Workshop report

230th ENMC international workshop: Improving future assessment and research in IgM anti-MAG peripheral neuropathy: a consensus collaborative effort

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1. Introduction

The 230th European Neuromuscular Centre (ENMC) international workshop occurred in Naarden, the Netherlands, from February 24th to 26th, 2017. The purposes of the workshop were: 1) to create an IgM associated peripheral neuropathy study group and achieve consensus regarding the registration of patients with IgM associated peripheral neuropathy in a patient-based registry, 2) to improve future assessment of patients with IgM associated peripheral neuropathy from haematological markers to clinical trials, and 3) to discuss promising therapies for future clinical trials. Seventeen clinicians and researchers (sixteen neurologists and one haematologist) from nine countries (Belgium, Curaçao, France, Italy, the Netherlands, Spain, Switzerland, the United Kingdom, and the United States of America) were present. A patient with IgM associated peripheral neuropathy, a representative of the GBS/CIDP Foundation International, and a PhD student, who received support from the ENMC Young Scientist Program, also attended.

2. Background

IgM associated peripheral neuropathy is a rare, immune-mediated peripheral neuropathy [1, 2]. The clinical picture is heterogeneous and the relationship between the paraprotein and the neuropathy is not always clear. The disease may cause functional disabilities in activities of daily life [3]. Despite several previous efforts, international consensus on how to assess and treat these patients is lacking [2].

The assessment of the disease progression and effect of treatment has proven to be difficult, partly because there is no clear consensus of what should be measured. Previous ENMC workshops on outcome measures in immune-mediated neuropathies [4-6] have largely failed to create an agreed upon core set of satisfactory outcome measures specifically for patients with IgM associated peripheral neuropathy. This failure is mainly attributable to the small number of patients and the indolent course of the disease.

After welcoming remarks by Alexandra Breukel, the ENMC Managing Director, Nicolette Notermans opened the meeting on behalf of the organizing committee.

3. Clinical presentation and needs from patients' perspectives

3.1 Heterogeneity of IgM associated peripheral neuropathy

Nicolette Notermans initiated the meeting by presenting the wide variety of clinical peripheral neuropathies associated with IgM paraproteins. An EFNS/PNS investigative and diagnostic guideline for IgM paraproteinaemic neuropathies was published in 2010 [7]. Most

IgM associated neuropathies are associated with monoclonal gammopathies of undetermined significance (MGUS). This condition is distinguished from malignant plasma cell dyscrasias (e.g.,Waldenström's macroglobulinemia, osteosclerotic myeloma, amyloidosis, lymphoma), however there is a cumulative probability of malignant transformation over time that is higher in the early years after diagnosis and occurs more frequently in patients with neuropathy [8].

The initial description of the IgM associated peripheral neuropathy was associated with IgM anti-MAG antibodies [7]. This "classical phenotype" has a slowly progressive, symmetric, predominantly sensory, ataxic neuropathy with relatively mild or no weakness. Nerve conduction studies showed predominant distal demyelination [7, 9]. Since those initial descriptions, it has become clear that this represents only one phenotype within the broad group of those with IgM associated peripheral neuropathies. Dr. Notermans shared three videos of patients with different clinical presentations. Patient 1, diagnosed over 20 years ago, has a severe disability due to sensory neuropathy with gait ataxia and distal and proximal weakness in arms and legs. Patient 2, diagnosed 15 years ago, has sensory symptoms and is mainly affected by the postural tremor of his hands. Patient 3, diagnosed 10 years ago, has a loss of sensory modalities in hands and feet in combination with distal weakness in legs. With these three diverging clinical presentations, Dr. Notermans exemplified the heterogeneity of this condition.

Richard Lewis also questioned whether IgM associated peripheral neuropathy is one distinct disease or several syndromes by further addressing the heterogeneity and prognosis. Classification systems have resulted in a number of terminologies. For example neuropathies associated with IgM paraprotein previously have been classified as anti-MAG mediated peripheral neuropathy, distal acquired demyelinating symmetric (DADS) peripheral neuropathy without anti-MAG antibodies, and IgM associated peripheral neuropathy with ganglioside antibodies, such as anti-GQ1b, anti-GM1, anti-GM2, anti-GD1a, and anti-GD1b. Although there are aspects of these disorders that are distinct, the symptoms are often similar and Professor Lewis therefore questioned the clinical value of these disease subcategories. The prognosis of IgM associated peripheral neuropathy is variable but a significant number of patients (16%) experience disability at 5 years after diagnosis [10]. The presence of anti-MAG antibodies appeared to be associated with lower risk for more severe disease progression [3].

Patients with malignant monoclonal gammopathies also can present with polyneuropathies that can be highly variable [11]. Because some patients with plasma cell

dyscrasias progress rapidly and develop substantial disability, the early identification of prognostic factors might help to target patients that should be treated more aggressively.

3.2 The needs from patients' perspectives

Lou Mazawey shared his experiences as a patient with IgM associated peripheral neuropathy. His disease has been through several phases and he is currently in remission with some disability. His primary expectation for treatment was to maintain or improve his quality of life. His main symptoms were impaired balance with walking difficulties and foot pain. Mr. Mazawey also acknowledged the variable clinical picture and different levels of disability he has observed in other patients who attended support groups.

Patricia Blomkwist-Markens presented a survey conducted in patients with IgM associated peripheral neuropathy. The survey showed the diversity of first symptoms amongst patients, varying from tingling/numbness in hands and/or feet, foot drop, pain and cramps in lower extremities, instability when walking, and severe fatigue. Almost all had progressive symptoms. Most (78%) had no other medical conditions. The primary challenges included walking instability, fatigue, pain, managing self-care and performing social activities due to disability, and emotionally accepting the new (and changing) situation.

David Cornblath suggested that from the perspective of patients there should be more attention to measuring quality of life, pain, fatigue and tremor since these were recognized by patients and the attendees as disabling and poorly measured. The Canadian Occupational Performance Measure (COPM) was mentioned as a patient-specific disability outcome measure, which is a validated tool for measuring progress in occupational therapy [12, 13]. Although it has some advantages, it is not linear nor directly comparable among patients, and it is not a commonly used outcome measure in clinical trials. Professor Cornblath also recognized the importance of carefully selecting appropriate primary and secondary outcomes for pivotal trials to reduce the likelihood of false negative or positive results.

4. Clinical trials in IgM associated peripheral neuropathy

4.1 Clinical trials and outcome measures in IgM associated peripheral neuropathy

Jean-Marc Léger gave an overview of all randomized clinical trials (RCTs) performed in IgM associated peripheral neuropathy, based on a Cochrane review by Lunn and Nobile-Orazio [2]. They analysed eight RCTs in which patients with anti-MAG peripheral neuropathy were treated with immune-modulating treatments such as intravenous immunoglobulin (IVIg), interferon alfa-2a, plasma exchange, cyclophosphamide and steroids,

and rituximab. According to low quality evidence from two studies, treatment with IVIg might produce some very short-term improvements. Treatment with interferon alfa-2a and chorambucil did not demonstrate any significant benefit. The combination of cyclophosphamide and corticosteroids compared to placebo showed similar outcomes. There are two RCTs of rituximab versus placebo with some concerns about inclusion criteria, outcome measures, and duration of the trials. In a meta-analysis rituximab was beneficial in improving disability scales, biological parameters and the patient global impression of change scores [14, 15]. However, Lunn and Nobile-Orazio [2] concluded the evidence for efficacy for any of the studied immune treatments in anti-MAG paraproteinemic neuropathy was inadequate because of the small numbers of treated patients and limited number of studies. Large well-designed randomized trials with homogeneous patient inclusion of at least 12 months duration are needed to assess existing or novel therapies.

Eduardo Nobile-Orazio provided an overview of the outcome measures used in IgM associated peripheral neuropathy trials. The outcome measures in the eight RCTs performed in IgM associated peripheral neuropathy were grouped into three domains, based on the International Classification of Functioning, Disability and Health (ICF): impairment, activity and participation, and quality of life [16]. Impairment measurements were the Medical Research Council (MRC) sumscore or scores, modified Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (mISS), ataxia scores, and Visual Analog Pain scales (VAS). Activity and participation measurements were the INCAT disability scale, 10 meter walking test (10-MWT), Clinical Neuropathy Disability Score (CNDS), Overall Disability Sum Score (ODSS), Overall Neuropathy Limitations Scale (ONLS), Rivermead Mobility Index (RMI) and modified Rankin Scale (mRS). Quality of life was measured using the Short Form-36 (SF-36). Biological markers were serum IgM concentration, anti-MAG titres and levels of CD19+ cells [2]. The overview highlighted the lack of uniformity of selected outcome measures among all the trials, and stressed that virtually all were ordinally based metrics with substantial deficiencies (as will be discussed by Catharina Faber) [17, 18].

4.2 Lessons learned from previous trials in IgM associated peripheral neuropathy

Ken Gorson elaborated on possible reasons for negative outcomes in previous IgM associated peripheral neuropathy trials. Negative outcomes may be caused by improper patient selection, including patients too mildly affected to measure change, those too severely affected to expect improvement, or patients with fixed disability after many years of disease. Furthermore, the duration of trials in the past often was too short and the selected outcome

measures are now considered inadequate, as previously noted. Some outcomes are indirect and of little relevance, for example improved electrophysiological nerve function may not reflect reduced disability for the patient. In some studies, drug dosages may not have been high enough to cause functional improvement. Before proceeding with new treatment trials, researchers need to resolve these recurrent shortcomings. First, investigators should determine more precisely the difference between IgM associated polyneuropathy patients with active moderate to severe disease and those with non-progressive or end stage disease. Second, larger numbers of participants should be recruited by including more centres in trials. Third, the best outcome metrics need to be utilized, or better ones developed. Fourth, the trial designs must use the correct drug dose or regimen and allow for long enough treatment and follow-up so investigators will be confident about observed outcomes.

5. The needs for proper outcome measure development

5.1 A Rasch analysis approach

Catharina Faber presented the basic requirements for the development of Rasch model outcome measures [19]. Outcome measures need to be simple, valid, reliable and responsive. Furthermore, outcome measures preferably should be interval or ratio measures, since these have a numerical value and the distance between one category and another is known. This allows the calculation of statistically valid sum scores and creates higher precision in our assessments [20]. In practice, outcome measures are frequently nominal or ordinal and have only descriptive value. Despite this they are often interpreted as a numerical value, where assumptions of linearity are made, sumscores are constructed and statistically invalid calculations are extracted from these data [21].

The Rasch model enables the transformation of ordinal data into interval data, increasing the level of measurement precision. The model states that the probability of a patient to complete a task is a function of both the difficulty of the task and the ability of the patient. According to the model a less disabled person will have a higher probability of completing a particular task compared to a more disabled person [19]. Through Guttman scaling the items can be placed in a hierarchical order, such that if a harder task is completed, then there is a high probability that easier tasks will also be completed [22]. The model assumes that the probability of a patient completing an item is a logistic function of the relative distance between the item location and the respondent location on a linear scale [22].

To obtain a scale at the interval level, all items and persons need to fulfil several Rasch methodology requirements (such as meeting Rasch model fit statistics, no evidence of

disordered thresholds, local dependency and item bias, proper targeting of patients on items, and unidimensionality) [20]. Items or patients not fulfilling these requirements should be removed or subjected to re-adjustments to fit the model's requirements.

5.2 The concept of minimal clinical important difference and defining a responder

Ingemar Merkies explained the concept of the minimal clinical important difference (MCID) and the importance of defining a responder. In clinical trials we want to measure true scores, for example of the fatigue or strength of our patients. Since the 'true scores' are not known, we use surrogate outcome measures to calculate an estimated score, which represents the 'true score'. Although we assume these estimated scores come close to the true scores, estimated scores have a standard error (SE). SE values translate to confidence intervals around the unknown true scores for subsequent estimated scores. An SE of ± 1.96 indicates that the estimated score falls in the confidence interval around the true score 95% of the time. A meaningful statistical change over time is generally considered to have been reached if the estimated score falls outside the 95% confidence interval (that is 1.96 SE points).

The MCID represents a change that would be considered meaningful and worthwhile by patients such that they would consider repeating the intervention [23]. However, traditional clinical trials tend to demonstrate effects of therapy by using p-values for either group comparisons or for comparisons of proportions of patients reaching an arbitrary predefined cut-off value between outcome measures. These traditional responsiveness techniques can be misleading, since statistical significance frequently does not correlate to a clinical meaningful change. The concept of MCID taking into account the varying SEs was proposed to overcome the shortcomings of the 'statistical significant difference'. Both anchor-based and distribution-based techniques to calculate MCID were discussed [24, 25]. Currently, there is no consensus on the concept of MCID and which technique to use in the future.

Luca Padua presented the paradox between the abilities of patients and their experienced quality of life, since patients with perceived greater disability, for example wheelchair users, can experience better quality of life than those with less perceived disabilities [26, 27]. This makes measuring quality of life a complex and dynamic procedure. Professor Padua also noted that physicians are not able to decide what outcome measures are of importance to the patients; we should leave patients free to express their opinion and determine what is relevant to them. By asking patients with anti-MAG peripheral neuropathy six simple questions (appendix 1), Professor Padua established that the most prevalent patient limitations are walking problems and hand dexterity, whereas less prevalent are balance problems, fatigue

and pain. When asking patients what should improve with therapy, balance problems were the most important improvement followed by hand dexterity. Although patients describe difficulties in walking as their main difficulty, their aims for improvement focus on balance.

5.3 What do we consider clinically relevant?

Michael Lunn elaborated on what clinicians see as clinically relevant in IgM associated peripheral neuropathy. What clinicians utilise as meaningful change in clinical trials is not always meaningful change in clinical practice. He stated that the primary outcome in any clinical trial should also be chosen to be clinically relevant for the results of a trial to be meaningful in day-to-day practice. Clinical trials often have very tight and strict inclusion criteria to improve homogeneity of the participants. However, these criteria destroy inclusivity and prevent treatment for phenotypic outliers, especially in a heterogeneous disease like IgM associated peripheral neuropathy. To be clinically relevant we have to be flexible within this context, especially with a rare disease, and we cannot be as methodologically "pure" as we might like to be.

6. IgM associated peripheral neuropathy registry

Mariëlle Pruppers presented the IMAGiNe study, an international, multi-centre, observational cohort study of patients with IgM associated peripheral neuropathy. The main objective of the study is to create a unique cohort of prospectively collected and highly standardized clinical data in addition to a biobank from a large group of well-defined patients with IgM associated peripheral neuropathy. From this set of patients new outcome measures will be constructed using the Rasch methodology. These outcome criteria will fulfil modern clinimetric requirements and will be sensitive to change. The data will be used to optimize the diagnostic criteria for possible clinical and electrophysiological subtypes of IgM associated neuropathy, to identify biomarkers to monitor and predict disease activity and response to treatment, and to predict models for treatment response and outcome in individual patients. These results will be valuable to design future studies; the ultimate goal is a more rigorous treatment trial design for this relatively rare group of patients. The study started in the Netherlands in 2016, and is open for all centres that are able to include at least 10 patients.

7. Pathogenesis of IgM associated peripheral neuropathy

7.1 Pathological features and immunological dynamics of IgM associated peripheral neuropathy

Andreas Steck presented the pathogenic role of IgM anti-MAG antibodies in the development of a demyelinating neuropathy. The peripheral neuropathy associated with IgM anti-MAG antibodies is classically a chronic, progressive, predominantly sensory and distal demyelinating neuropathy. There is strong evidence for a pathogenic role of these IgM antibodies in demyelination and neuropathy development. Therapeutic reduction of the antibody concentration can result in clinical stabilisation or improvement in some instances [28, 29]. IgM deposits have been demonstrated on affected myelin sheaths by a number of methods. The widening of myelin lamellae found in anti-MAG neuropathy [30] is pathognomic for the disease, and there is a correlation between IgM anti-MAG penetration into myelinated fibres and the extent of widening [31]. It is postulated that the binding of IgM autoantibodies to the HNK-1 epitope on MAG leads to disintegration of the myelin sheaths, resulting in a progressive demyelinating polyneuropathy. Collapse of the neurofilament cytoskeleton in anti-MAG neuropathies may cause subsequent axonal degeneration [32]. Studies of skin biopsies have recently shown that IgM deposition induces changes in axons of dermal myelinated skin nerves [33].

Animal models have been established for anti-MAG neuropathy by the passive transfer of patients' IgM antibodies into healthy experimental animals [34-38]. The development of a glycopolymer that acts as an autoantibody scavenger mimicking the natural HNK-1 epitope, led to the removal of pathogenic antibodies in an immunological mouse model of anti-MAG neuropathy. This novel therapeutic approach could be promising for future clinical studies [39].

7.2 Nerve conduction and sonography studies in IgM associated peripheral neuropathy

Peter Van den Bergh addressed the electrophysiological characteristics in IgM associated peripheral neuropathy. Electrophysiological studies in IgM associated peripheral neuropathy show disproportionate distal slowing, prolongation of the distal motor latency (DML), and a decrease in the terminal latency index (TLI). This disproportionate distal slowing may reflect a length-dependent process characterized by distal slowing and axon loss, which are more prominent in longer axons, and also by a gradual increase of conduction slowing in a proximal to distal gradient along the length of the nerve [40].

This electrophysiological length dependency is the key neurophysiological feature that may distinguish IgM associated peripheral neuropathy from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Studies comparing electrophysiological

abnormalities in the former group with those from patients with CIDP show that in IgM anti-MAG patients the peroneal compound muscle action potential (CMAP) is more often absent, the TLI is decreased more frequently, sural sensory potentials are more often absent, and conduction blocks are rarely observed [41]. In contrast, in CIDP the modified F-ratio (MFR, which compares spinal cord to elbow and wrist to thenar segment latencies), is significantly higher than in the IgM anti-MAG group [42].

Stephan Goedee presented sonography as a non-invasive technique to dissect changes in macroscopic nerve morphology. The nerve size over the length of the nerve is the most studied sonomorphologic parameter. In the past, three significant ultrasound studies have been published in IgM associated peripheral neuropathy, which have shown varying degrees of nerve enlargement [43, 44]. This could be due to the heterogeneous study populations and the use of non-standardised high-resolution ultrasound (HRUS) protocols. Dr. Goedee found larger nerve sizes in proximal segments in patients with IgM associated peripheral neuropathy similar to CIDP, but no association with anti-MAG status (unpublished data). The combination of both HRUS and nerve conduction studies may capture certain morphologic and functional features of IgM associated peripheral neuropathy, but currently HRUS provides limited additional diagnostic value in IgM associated peripheral neuropathy.

7.3 Immunological dynamics in IgM associated peripheral neuropathy

Hugh Willison discussed the immunological dynamics of IgM associated peripheral neuropathy. IgM paraproteins are believed to arise from somatically hypermutated B cells that acquire IgM secretory capacity [45]. On the basis of the causal relationship between B cell activation and IgM associated peripheral neuropathy, B cell targeting therapies have been tested. Rituximab is a monoclonal antibody directed against CD20, a protein present on the surface of both normal and malignant human B cells. CD20 is not found on pre-B-cells or plasma cells. Treatment with rituximab results in a rapid and sustained depletion of circulating and tissue-based B-cells [14] and the long-term immunomodulatory effects of rituximab in anti-MAG peripheral neuropathy are mediated by the sustained reduction in the expanded autoreactive IgM memory B-cells [45]. Clinical disease remission has been associated with sustained elimination of IgM memory B-cells. Conversely, high load and clonal persistence of IgM memory B cell clones, despite efficient depletion of circulating B cells, was associated with a poor clinical response to rituximab [45]. This suggests that at least a fraction of disease-relevant B cells are not accessible or susceptible to CD20 immunotherapy [45]. Rituximab also leads to significant reductions in IgM levels. This is

probably due to the depletion of CD27 memory B cells, the precursors of the short-lived plasma cells. The IgM levels therefore may decline after rituximab treatment and return slowly at a rate controlled by the replenishment of memory and short-lived plasma cells. Whether this effect relates to the beneficial effect of rituximab in anti-MAG peripheral neuropathies remains unclear [14].

The cytokines B Cell-Activating Factor (BAFF) and A Proliferation-Inducing Ligand (APRIL) are produced by myeloid and stromal cells and are required for the developmental survival of B cells at various stages. Plasma cell survival requires APRIL or BAFF signalling through B-cell maturation antigen. Dysregulation of BAFF is associated with autoimmune diseases and targeting soluble BAFF using belimumab has shown benefit for patients with lupus nephritis [46]. Anti-BAFF treatment or treatments that block both BAFF and APRIL might be future possibilities for the treatment of IgM associated peripheral neuropathy [46].

Luis Querol presented data about anti-MAG antibody testing and its relevance in the clinic. Presence of IgM anti-MAG antibodies is significantly associated with neuropathy [28], though the correlation between IgM anti-MAG titres and neuropathy severity is debated, as the severity of neuropathy does not always correlate with serum antibody levels. Some uncontrolled studies treating small numbers of patients with rituximab or cytostatics suggest that the decrease of IgM anti-MAG titres is associated with a decrease of neuropathy severity [29, 47]. However, adequate evidence from large well-designed randomized controlled trials to substantiate this claim is lacking [2]. Therefore the monitoring of anti-MAG titre levels currently has no place in monitoring disease severity or treatment response. Some technical issues in testing the autoantibodies were addressed. The nature of the antigen, such as binding location, post-traductional modifications and interspecies homology, is not yet fully discovered [48-51]. Also, due to the variations in the sensitivity and specificity of the available immunological diagnostic test methods, accurate identification of IgM anti-MAG autoantibodies proves to be a challenge [52].

Mutations in the MYD88 (L265P) gene are especially prevalent in patients with Waldenström's macroglobulinaemia (WM), and also occur in approximately 50% of patients with IgM MGUS [53, 54]. Patients with IgM MGUS who have the MYD88 (L265P) mutation have significantly higher levels of IgM compared to IgM MGUS patients with wild-type MYD88 (L265P) [53]. Furthermore, MGUS associated neuropathy patients with the MYD88 (L265P) mutation had a shorter time to progression to WM than those with the wild-type genotype [54].

7.4 Immunological dynamics in other neuromuscular disorders

Ludo van der Pol discussed the lack of relevant experimental *in vivo* and *in vitro* models for IgM MGUS associated peripheral neuropathy, which impedes progress in understanding the pathogenesis. Inflammatory neuropathies are often characterized by the presence of relatively low affinity IgM or IgG antibodies that bind to glycolipids or glycoproteins. Little is known about the biology of B-cells that produce antibodies against these structures. This complicates the development of rational treatment strategies with so-called “biologicals”.

In the past 10-15 years the development of animal models for Guillain-Barré syndrome (GBS) variants in both mouse and rabbit has shown that antibodies against glycolipids and glycoproteins have pathogenic properties. For example, antibody-mediated deposition of complement factors caused dysfunction of the neuromuscular junction in a mouse model and induced changes in the architecture of the nodes of Ranvier and paranodal junctions in a rabbit model for GBS. More recent developments include the use of human motor neurons generated from induced pluripotent stem cells to study effects of glycolipid-specific antibodies. Sera from patients with multifocal motor neuropathy (MMN) that contain IgM antibodies against the ganglioside GM1 induce complement-dependent and independent effects, including changes in calcium homeostasis and neurite damage. The addition of immunoglobulin preparations or complement-specific antibodies partially attenuated these pathogenic effects [55]. A recent refinement of this approach uses rat Schwann cells with iPS-derived human motor neurons to generate myelinated axons. These models may be useful in the future to study antibody-mediated effects in IgM MGUS associated peripheral neuropathy.

8. Potential drugs in IgM associated peripheral neuropathy

Shirley D’Sa discussed treatment of IgM MGUS and Waldenström’s macroglobulinaemia associated peripheral neuropathy. Treatment choices are influenced by burden of the disease, evidence for treatment benefit, and costs of the treatment. Available classes of drug therapy include: corticosteroids, calcineurin inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, cytostatics, monoclonal antibodies, and a number of biologics, including Bruton tyrosine kinase (BTK) inhibitors.

Occasionally haematological treatment takes a precedent decision in therapy. Treatment in IgM associated peripheral neuropathy is only started with a neurological indication when there is measurably progressive disease causing disability in combination with short disease duration (preferably less than 2 years from onset); the decision to treat is often made on a case-by-case judgement. There is low to moderate quality evidence that rituximab is of

benefit in the treatment of anti-MAG demyelinating neuropathy. 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 [2, 56-58].

Factors predictive of a response to treatment with rituximab in anti-MAG neuropathy remain to be elucidated. However, short disease duration (less than 2 years), active progression at time of treatment and preservation of nerve density in biopsies might predict response to treatment [59]. Serum anti-MAG titres are currently not useful to monitor the severity of neuropathy or the response to treatment. It has been suggested that a significant drop in antibody serum levels might be necessary to achieve a response, but the depth of optimal haematological remission to be achieved is not known [60]. Complete elimination of the clonal IgM is probably neither practical nor possible. Clinical stability rather than improvement is the most likely outcome of treatment although rare dramatic improvements are reported.

Promising therapies for future perspectives are carfilzomib which has been assessed in combination with rituximab and dexamethasone (CaRD) [61], ixazomib, everolimus (an oral mTOR inhibitor) [62], the BTK inhibitors ibrutinib [63], acalabrutinib [64], BGB-3111 [65] and IMO-8400 [66] (oligonucleotides specifically designed to inhibit toll-like receptor signalling pathways for which MYD88 is a key linker protein), and daratumumab, a human antibody to CD38 [67]. Clinical trials of emerging therapies are urgently needed in this clinical setting.

9. Conclusion and recommendations

The organizing committee summarised the workshop and developed plans for future research in IgM associated peripheral neuropathy. The IMAGiNe study will serve as a platform for a collaborative effort in creating an IgM associated peripheral neuropathy registry. The main aim is to create a unique cohort of prospectively collected and highly standardized clinical data of a large group of well-defined patients with IgM associated peripheral neuropathy with and without anti-MAG antibodies. We will collect comprehensive demographic and historic data, as well as data on antibody status. Furthermore, we will collect haematological, neurophysiological and therapeutic records. Efforts will be made to include as many centres as possible. Centres that enrol at least 10 patients are eligible to participate.

Data will be collected at the level of impairment, activity and participation, and quality of life. We will measure symptoms such as weakness, loss of sensation, impaired balance, ataxia, tremor and pain in pre-selected outcome measures with newly devised metrics if needed. All these are important to define the voice of the patient, though the most relevant outcome will be to measure meaningful limitations at the level of activity and participation. The core set of outcome measures selected for the IMAGiNe study contains the PI-NRS, EQ-5D, PGIC, and we will attempt to develop an IgM-specific RODS. Other outcome measures and recording methods should be explored, such as web-based formats for patients and health-care professionals, and activity measurements with activity devices/smart phones. A biobank will be formed with local storage of blood samples to identify genetic and serological markers for disease course and outcome.

We will explore new avenues in diagnosis, disease classification, pathogenesis and treatment in close collaboration with our haematological colleagues. We aim to commence our first clinical trial of combination therapy utilizing novel outcomes by the end of 2018, and review progress through the ENMC, presenting and publishing significant data by 2022.

10. Participants

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Appendix 1

Six questions Padua asked his patients with anti-MAG peripheral neuropathy:

1. Which is the main limitation due to the neuropathy?
2. Which are the most limiting sensory symptoms?
3. Which is the main limitation due to movement involvement?
4. How much pain limits the activities of daily living (ADL)?
5. What should be asked more during medical visits?
6. What should improve with therapy?