness reminiscent of CIDP (Katz, *et al* 2000).

Antibody targets for the paraprotein are seldom found but the uniform clinical picture is well recognised and the link is presumed, likely constituting one of the "IgM-related disorders" within the criteria proposed by Owen *et al* (Owen, *et al* 2003).

Rapid progression, a mixed axonal and demyelinating or an axonal predominant PN should raise the possibility of primary (AL) amyloidosis, especially if neuropathic pain or autonomic dysfunction are present (Vital, *et al* 2004) or cryoglobulinaemia (Gemignani, *et al* 2005) if appropriate features are present.

A number of studies of anti-MAG-negative IgM-associated PN have been reported. Response to immunotherapy approaches including intravenous immunoglobulin (IVIG), corticosteroids, plasma exchange, or a combination is poorer in IgM-PN/DADS than idiopathic CIDP (Larue, *et al* 2011, Simmons, *et al* 1993a). Although short-term improvement has been shown, no long term benefit has been shown for IVIG in IgM MGUS-associated PN (Comi, *et al* 2002, Dalakas 1996).

Although these approaches have not been tested prospectively, in patients with rapid worsening neuropathy a trial of IVIG, steroids or plasma exchange may prevent irreversible disability in case the IgM is irrelevant. Other agents including chlorambucil and interferon-alpha have not been pursued beyond early studies because of toxicity and lack of perceived effect or no benefit in trials (Mariette, *et al* 2000, Oksenhendler, *et al* 1995)

Recommendations

- In patients without significant disability or haematological reason for treatment, there is no indication for immunosuppressive or immunomodulatory treatment, but ongoing surveillance is recommended to detect change that requires intervention.
- Conversely, in patients with significant or progressive disability associated with a demyelinating non-MAG associated IgM MGUS with a co-existent neuropathy, immunosuppressive or immunomodulatory treatment may be considered.
- In treated patients who are unresponsive to measures such as IVIG, steroids or plasma exchange, agents such as rituximab, in combinations with alkylators, purine analogues and steroids should be considered after discussion between a neurologist and a haematologist.
- Symptomatic treatment for tremor (propranolol, clonazepam, topiramate, gabapentin, barbiturates, botulinum toxin) and paraesthesia (gabapentinoids, tricyclic or newer antidepressant drugs) should be considered, and reassurance that symptoms are unlikely to

worsen significantly for years. Such patients should remain under review to identify evidence for clinical evolution.

Anti-MAG antibody-associated PN

Up to 50% of patients with IgM-associated demyelinating PN have anti-myelin associated glycoprotein (MAG) antibodies, far more commonly IgM κ rather than λ (Nobile-Orazio, *et al* 1994) either in the setting of IgM MGUS or WM (Baldini, *et al* 1994). Men are more often affected than women and from unsteadiness, tremor or sometimes distal weakness the typical age of onset is in the 7th decade and the course of the disease is insidious. In up to 50% patients, significant disability develops 10-15 years following the diagnosis (Nobile-Orazio, *et al* 2000).

All patients with IgM-associated demyelinating PN should be tested for anti-MAG antibodies. A clinically significant result is 'strongly positive' (for example > 70000 Bühlmann units (BTU)). 'Weakly positive' (1000 – 7000 BTU) or 'positive' (7000 - 70000 BTU) anti-MAG antibodies are less specific for typical anti-MAG neuropathy and may occur in the absence of a PN or alongside an unconnected neuropathy. Low titres of anti-MAG IgM (1:200 or less) have been detected in 17 of 101 control patients without IgM M-proteins (Nobile-Orazio, *et al* 1989).

If the anti-MAG assay is negative in the presence of an IgM-associated PN, testing for IgM antibodies against other neural targets including the gangliosides GM1, GD1a, GD1b, GT1b, GM2 and GM3 and the paragloboside SGPG should be undertaken. Positive results may be supportive of a link between the paraprotein and the PN. If these antibodies are present, the probability of an association is increased but not proven. GM1 antibodies may be causally associated with a multifocal motor neuropathy, as can IgM GD1b antibodies. IgM disialosyl antibodies associate with CANOMAD (see below). Of IgM-related demyelinating neuropathies, 30-40% still have no identifiable antibody.

The electrophysiological features associated with anti-MAG IgM demyelinating PN are readily recognisable with slowing of the main trunk velocity but disproportionate prolongation of the distal motor latency (DML). Conduction block and abnormal temporal dispersion, more typically seen in CIDP, are very rare in this setting (Notermans, *et al* 2000).

A Cochrane Review summarises the evidence for treatments of IgM anti-MAG neuropathy (Lunn and Nobile-Orazio 2012). IVIG may have some limited benefit in the short term (timescale of weeks), but this is of little clinical use. Corticosteroids alone are not effective (Nobile-Orazio, *et al* 2000), but may be beneficial in combination with other agents such as cyclophosphamide (Niermeijer, *et al* 2007). The purine analogues have demonstrated a modest improvement in some studies (Ghosh, *et al* 2002, Niermeijer, *et al* 2006), and although tolerance of these agents was reported as good, the studies were small. For occasional patients with rapidly worsening neuropathy especially with signs of motor disability, combinations of active agents or even high dose therapy have been attempted.

There are several non-randomised studies of rituximab in anti-MAG-associated PN many reporting positive benefit in small groups of patients (Briani, *et al* 2011, Hospital, *et al* 2013, Renaud, *et al* 2006, Renaud, *et al* 2003, Zara, *et al* 2011). Five published studies reported a worsening of the PN following rituximab (Broglia and Lauria 2005, Gironi, *et al* 2006, Sala, *et al* 2014, Stork, *et al* 2013, Weiss and Becker 2014). In the largest report (10 patients) of deterioration (Sala, *et al* 2014) worsening was acute and severe, and occurred during the treatment period, possibly related to an IgM flare. All the patients improved after deterioration but at final evaluation only one improved compared to baseline, five worsened and four stabilized.

Two randomised controlled trials of rituximab have been negative in their primary outcome measures, but the trials were both underpowered and the outcome measures inadequate (Dalakas, *et al* 2009,

Leger, *et al* 2013). Secondary outcome measures including patient impression of change were positive and a Cochrane Systematic review containing a meta-analysis highlights significant therapeutic benefit {Lunn and Nobile-Orazio in press}.

Factors predictive of a response to rituximab in anti-MAG neuropathy remain to be elucidated. Short disease duration (less than 2 years), active progression at time of treatment and preservation of nerve density in biopsies might predict response (Treon SP 2010). Anti-MAG titres and levels of IgM paraprotein are neither related to the severity of neuropathy nor predictive of response to treatment. It has been suggested that a significant drop in antibody titres might be necessary to achieve a response but the depth of optimal haematological remission is not known (Benedetti, *et al* 2007). Complete elimination of the clonal IgM is probably not practical or possible.

Stability rather than improvement is the most likely outcome of treatment although rare dramatic improvements are reported.

Recommendation:

- There is moderate quality evidence that rituximab is of benefit in the treatment of anti-MAG demyelinating neuropathy. The standard dose of 375mg/m² administered weekly for 4 weeks as used in most studies is recommended.
- In patients with significant or progressive disability associated with a demyelinating anti-MAG associated IgM MGUS with a co-existent neuropathy, immunosuppressive or immunomodulatory treatment may be considered as an alternative to Rituximab depending on availability, comorbidity and patient preference.
- Measurably progressive disease causing disability is an indication to consider definitive treatment given earlier (<2 years from onset where possible) rather than later.
- Anti-MAG titres and levels of IgM paraprotein are neither related to the severity of neuropathy nor predictive of response to treatment.

Waldenströms-associated peripheral neuropathy

Symptoms of PN are present in about 20% of patients with WM at diagnosis, and up to 50% are affected at some time in the course of their disease (Levine, *et al* 2006), most often a distal chronic symmetrical predominantly sensory polyneuropathy. Nerve conduction studies show evidence of demyelination with prolonged DML and reduced conduction velocities in the cases associated with MAG antibodies. There are many exceptions with axonal neuropathies or mixed axonal and demyelinating neuropathies seen, especially when anti-MAG assay is negative (Viala, *et al* 2012).

When significant titres of anti-MAG antibodies (for example ‘strongly positive’ or >70,000 BTU) are present, they are probably pathogenic in the WM setting. If atypical clinical or electrophysiological features are present, other pathologies including amyloidosis, cryoglobulinaemia, vasculitis or direct tumoural invasion of peripheral nerves may be instrumental and appropriate investigations carried out as above.

Where neurotoxic therapy has been used, chemotherapy-induced PN, which is almost always axonal with rare exceptions, may be present and will need to be distinguished from WM-associated PN, based on the temporal pattern, character and electrophysiology.

The criteria for the initiation of therapy in symptomatic WM are well established (Dimopoulos, *et al* 2014) and include PN due to WM.

There are no trial data specifically assessing the efficacy of treatment options in WM-associated PN. Treon *et al* reported on the incidence, characteristics and treatment outcome of 199 disease-related PN identified in 900 WM patients. Among 122 PN patients evaluated for neuropathic antibodies, 24.5%, 1.64%, and 0.81% were positive for MAG, GM1, and sulfatide antibodies, respectively (Treon SP 2010). Thirteen of 61 (21.3%) patients examined for amyloid were confirmed positive. One hundred and fifty-one PN patients received chemotherapy comprising an alkylator, purine analogue or rituximab; or rituximab / purine analogue combination, cyclophosphamide, thalidomide or bortezomib. Of these, 71 (47%) had improvement and 8 (5.3%) had complete resolution of PN following therapy. Symptomatic improvement was more likely with non-amyloid related PN, in patients who achieved a major haematological response, those who received therapy within 24 months of the onset and those who received rituximab combination vs. any monotherapy vs. rituximab alone.

It is important to be aware that a paradoxical increase in IgM levels following rituximab (‘flare’) occurs in 30% to 70% of patients immediately after completing the rituximab course (Treon, *et al* 2004) and may be associated with a worsening of existing PN (Noronha, *et al* 2006), although this has been reported to be temporary. This phenomenon may be severe and resemble an acute inflammatory demyelinating neuropathy requiring appropriate management. Appropriate precautions should be taken in patients considered at high risk of a flare (IgM > 40 g/L), such as deferring rituximab until cycle 2 of combination chemotherapy or performing prior plasma exchange.

Avoidance of neurotoxic agents is important, although the speed of response to proteasome inhibitor-containing therapy may outweigh the risk of worsening the PN. Alternative dosing strategies such as weekly dosed bortezomib or second generation agents like carfilzomib show promise in this regard (Alsina, *et al* 2012, Treon, *et al* 2014). Vinca alkaloids have no place in WM patients since they are associated with increased neuropathy rates without increasing response rate (Ioakimidis, *et al* 2009). Ibrutinib has shown symptomatic improvement in WM associated PN that progressed after rituximab and could also be considered in WM patients with symptomatic IgM related PN (Treon SP 2015).

Plasmapheresis (Cortese, *et al* 2011), corticosteroids and IVIG are of little or no value (Treon SP 2010) in the treatment of WM-associated neuropathies.

WM-related CNS manifestations, including Bing-Neel Syndrome (Castillo, *et al* 2016) and myelopathy are not within the scope of this review and will be addressed elsewhere.

Recommendations:

- Patients with slowly progressing WM or PN do not require immediate therapy.
- Where treatment is required, treatments such as Rituximab, Dexamethasone, Cyclophosphamide and Rituximab (DRC), Bendamustine-Rituximab (BR), Carfilzomib, Rituximab, Dexamethasone (CARD) or purine analogue combinations are possible options.
- When indicated, treatment of appropriate intensity to remit both the systemic disease and the neurological component is required.
- Ibrutinib, where available could be considered in the setting of intolerance of chemotherapy-based therapies or if previous therapies have failed.
- Appropriate precautions should be taken in patients considered at high risk of a flare (IgM > 40 g/L), such as deferring rituximab until cycle 2 of combination chemotherapy or performing prior plasma exchange.
- Avoidance of neurotoxic agents is important; the vinca alkaloids have no place in the management of WM, particularly those with PN.
- Plasmapheresis, corticosteroids and IVIG are of little or no value in the treatment of WM-associated neuropathies.

CANOMAD

Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl ganglioside (IgM Anti-GD1b/GT1b/GQ1b) antibodies (CANOMAD) is a rare chronic neuropathy which presents as a chronic peripheral sensory ataxia, ophthalmoplegia and sometimes other cranial nerve involvement (Willison, *et al* 2001). NCS show a mixed picture of axonal loss and demyelination features including very low or absent sensory action potentials and degrees of slow motor conduction velocities. It is important to exclude alternative, infiltrative causes of cranial nerve abnormalities.

Clinical improvement has been noted following IVIG and Rituximab (Loscher, *et al* 2013).

Recommendations:

None specific; each case must be treated on its own merit following discussion between haematologist and neurologist.

AL Amyloidosis

AL amyloidosis should always be considered as a possible cause of a paraproteinaemic neuropathy. PN is reported as a symptomatic clinical feature in up to 20% of patients with AL amyloidosis, and evidence for a subclinical PN is found in 35% of patients (Matsuda, *et al* 2011, Rajkumar, *et al* 1998). Common presentations include a progressive, painful small fibre predominant length-dependent PN which typically starts in the feet, accompanied by an autonomic neuropathy in about 65% of cases (Rajkumar, *et al* 1998). Amyloid causes direct nerve damage through the presumed action of fibrils in the endoneurium and the endoneurial vessels. Amyloid can also cause nerve damage by other mechanisms for example entrapment neuropathies including carpal tunnel syndrome, and neural or radicular tumorous infiltration resulting in multifocal mononeuropathies, lumbosacral or brachial radiculopathies and cranial neuropathies in the absence of a polyneuropathy (Matsuda, *et al* 2011, Rajkumar, *et al* 1998).

Amyloid is most often a systemic disease with other organ involvement and this is a strong pointer to an amyloid PN. Other features should be actively sought, such as cardiac insufficiency and arrhythmia, renal impairment with proteinuria, autonomic neuropathy, GI bleeding, macroglossia and bleeding diatheses. Early recognition is more likely to curtail irreversible organ damage and reduce mortality. Notwithstanding pre-existing co-morbidities, screening for AL amyloidosis can be performed using two biomarkers, serum NT-proBNP and urinary albumin, that detect early amyloidosis in 97% of patients (Merlini, *et al* 2013). Heart damage is a major determinant of survival, and staging with cardiac biomarkers guides treatment (Merlini, *et al* 2014).

Nerve conduction studies show a symmetrical, axonal sensorimotor neuropathy but occasionally patchy presentations or slowing (reported as ‘demyelination’) are found. A definitive diagnosis requires the demonstration of amyloid in a tissue. The most accessible and innocuous site is periumbilical abdominal fat that shows Congo red positive deposits in 80% of patients (Fernandez de Larrea, *et al* 2015). When combined with similar analysis of bone marrow, the sensitivity reaches 90% or more. In the rare patients in whom both biopsies are negative, a nerve biopsy might be considered. The sensitivity of nerve biopsy for detecting amyloid varies from 30-100% (Simmons, *et al* 1993b), depending upon the size and site of the biopsy and the expertise of the pathologist.

Urgent measures to suppress the clone responsible for the production of the amyloid protein are essential. Where possible, high dose therapy and autologous stem cell transplantation is the treatment of choice, resulting in a 53% 10-year survival for those achieving a complete response (Sanchorawala and Seldin 2007). Best outcomes are likely to be achieved in centres which specialise in this condition. For transplant ineligible patients (75-80% cases), melphalan-dexamethasone (Palladini, *et al* 2007) or bortezomib-based combinations are effective (Merlini, *et al* 2013). Bortezomib needs to be administered with particular caution due to its neurotoxic potential, which can be reduced by subcutaneous administration and weekly scheduling. There is minimal evidence for the effect of carfilzomib in this setting and there is some concern about possible cardiotoxicity (Atrash, *et al* 2015). For relapsing patients, Lenalidomide (Palladini, *et al* 2012, Sanchorawala, *et al* 2013) and Pomalidomide (Dispenzieri, *et al* 2012) are recommended.

Recommendations

- Treatment of AL amyloidosis should be risk-adapted and response-tailored and neurotoxic agents used with caution.

- High dose therapy and autologous stem cell transplantation is the treatment of choice in suitable patients and should be carried out in centres with appropriate expertise.
- Melphalan-dexamethasone or bortezomib-based combinations are recommended in transplant-ineligible patients.
- Lenalidomide and Pomalidomide are a good options for refractory/relapsed patients.

Small fibre neuropathy

Typical small fibre neuropathy presents with length dependent burning pain beginning in the feet and may spread more proximally in a length dependent fashion. Symptoms are worse at night where they can disturb sleep resulting in fatigue and increased daytime pain.

Similar small fibre symptoms, presenting as patchy dermatomal sensory disturbance subsequently coalescing are due to small fibre involvement of the sensory ganglia of lesser understood pathology.

The diagnosis of a small fibre neuropathy is made on the basis of the history; the only clinical sign is a length-dependent sensory alteration to pinprick or temperature. This may be patchy with ganglion involvement. Investigations to prove small fibre involvement are quantitative sensory tests and skin biopsies stained for epidermal nerve fibres (distal small fibre neuropathy) which can be quantified in microscopy.

Treatment is symptomatic with gabapentinoids, tricyclic or newer antidepressants (Hoeijmakers, *et al* 2012, Themistocleous, *et al* 2014).

Recommendations

- Evidence-based justification for treating a WM or MGUS-associated small fibre neuropathy is completely lacking.
- Treatment is usually symptomatic with tricyclic antidepressants, newer SSRI/SNRI drugs, opioids and gabapentinoids (very low quality evidence).

Clinical Outcome Measures

Historically, outcome measures have focused on assessment of impairment based on muscle strength and sensory testing and disability, using classical test theory derived scales.

The Medical Research Council (MRC) sum score and the Neuropathy Impairment Score (NIS) sums the scores muscles to represent the overall strength of a patient (Dyck, *et al* 2003). Sensory scores, including the Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (ISS) and Neuropathy Impairment Sensory score (NIS_{sens}) are similarly used to capture the sensory status of a patient (Dyck, *et al* 2005) but these measures require detailed and consistent neurological assessment and may not show meaningful changes over time.

Disability measures have been developed for inflammatory neuropathies, and the overall neuropathy limitations score or ONLS (van Nes, *et al* 2008) is a standard measure for FDA licensing requirements. Disability measures more accurately reflect meaningful change in a patient's condition.

Rasch Theory-built scales linearly reflect patient function over the whole range of abilities and are designed and validated for individual diseases. The Inflammatory Rasch-Built Overall Disability Scale (I-RODS) designed as part of the Peripheral Neuropathy Outcome Measurement Standardisation (PeriNomS) study (Draak, *et al* 2014, Merkies, *et al* 2003, Vanhoutte, *et al* 2012) is a valid disability scale for inflammatory neuropathies which captures meaningful changes over time.

Recommendations:

- The I-RODS more often captures clinically meaningful changes over time, with a greater magnitude of change, compared with the INCAT-ONLS disability scale and its use is therefore suggested in future trials involving patients with inflammatory neuropathies.

Models of Care

The clinical entities that comprise IgM-associated PNs are managed in a variety of clinical settings, by haematologists, oncologists and neurologists. In order to achieve successful outcomes for these patients, joint working across disciplines offers a favourable approach that should overcome the barriers of working in isolation and risking a failure to perform appropriate diagnostics as well as offer optimum therapeutic and supportive input.

Physical and occupational therapists play a vital role in helping to improve and maintain functions that may be limited by PN including exercise intervention to help improve strength (Streckmann, *et al* 2014), balance and coordination activities which can help decrease the risk of falling (Riva, *et al* 2014). Tailored home exercise is acceptable to individuals with inflammatory neuropathies and is associated with significant improvements in activity limitation, fatigue, quality of life and mood (White, *et al* 2015). Patient education can focus on improving safety, preventing injury, and finding alternative ways to perform certain tasks.

Provision of appropriate and well-fitting orthotic supports, can improve the efficiency of movement as well as harvesting energy from gait (Alam, *et al* 2014).

Recommendations:

- A suggested model of care is a combined neurological and haematological clinic, in which patients are seen jointly by a specialist neurologist and haematologist and a decision can be made about the sequence of investigations, interventions and the formulation of a treatment plan.
- Appropriate and timely referral to physical, occupational and orthotic professionals is recommended in order to maximise safety and function.

Future Perspectives

A number of biological agents are currently under investigation in WM, may prove particularly suited to the treatment of patients with paraproteinaemic neuropathies, given their non-neurotoxic side effect profiles.

Next generation proteasome inhibitors, such as carfilzomib has been assessed in combination with rituximab and dexamethasone (Treon, *et al* 2014) shows an ORR of 87% and a low risk of neurotoxicity. Everolimus, an oral mTOR inhibitor (Treon SP 2013) (ORR 72% in the upfront setting) has some grade ≥ 2 adverse events which do not include PN. Other effective agents which have favourable side effect profiles in this setting include the BTK inhibitors ibrutinib (Treon, *et al* 2015), acalabrutinib (Wu, *et al* 2016), and BG -3111 (Constantine Tam 2015) and IMO-8400 (Sheeba K. Thomas 2015), an oligonucleotide specifically designed to inhibit toll-like receptor signaling pathways, for which MYD88 is a key linker protein. Daratumumab, a human antibody to CD38, has also shown encouraging responses (Phipps, *et al* 2015) and may be particularly suited to those instances when the clinical features are a consequence of the M protein such as hyperviscosity and neuropathy.

Conclusions

There is much to be done to improve outcomes for patients with IgM and Waldenströms-associated peripheral neuropathies. Starting with early recognition of the problem, appropriate causal attribution achieved through sensitive diagnostics which are not overly invasive, timely therapeutic intervention with effective and non-neurotoxic therapies, achievement of an appropriate degree of clonal reduction for optimum clinical outcomes and the use of reproducible and readily applicable tools to measure outcomes. Clinical trials of emerging therapies are urgently needed in this clinical setting.

Author Contributions

The entire authorship made up the Consensus Panel which reviewed this subject and devised the strategy for the paper. SD, MJK, MPL wrote the paper, JJC, MD, EK, EL, VL, GM, SPT and JMV contributed to various sections of the paper and reviewed the completed document.

Author Disclosures

SD: Honoraria from Janssen; JJC: Honoraria from Alexion, Biogen, Celgene and Otsuka; research funding from Abbvie, Gilead, Millennium and Pharmacyclics, MD: Honoraria and advisory roles with Celgene, Janssen, Amgen, Novartis; EK: Honoraria from Janssen, Onyx, Takeda; VL: Honoraria, advisory role and on Speakers' Bureau with Roche, Janssen, Gilead, Glaxo Smith Kline, Honoraria and on Speakers' Bureau with MuniPharma; GM: Honoraria from Janssen, Takeda; SPT: Advisory role with Janssen and Pharmacyclics; JMV: none; MPL: none

Acknowledgements

The authors would like to acknowledge the contribution of Dr Jindriska Lindsay (Kent, United Kingdom) for reviewing the manuscript, and the staff of the Bing Center for WM for facilitating the consensus panels that enabled this manuscript,

References

- (1991) Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. *Neurology*, **41**, 617-618.
- Alam, M., Choudhury, I.A. & Bin Mamat, A. (2014) Mechanism and design analysis of articulated ankle foot orthoses for drop-foot. *ScientificWorldJournal*, **2014**, 867869.
- Alsina, M., Trudel, S., Furman, R.R., Rosen, P.J., O'Connor, O.A., Comenzo, R.L., Wong, A., Kunkel, L.A., Molineaux, C.J. & Goy, A. (2012) A phase I single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. *Clin Cancer Res*, **18**, 4830-4840.
- Atrash, S., Tullos, A., Panozzo, S., Bhutani, M., Van Rhee, F., Barlogie, B. & Usmani, S.Z. (2015) Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib. *Blood Cancer J*, **5**, e272.
- Baldini, L., Nobile-Orazio, E., Guffanti, A., Barbieri, S., Carpo, M., Cro, L., Cesana, B., Damilano, I. & Maiolo, A.T. (1994) Peripheral neuropathy in IgM monoclonal gammopathy and Waldenstrom's macroglobulinemia: a frequent complication in elderly males with low MAG-reactive serum monoclonal component. *Am J Hematol*, **45**, 25-31.
- Benedetti, L., Briani, C., Grandis, M., Vigo, T., Gobbi, M., Ghiglione, E., Carpo, M., Cocito, D., Caporale, C.M., Sormani, M.P., Mancardi, G.L., Nobile-Orazio, E. & Schenone, A. (2007) Predictors of response to rituximab in patients with neuropathy and anti-myelin associated glycoprotein immunoglobulin M. *J Peripher Nerv Syst*, **12**, 102-107.
- Briani, C., Vitaliani, R., Grisold, W., Honnorat, J., Graus, F., Antoine, J.C., Bertolini, G., Giometto, B. & Euronetwork, P.N.S. (2011) Spectrum of paraneoplastic disease associated with lymphoma. *Neurology*, **76**, 705-710.
- Broglio, L. & Lauria, G. (2005) Worsening after rituximab treatment in anti-mag neuropathy. *Muscle Nerve*, **32**, 378-379.
- Castillo, J.J., D'Sa, S., Lunn, M.P., Minnema, M.C., Tedeschi, A., Lansigan, F., Palomba, M.L., Varettoni, M., Garcia-Sanz, R., Nayak, L., Lee, E.Q., Rinne, M.L., Norden, A.D., Ghobrial, I.M. & Treon, S.P. (2016) Central nervous system involvement by Waldenstrom macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study. *Br J Haematol*, **172**, 709-715.
- Comi, G., Roveri, L., Swan, A., Willison, H., Bojar, M., Illa, I., Karageorgiou, C., Nobile-Orazio, E., van den Bergh, P., Swan, T., Hughes, R., Aubry, J., Baumann, N., Hadden, R., Lunn, M., Knapp, M., Leger, J.M., Bouche, P., Mazanec, R., Meucci, N., van der Meche, F., Toyka, K., Inflammatory Neuropathy, C. & Treatment, G. (2002) A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. *J Neurol*, **249**, 1370-1377.
- Constantine Tam, A.P.G., Stephen Opat, Matthew Ku, Michael Gilbertson, Mary Ann Anderson, John F. Seymour, David S. Ritchie, Carmen Dicorleto, Belinda Dimovski, Eric Hedrick, Jianxin Yang, Lai Wang, Lusong Luo, Ling Xue, Andrew W. Roberts (2015) The BTK Inhibitor, Bgb-3111, Is Safe, Tolerable, and Highly Active in Patients with Relapsed/ Refractory B-Cell Malignancies: Initial Report of a Phase 1 First-in-Human Trial. In: *Blood*, Vol. 126, p. 832.
- Cortese, I., Chaudhry, V., So, Y.T., Cantor, F., Cornblath, D.R. & Rae-Grant, A. (2011) Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*, **76**, 294-300.
- Dalakas, M.C. (1996) Clinical benefits and immunopathological correlates of intravenous immune globulin in the treatment of inflammatory myopathies. *Clin Exp Immunol*, **104 Suppl 1**, 55-60.

- Dalakas, M.C., Rakocevic, G., Salajegheh, M., Dambrosia, J.M., Hahn, A.F., Raju, R. & McElroy, B. (2009) Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol*, **65**, 286-293.
- DeVellis, R.F. (2006) Classical test theory. *Med Care*, **44**, S50-59.
- Dimopoulos, M.A., Kastiris, E., Owen, R.G., Kyle, R.A., Landgren, O., Morra, E., Leleu, X., Garcia-Sanz, R., Munshi, N., Anderson, K.C., Terpos, E., Ghobrial, I.M., Morel, P., Maloney, D., Rummel, M., Leblond, V., Advani, R.H., Gertz, M.A., Kyriakou, C., Thomas, S.K., Barlogie, B., Gregory, S.A., Kimby, E., Merlini, G. & Treon, S.P. (2014) Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. *Blood*, **124**, 1404-1411.
- Dispenzieri, A., Buadi, F., Laumann, K., LaPlant, B., Hayman, S.R., Kumar, S.K., Dingli, D., Zeldenrust, S.R., Mikhael, J.R., Hall, R., Rajkumar, S.V., Reeder, C., Fonseca, R., Bergsagel, P.L., Stewart, A.K., Roy, V., Witzig, T.E., Lust, J.A., Russell, S.J., Gertz, M.A. & Lacy, M.Q. (2012) Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. *Blood*, **119**, 5397-5404.
- Dispenzieri, A. & Kyle, R.A. (2005) Neurological aspects of multiple myeloma and related disorders. *Best Pract Res Clin Haematol*, **18**, 673-688.
- Draak, T.H., Vanhoutte, E.K., van Nes, S.I., Gorson, K.C., Van der Pol, W.L., Notermans, N.C., Nobile-Orazio, E., Leger, J.M., Van den Bergh, P.Y., Lauria, G., Bril, V., Katzberg, H., Lunn, M.P., Pouget, J., van der Kooi, A.J., Hahn, A.F., Doorn, P.A., Cornblath, D.R., van den Berg, L.H., Faber, C.G., Merkies, I.S. & PeriNom, S.S.G. (2014) Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. *Neurology*, **83**, 2124-2132.
- Dyck, P.J., Boes, C.J., Mulder, D., Millikan, C., Windebank, A.J., Dyck, P.J. & Espinosa, R. (2005) History of standard scoring, notation, and summation of neuromuscular signs. A current survey and recommendation. *J Peripher Nerv Syst*, **10**, 158-173.
- Dyck, P.J., Litchy, W.J., Daube, J.R., Harper, C.M., Dyck, P.J., Davies, J. & O'Brien, P.C. (2003) Individual attributes versus composite scores of nerve conduction abnormality: sensitivity, reproducibility, and concordance with impairment. *Muscle Nerve*, **27**, 202-210.
- Fernandez de Larrea, C., Verga, L., Morbini, P., Klersy, C., Lavatelli, F., Foli, A., Obici, L., Milani, P., Capello, G.L., Paulli, M., Palladini, G. & Merlini, G. (2015) A practical approach to the diagnosis of systemic amyloidoses. *Blood*.
- Gemignani, F., Brindani, F., Alfieri, S., Giuberti, T., Allegri, I., Ferrari, C. & Marbini, A. (2005) Clinical spectrum of cryoglobulinaemic neuropathy. *J Neurol Neurosurg Psychiatry*, **76**, 1410-1414.
- Ghosh, A., Littlewood, T. & Donaghy, M. (2002) Cladribine in the treatment of IgM paraproteinemic polyneuropathy. *Neurology*, **59**, 1290-1291.
- Gironi, M., Saresella, M., Ceresa, L., Calvo, M., Ferrante, P., Merli, F. & Nemni, R. (2006) Clinical and immunological worsening in a patient affected with Waldenstrom macroglobulinemia and anti-mag neuropathy after treatment with rituximab. *Haematologica*, **91**, ECR17.
- Gosselin, S., Kyle, R.A. & Dyck, P.J. (1991) Neuropathy associated with monoclonal gammopathies of undetermined significance. *Ann Neurol*, **30**, 54-61.
- Grisariu, S., Avni, B., Batchelor, T.T., van den Bent, M.J., Bokstein, F., Schiff, D., Kuitinen, O., Chamberlain, M.C., Roth, P., Nemets, A., Shalom, E., Ben-Yehuda, D., Siegal, T. & International Primary, C.N.S.L.C.G. (2010) Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report. *Blood*, **115**, 5005-5011.
- Haldorsen, I.S., Espeland, A. & Larsson, E.M. (2011) Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. *AJNR Am J Neuroradiol*, **32**, 984-992.
- Hoeijmakers, J.G., Faber, C.G., Lauria, G., Merkies, I.S. & Waxman, S.G. (2012) Small-fibre neuropathies--advances in diagnosis, pathophysiology and management. *Nat Rev Neurol*, **8**, 369-379.

- Hospital, M.A., Viala, K., Dragomir, S., Levy, V., Cohen-Aubart, F., Neil, J., Musset, L., Choquet, S., Leger, J.M. & Leblond, V. (2013) Immunotherapy-based regimen in anti-MAG neuropathy: results in 45 patients. *Haematologica*, **98**, e155-157.
- Ioakimidis, L., Patterson, C.J., Hunter, Z.R., Soumerai, J.D., Manning, R.J., Turnbull, B., Sheehy, P. & Treon, S.P. (2009) Comparative outcomes following CP-R, CVP-R, and CHOP-R in Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma*, **9**, 62-66.
- Joint Task Force of the E. & the, P.N.S. (2006) European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst*, **11**, 9-19.
- Katz, J.S., Saperstein, D.S., Gronseth, G., Amato, A.A. & Barohn, R.J. (2000) Distal acquired demyelinating symmetric neuropathy. *Neurology*, **54**, 615-620.
- Keraliya, A.R., Krajewski, K.M., Giardino, A.A., Tirumani, S.H., Shinagare, A.B., Ramaiya, N.H. & Jagannathan, J.P. (2015) Imaging of Nervous System Involvement in Hematologic Malignancies: What Radiologists Need to Know. *AJR Am J Roentgenol*, **205**, 604-617.
- Kissel, J.T. & Mendell, J.R. (1996) Neuropathies associated with monoclonal gammopathies. *Neuromuscul Disord*, **6**, 3-18.
- Klein, C.J., Vrana, J.A., Theis, J.D., Dyck, P.J., Dyck, P.J., Spinner, R.J., Mauermann, M.L., Bergen, H.R., 3rd, Zeldenrust, S.R. & Dogan, A. (2011) Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. *Arch Neurol*, **68**, 195-199.
- Kyle, R.A., Therneau, T.M., Rajkumar, S.V., Larson, D.R., Plevak, M.F., Offord, J.R., Dispenzieri, A., Katzmann, J.A. & Melton, L.J., 3rd (2006) Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*, **354**, 1362-1369.
- Larue, S., Bombelli, F., Viala, K., Neil, J., Maisonobe, T., Bouche, P., Musset, L., Fournier, E. & Leger, J.M. (2011) Non-anti-MAG DADS neuropathy as a variant of CIDP: clinical, electrophysiological, laboratory features and response to treatment in 10 cases. *Eur J Neurol*, **18**, 899-905.
- Lauria, G., Morbin, M., Lombardi, R., Capobianco, R., Camozzi, F., Pareyson, D., Manconi, M. & Geppetti, P. (2006) Expression of capsaicin receptor immunoreactivity in human peripheral nervous system and in painful neuropathies. *J Peripher Nerv Syst*, **11**, 262-271.
- Leger, J.M., Viala, K., Nicolas, G., Creange, A., Vallat, J.M., Pouget, J., Clavelou, P., Vial, C., Steck, A., Musset, L., Marin, B. & Group, R.S. (2013) Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology*, **80**, 2217-2225.
- Levine, T., Pestronk, A., Florence, J., Al-Lozi, M.T., Lopate, G., Miller, T., Ramneantu, I., Waheed, W., Stambuk, M., Stone, M.J. & Choksi, R. (2006) Peripheral neuropathies in Waldenstrom's macroglobulinaemia. *J Neurol Neurosurg Psychiatry*, **77**, 224-228.
- Loscher, W.N., Woertz, A., Wallnofer, M., Wanschitz, J.V. & Luef, G. (2013) Successful treatment of CANOMAD with IVIg and rituximab. *J Neurol*, **260**, 1168-1170.
- Lunn, M.P. & Nobile-Orazio, E. (2012) Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database Syst Rev*, **5**, CD002827.
- Mariette, X., Brouet, J.C., Chevret, S., Leger, J.M., Clavelou, P., Pouget, J., Vallat, J.M. & Vial, C. (2000) A randomised double blind trial versus placebo does not confirm the benefit of alpha-interferon in polyneuropathy associated with monoclonal IgM. *J Neurol Neurosurg Psychiatry*, **69**, 279-280.
- Martyn, C.N. & Hughes, R.A. (1997) Epidemiology of peripheral neuropathy. *J Neurol Neurosurg Psychiatry*, **62**, 310-318.
- Matsuda, M., Gono, T., Morita, H., Katoh, N., Kodaira, M. & Ikeda, S. (2011) Peripheral nerve involvement in primary systemic AL amyloidosis: a clinical and electrophysiological study. *Eur J Neurol*, **18**, 604-610.
- Merkies, I.S., Lauria, G. & Faber, C.G. (2012) Outcome measures in peripheral neuropathies: requirements through statements. *Curr Opin Neurol*, **25**, 556-563.

- Merkies, I.S., Schmitz, P.I., van der Meche, F.G., Samijn, J.P., van Doorn, P.A., Inflammatory Neuropathy, C. & Treatment, G. (2003) Connecting impairment, disability, and handicap in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry*, **74**, 99-104.
- Merlini, G., Comenzo, R.L., Seldin, D.C., Wechalekar, A. & Gertz, M.A. (2014) Immunoglobulin light chain amyloidosis. *Expert Rev Hematol*, **7**, 143-156.
- Merlini, G., Wechalekar, A.D. & Palladini, G. (2013) Systemic light chain amyloidosis: an update for treating physicians. *Blood*, **121**, 5124-5130.
- Niermeijer, J.M., Eurelings, M., Lokhorst, H., Franssen, H., Fijnheer, R., Wokke, J.H. & Notermans, N.C. (2006) Neurologic and hematologic response to fludarabine treatment in IgM MGUS polyneuropathy. *Neurology*, **67**, 2076-2079.
- Niermeijer, J.M., Eurelings, M., van der Linden, M.W., Lokhorst, H.M., Franssen, H., Fischer, K., Teunissen, L.L., van den Berg, L.H., Schobben, F., Wokke, J.H. & Notermans, N.C. (2007) Intermittent cyclophosphamide with prednisone versus placebo for polyneuropathy with IgM monoclonal gammopathy. *Neurology*, **69**, 50-59.
- Nobile-Orazio, E., Francomano, E., Daverio, R., Barbieri, S., Marmioli, P., Manfredini, E., Carpo, M., Moggio, M., Legname, G., Baldini, L. & et al. (1989) Anti-myelin-associated glycoprotein IgM antibody titers in neuropathy associated with macroglobulinemia. *Ann Neurol*, **26**, 543-550.
- Nobile-Orazio, E., Latov, N., Hays, A.P., Takatsu, M., Abrams, G.M., Sherman, W.H., Miller, J.R., Messito, M.J., Saito, T., Tahmouh, A. & et al. (1984) Neuropathy and anti-MAG antibodies without detectable serum M-protein. *Neurology*, **34**, 218-221.
- Nobile-Orazio, E., Manfredini, E., Carpo, M., Meucci, N., Monaco, S., Ferrari, S., Bonetti, B., Cavaletti, G., Gemignani, F., Durelli, L. & et al. (1994) Frequency and clinical correlates of anti-neural IgM antibodies in neuropathy associated with IgM monoclonal gammopathy. *Ann Neurol*, **36**, 416-424.
- Nobile-Orazio, E., Meucci, N., Baldini, L., Di Troia, A. & Scarlato, G. (2000) Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies. *Brain*, **123 (Pt 4)**, 710-717.
- Noronha, V., Fynan, T.M. & Duffy, T. (2006) Flare in neuropathy following rituximab therapy for Waldenstrom's macroglobulinemia. *J Clin Oncol*, **24**, e3.
- Notermans, N.C., Franssen, H., Eurelings, M., Van der Graaf, Y. & Wokke, J.H. (2000) Diagnostic criteria for demyelinating polyneuropathy associated with monoclonal gammopathy. *Muscle Nerve*, **23**, 73-79.
- Oksenhendler, E., Chevret, S., Leger, J.M., Louboutin, J.P., Bussel, A. & Brouet, J.C. (1995) Plasma exchange and chlorambucil in polyneuropathy associated with monoclonal IgM gammopathy. IgM-associated Polyneuropathy Study Group. *J Neurol Neurosurg Psychiatry*, **59**, 243-247.
- Owen, R.G., Kyle, R.A., Stone, M.J., Rawstron, A.C., Leblond, V., Merlini, G., Garcia-Sanz, R., Ocio, E.M., Morra, E., Morel, P., Anderson, K.C., Patterson, C.J., Munshi, N.C., Tedeschi, A., Joshua, D.E., Kastiris, E., Terpos, E., Ghobrial, I.M., Leleu, X., Gertz, M.A., Ansell, S.M., Morice, W.G., Kimby, E., Treon, S.P. & macroglobulinaemia, V.I.I.W.o.W. (2013) Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol*, **160**, 171-176.
- Owen, R.G., Treon, S.P., Al-Katib, A., Fonseca, R., Greipp, P.R., McMaster, M.L., Morra, E., Pangalis, G.A., San Miguel, J.F., Branagan, A.R. & Dimopoulos, M.A. (2003) Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*, **30**, 110-115.
- Palladini, G., Russo, P., Foli, A., Milani, P., Lavatelli, F., Obici, L., Nuvolone, M., Brugnattelli, S., Invernizzi, R. & Merlini, G. (2012) Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide. *Ann Hematol*, **91**, 89-92.

- Palladini, G., Russo, P., Nuvolone, M., Lavatelli, F., Perfetti, V., Obici, L. & Merlini, G. (2007) Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood*, **110**, 787-788.
- Periquet, M.I., Novak, V., Collins, M.P., Nagaraja, H.N., Erdem, S., Nash, S.M., Freimer, M.L., Sahenk, Z., Kissel, J.T. & Mendell, J.R. (1999) Painful sensory neuropathy: prospective evaluation using skin biopsy. *Neurology*, **53**, 1641-1647.
- Phipps, C., Chen, Y., Gopalakrishnan, S. & Tan, D. (2015) Daratumumab and its potential in the treatment of multiple myeloma: overview of the preclinical and clinical development. *Ther Adv Hematol*, **6**, 120-127.
- Rajabally, Y.A. (2011) Neuropathy and paraproteins: review of a complex association. *Eur J Neurol*, **18**, 1291-1298.
- Rajkumar, S.V., Gertz, M.A. & Kyle, R.A. (1998) Prognosis of patients with primary systemic amyloidosis who present with dominant neuropathy. *Am J Med*, **104**, 232-237.
- Renaud, S., Fuhr, P., Gregor, M., Schweikert, K., Lorenz, D., Daniels, C., Deuschl, G., Gratwohl, A. & Steck, A.J. (2006) High-dose rituximab and anti-MAG-associated polyneuropathy. *Neurology*, **66**, 742-744.
- Renaud, S., Gregor, M., Fuhr, P., Lorenz, D., Deuschl, G., Gratwohl, A. & Steck, A.J. (2003) Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. *Muscle Nerve*, **27**, 611-615.
- Riva, N., Faccendini, S., Lopez, I.D., Fratelli, A., Velardo, D., Quattrini, A., Gatti, R., Comi, G., Comola, M. & Fazio, R. (2014) Balance exercise in patients with chronic sensory ataxic neuropathy: a pilot study. *J Peripher Nerv Syst*, **19**, 145-151.
- Sala, E., Robert-Varvat, F., Paul, S., Camdessanche, J.P. & Antoine, J.C. (2014) Acute neurological worsening after Rituximab treatment in patients with anti-MAG neuropathy. *J Neurol Sci*, **345**, 224-227.
- Sanchorawala, V., Patel, J.M., Sloan, J.M., Shelton, A.C., Zeldis, J.B. & Seldin, D.C. (2013) Melphalan, lenalidomide and dexamethasone for the treatment of immunoglobulin light chain amyloidosis: results of a phase II trial. *Haematologica*, **98**, 789-792.
- Sanchorawala, V. & Seldin, D.C. (2007) An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. *Amyloid*, **14**, 261-269.
- Shaikh, F., Chan, A.C., Awan, O., Jerath, N., Reddy, C., Khan, S.A. & Graham, M.M. (2015) Diagnostic Yield of FDG-PET/CT, MRI, and CSF Cytology in Non-Biopsiable Neurolymphomatosis as a Herald Sign of Recurrent Non-Hodgkin's Lymphoma. *Cureus*, **7**, e319.
- Sheeba K. Thomas, W.A.H., Joseph Thaddeus Beck, Gabrail Nashat, M. Lia Palomba, Stephen M Ansell, Herbert Eradat, Edward N. Libby III, Ranjana H Advani, Julio Hajdenberg, Leonard T Heffner, James Hoffman, David H. Vesole, Lindsey Simov, Nancy Wyant, Julie Brevard, James O'Leary, Sudhir Agrawal (2015) Preliminary Results from a Phase 1/2, Open-Label, Dose-Escalation Clinical Trial of IMO-8400 in Patients with Relapsed or Refractory Waldenstrom's Macroglobulinemia. In: *The American Society of Haematology Annual Meeting*, Vol. 126, p. 1540. Blood, San Diego.
- Simmons, Z., Albers, J.W., Bromberg, M.B. & Feldman, E.L. (1993a) Presentation and initial clinical course in patients with chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients without and with monoclonal gammopathy. *Neurology*, **43**, 2202-2209.
- Simmons, Z., Blaivas, M., Aguilera, A.J., Feldman, E.L., Bromberg, M.B. & Towfighi, J. (1993b) Low diagnostic yield of sural nerve biopsy in patients with peripheral neuropathy and primary amyloidosis. *J Neurol Sci*, **120**, 60-63.
- Smith, I.S. (1994) The natural history of chronic demyelinating neuropathy associated with benign IgM paraproteinaemia. A clinical and neurophysiological study. *Brain*, **117 (Pt 5)**, 949-957.

- Stork, A.C., Notermans, N.C., Vrancken, A.F., Cornblath, D.R. & van der Pol, W.L. (2013) Rapid worsening of IgM anti-MAG demyelinating polyneuropathy during rituximab treatment. *J Peripher Nerv Syst*, **18**, 189-191.
- Streckmann, F., Zopf, E.M., Lehmann, H.C., May, K., Rizza, J., Zimmer, P., Gollhofer, A., Bloch, W. & Baumann, F.T. (2014) Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports Med*, **44**, 1289-1304.
- Tatum, A.H. (1993) Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM anti-myelin-associated glycoprotein. *Ann Neurol*, **33**, 502-506.
- Themistocleous, A.C., Ramirez, J.D., Serra, J. & Bennett, D.L. (2014) The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol*, **14**, 368-379.
- Thomas, P.K. & King, R.H. (1974) Peripheral nerve changes in amyloid neuropathy. *Brain*, **97**, 395-406.
- Treon, S.P., Branagan, A.R., Hunter, Z., Santos, D., Tournhilac, O. & Anderson, K.C. (2004) Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. *Ann Oncol*, **15**, 1481-1483.
- Treon SP, H.C., Ioakimidis L, et al (2010) Clinical characteristics and treatment outcome of disease-related peripheral neuropathy in Waldenstrom's macroglobulinemia (WM). In: ASCO, Vol. 28, p. 15s. *J Clin Oncol*.
- Treon SP, T.C., Meid K et al. (2013) Prospective, multicenter study of the Mtor inhibitor everolimus (RAD001) as primary therapy in Waldenstrom's macroglobulinemia. In: *ASH*, Vol. 122. Blood.
- Treon, S.P., Tripsas, C.K., Meid, K., Kanan, S., Sheehy, P., Chuma, S., Xu, L., Cao, Y., Yang, G., Liu, X., Patterson, C.J., Warren, D., Hunter, Z.R., Turnbull, B., Ghobrial, I.M. & Castillo, J.J. (2014) Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenstrom's macroglobulinemia. *Blood*, **124**, 503-510.
- Treon, S.P., Tripsas, C.K., Meid, K., Warren, D., Varma, G., Green, R., Argyropoulos, K.V., Yang, G., Cao, Y., Xu, L., Patterson, C.J., Rodig, S., Zehnder, J.L., Aster, J.C., Harris, N.L., Kanan, S., Ghobrial, I., Castillo, J.J., Laubach, J.P., Hunter, Z.R., Salman, Z., Li, J., Cheng, M., Clow, F., Graef, T., Palomba, M.L. & Advani, R.H. (2015) Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med*, **372**, 1430-1440.
- Treon SP, X.L., Hunter ZR. (2015) MYD88 mutations and ibrutinib responses in Waldenstrom's Macroglobulinemia. *N Engl J Med*, **In press**.
- van Nes, S.I., Faber, C.G. & Merkies, I.S. (2008) Outcome measures in immune-mediated neuropathies: the need to standardize their use and to understand the clinimetric essentials. *J Peripher Nerv Syst*, **13**, 136-147.
- Vanhoutte, E.K., Faber, C.G., van Nes, S.I., Jacobs, B.C., van Doorn, P.A., van Koningsveld, R., Cornblath, D.R., van der Kooi, A.J., Cats, E.A., van den Berg, L.H., Notermans, N.C., van der Pol, W.L., Hermans, M.C., van der Beek, N.A., Gorson, K.C., Eurelings, M., Engelsman, J., Boot, H., Meijer, R.J., Lauria, G., Tennant, A., Merkies, I.S. & PeriNom, S.S.G. (2012) Modifying the Medical Research Council grading system through Rasch analyses. *Brain*, **135**, 1639-1649.
- Viala, K., Stojkovic, T., Doncker, A.V., Maisonobe, T., Lenglet, T., Bruneteau, G., Musset, L., Neil, J., Leger, J.M. & Leblond, V. (2012) Heterogeneous spectrum of neuropathies in Waldenstrom's macroglobulinemia: a diagnostic strategy to optimize their management. *J Peripher Nerv Syst*, **17**, 90-101.
- Vital, C., Vital, A., Bouillot-Eimer, S., Brechenmacher, C., Ferrer, X. & Lagueny, A. (2004) Amyloid neuropathy: a retrospective study of 35 peripheral nerve biopsies. *J Peripher Nerv Syst*, **9**, 232-241.
- Weiss, M.D. & Becker, P. (2014) Paradoxical worsening of anti-myelin-associated glycoprotein polyneuropathy following rituximab. *Muscle Nerve*, **49**, 457-458.

- White, C.M., Hadden, R.D., Robert-Lewis, S.F., McCrone, P.R. & Petty, J.L. (2015) Observer blind randomised controlled trial of a tailored home exercise programme versus usual care in people with stable inflammatory immune mediated neuropathy. *BMC Neurol*, **15**, 147.
- Willison, H.J., Chancellor, A.M., Paterson, G., Veitch, J., Singh, S., Whitelaw, J., Kennedy, P.G. & Warlow, C.P. (1993) Antiglycolipid antibodies, immunoglobulins and paraproteins in motor neuron disease: a population based case-control study. *J Neurol Sci*, **114**, 209-215.
- Willison, H.J., O'Leary, C.P., Veitch, J., Blumhardt, L.D., Busby, M., Donaghy, M., Fuhr, P., Ford, H., Hahn, A., Renaud, S., Katifi, H.A., Ponsford, S., Reuber, M., Steck, A., Sutton, I., Schady, W., Thomas, P.K., Thompson, A.J., Vallat, J.M. & Winer, J. (2001) The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain*, **124**, 1968-1977.
- Wu, J., Zhang, M. & Liu, D. (2016) Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. *J Hematol Oncol*, **9**, 21.
- Yeung, K.B., Thomas, P.K., King, R.H., Waddy, H., Will, R.G., Hughes, R.A., Gregson, N.A. & Leibowitz, S. (1991) The clinical spectrum of peripheral neuropathies associated with benign monoclonal IgM, IgG and IgA paraproteinaemia. Comparative clinical, immunological and nerve biopsy findings. *J Neurol*, **238**, 383-391.
- Zara, G., Zambello, R. & Ermani, M. (2011) Neurophysiological and clinical responses to rituximab in patients with anti-MAG polyneuropathy. *Clin Neurophysiol*, **122**, 2518-2522.