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Review

Polyneuropathy Associated with IgM Monoclonal Gammopathy; Advances in Genetics and Treatment, Focusing on Anti-MAG Antibodies

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Abstract: With increasing age, the chances of developing either MGUS or polyneuropathy increase as well. In some cases, there is a causative relationship between the IgM M-protein and polyneuropathy. In approximately half of these cases, IgM targets the myelin-associated glycoprotein (MAG). This results in chronic polyneuropathy with slowly progressive, predominantly sensory neurological deficits and distally demyelinating features in nerve conduction studies. Despite the disease being chronic and developing slowly, it can cause considerable impairment. We reviewed English medical publications between 1980 and May 2022 on IgM gammopathy-associated polyneuropathy, with special attention to studies addressing the pathophysiology or treatment of anti-MAG polyneuropathy. Treatment options have been limited to a temporizing effect of intravenous immunoglobulins in some patients and a more sustained effect of rituximab but in only 30 to 55 percent of patients. An increase in our knowledge concerning genetic mutations, particularly the $MYD88^{L265P}$ mutation, led to the development of novel targeted treatment options such as BTK inhibitors. Similarly, due to the increasing knowledge of the pathophysiology of anti-MAG polyneuropathy, new treatment options are emerging. Since anti-MAG polyneuropathy is a rare disease with diverse symptomatology, large trials with good outcome measures are a challenge.

Keywords: IgM; monoclonal gammopathy; MGUS; Waldenström's macroglobulinemia; anti-MAG; polyneuropathy; MYD88; CXCR4

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1. Introduction

An M-protein develops in the context of a proliferative disorder of an antibody (Ig) secreting post-germinal center B-cells or plasma cells, which range from a premalignant disorder (i.e., monoclonal gammopathy of an undetermined significance, abbreviated as MGUS) to malignant disorders such as multiple myeloma (MM), Waldenström's macroglobulinemia (WM) or chronic lymphocytic leukemia [1].

MGUS can be divided into three major groups: IgM gammopathies, non-IgM gammopathies and light chain gammopathies [2,3]. In the case of an IgM MGUS, there are no signs of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder. In addition, the serum IgM monoclonal protein is <30 g/L and, if present, the clonal bone marrow plasma cells are <10% [2]. MGUS is a common

disorder especially in the elderly, with prevalence in the general population ranging from approximately 3% [4,5], up to 5.1% [6] or even 6.9% [7] with more sensitive screening techniques of recent years. There is an increase in prevalence with age, with MGUS being diagnosed in 2.3%, 6.2% and 12.9% in age groups 40–59, 60–79 and 80–103 years, respectively [8]. Patients with IgM MGUS can experience clinical symptoms resulting from autoimmune or other properties of the IgM M-protein and are thus called monoclonal gammopathies with clinical significance [9,10]. When these M-protein-related mechanisms cause neurological diseases such as polyneuropathy (PNP), it is called monoclonal gammopathy of neurological significance [11].

Since MGUS is a precursor of malignant disorders, there is a risk of the development of a malignant disorder of approximately 1% each year [1]. IgM MGUS has a rate of progression to malignant disorders of 1.5% each year, markedly higher than the overall progression rate of non-IgM MGUS [12]. IgM MGUS usually develops into WM or lymphoma, rather than MM or (AL) amyloidosis [12].

Like MGUS, chronic PNP is also common, with an age-standardized prevalence of 4% in the general population [13], increasing to approximately 7–13% in the elderly [13,14]. Thus, MGUS and a chronic PNP could very well coincide in an elderly person. However, several studies show an especially elevated prevalence of PNP within MGUS cohorts, ranging from 7% to 42% [15–18]. Saemundur et al. found a risk ratio of 2.7 for PNP in an MGUS population compared to matched controls (comparable median age and stratified for diabetes mellitus), indicating a positive association between MGUS and PNP [18]. The percentage of an M-protein in patients with otherwise unexplained PNP is 10% [19], higher than the prevalence of gammopathies in the general population. A significantly larger number of PNP is caused by IgM compared to IgG or IgA gammopathies [15–17,20]. Baldini et al. described 45% of IgM MGUS patients with PNP [21]. Thus, there could be a causal relationship, especially for the IgM isotype. A causal relationship between IgM monoclonal gammopathy and PNP has become more robust, especially after the discovery of associated antigens such as the myelin-associated glycoprotein (MAG) [22–28].

The increase in our knowledge of pathophysiology and genetic alteration in IgM gammopathies itself and its related polyneuropathies, may lead to new therapy options. These therapies should be effective in treating both hematologic and neurologic diseases. The aim of this review is to give an up-to-date overview of the literature on IgM gammopathy-associated polyneuropathy, with particular attention to anti-MAG antibodies, as this is the most prevalent variant of IgM M-protein-associated PNP.

2. Methods

This aim led to a search string that we used for the PubMed and Cochrane databases. This search string comprises four components: “polyneuropathy”, “IgM”, “gammopathy” and “antibodies”.

> *(polyneuropath*[Title/Abstract] OR “Polyneuropathies”[Mesh:NoExp] OR neuropath* [Title/Abstract]) AND (“Immunoglobulin M”[Mesh] OR IgM[Title/Abstract] OR immunoglobulin M[Title/Abstract] OR MGUS[Title/Abstract] OR monoclonal gammopathy of undetermined significance[Title/Abstract] OR anti-MAG[Title/Abstract])*

We excluded case reports and only included articles with full-text availability that were written in English between 1980 and May 2022. This search generated 395 results on 27 May 2022. Thereafter, J.M. screened the abstracts and only included articles covering all components of the research question, which resulted in 259 articles (7 articles had no full-text availability). A subsequent selection was made using articles that address epidemiological and clinical features of IgM gammopathy-associated PNP in general, or pathophysiology and treatment of IgM anti-MAG PNP in particular. Regarding treatment, original trials and observational studies were included, along with recent (systematic) reviews. If available, we used randomized controlled trials and meta-analyses instead of other trial designs for treatment options. In the case of (updated versions of) similar

reviews, the newest version was included to ensure up-to-date knowledge. This yielded 81 studies.

3. Discussion

3.1. Pathophysiology of IgM Gammopathies

The default immunoglobulin produced by B-cells is of the IgM isotype. Given that IgM MGUS develops more frequently into lymphoma or WM and rarely to (IgM) MM, it has been concluded that IgM MGUS typically arises from a CD20+ post-germinal lymphoplasmacytic cell that has not undergone switch recombination [2]. Specific immunoglobulin heavy chain (IGH) variable gene usage in IgM MGUS and WM patients suggests a cell of origin that may have appeared during a physiological immune response, with subsequent secondary (genetic) events leading to a (pre-)malignant transformation [29].

IgM MGUS and WM patients share clonal B-cells with similar phenotypic and molecular signatures, but specific genetic alterations commonly present in WM, i.e., +4, del(6q23.3–6q25.3), +12, and +18q11–18q23 (up to 73% in WM), are less frequently detected in IgM MGUS (approximately 20%). This suggests a multistep process with a primary genetic alteration allowing the B-cell to proliferate and avoid apoptosis [30]. A second hit in some cases could be the occurrence of del6q (4% in IgM MGUS compared to 30% in symptomatic WM) [31]. In addition, there might be a role for specific copy number variants as well, since the number of copy number alterations significantly increases from IgM MGUS (36%) to smoldering WM (73%) to symptomatic WM (82%) [30].

3.2. Genetic Mutations

In both IgM MGUS and WM, there is a recurring somatic mutation in the gene that encodes the myeloid differentiation factor 88 (MYD88). This $MYD88^{L265P}$ mutation (a switch of leucine to proline at amino acid position 265) was demonstrated in 90% of WM patients and in 10% of IgM MGUS patients [32]. Subsequent studies demonstrated an even higher frequency of 95% in WM patients and 44–87% in IgM MGUS patients [33–38]. The percentage differs according to the methods of MYD88 mutation detection, and although $MYD88^{L265P}$ is prevalent in the majority of IgM MGUS patients, the median mutation level was shown to be almost one logarithm lower in IgM MGUS compared to WM [36]. Rarely, the mutation is present in other (non-IgM) small B-cell lymphomas and large B-cell lymphomas. However, in MM, even of the IgM paraprotein subtype, the $MYD88^{L265P}$ mutation has not been found at all [39].

MYD88 is a Toll-interleukin receptor domain-containing adaptor protein that is part of the interleukin-1 receptor (IL-1R) and Toll-like receptor (TLR) pathways, except for TLR3, and plays an important role in the innate immune system [40,41]. MYD88 binds with IL-1R-associated kinase 4 (IRAK4), which auto-phosphorylates and trans-phosphorylates IRAK2/1 forming a large multimeric molecule: the "myddosome" [42,43]. This myddosome triggers further downstream signaling, eventually stimulating activation of the IκB kinase (IKK) complex. This facilitates phosphorylation and degradation of the inhibitor of NF-κB (IκBα), allowing canonical NF-κB signaling [44,45]. NF-κB promotes cell survival by initiating the transcription of genes encoding stress-response enzymes, cell-adhesion molecules, proinflammatory cytokines, and anti-apoptotic proteins [46]. This is important for the growth and survival of WM cells [47].

$MYD88^{L265P}$ stimulates IRAK1 phosphorylation, leading to continuous myddosome formation and increased NF-κB signaling [48]. Inhibition of MYD88 signaling decreases NF-κB activity and decreases survival of activated B-cell-type diffuse large cell lymphoma cells expressing $MYD88^{L265P}$. Moreover, mutated MYD88 triggers HCK and IL-6 transcription, eliciting pro-survival signaling and inducing Bruton's tyrosine kinase (BTK) signaling [49].

BTK, an important adapter protein in B-cell receptor (BCR) signaling, also activates NF-κB. Triggering of the BCR activates NF-κB by IKK-dependent phosphorylation and proteasomal degradation of IκB-α. BCR triggering leads to phosphorylation of the B-cell linker (BLNK) adaptor, resulting in the recruitment of phospholipase C-isoform γ (PLC-γ) and BTK in the same complex, allowing the BTK-dependent phosphorylation and activation of PLC-γ. Activation of PLC-γ ultimately leads to NF-κB activation [50]. Intervening in this pathway by means of Bruton's tyrosine kinase inhibitors such as ibrutinib and several second-generation drugs has been proven effective in treating WM [51,52].

In WM, the next most common somatic variant after $MYD88^{L265P}$ is in the C-terminal domain of the CXCR4 gene, which encodes for C-X-C chemokine receptor type 4. CXCR4 is a classical G-protein-coupled receptor. It is ubiquitously expressed in the human body and binds to CXCL12 (also known as stromal cell-derived factor-1 or SDF-1) [53]. CXCR4 is mutated in 24% [35] to 38% [54] or even 50% [55] of all WM patients, mostly along with $MYD88^{L265P}$ [35,54,55]. CXCR4 mutations have been reported in 4–20% of IgM MGUS patients [37].

CXCL12 binding induces conformational changes, leading to the activation of multiple signaling pathways involved in the activation and phosphorylation of cellular proteins and transcription factors to regulate the proliferation and migration of genes [56]. High expression of CXCR4 is observed in many (hematological) malignancies, with literature indicating that the binding of CXCL12 to CXCR4 on tumor cells of various types enhances proliferation [57]. CXCL12 can promote tumor growth and angiogenesis, participate in tumor metastasis and contribute to tumor immunosuppressive networks [58]. In contrast to MYD88 mutations, mutated CXCR4 is subclonal with the possibility to have several different CXCR4 mutations within an individual [59]. Most CXCR4 mutations lead to the loss of regulatory serines and promote sustained CXCL12-mediated activation [60].

3.3. Polyneuropathy in IgM Gammopathies

Myelin is used as an isolating layer in the majority of peripheral nerves to conduct a nerve impulse rapidly and efficiently, preventing the dissipation of the signal into the surrounding structures [61,62]. Myelin is formed by Schwann cells in the peripheral nervous system. Myelinated parts of the nerve are alternated by short unmyelinated parts, the nodes of Ranvier, to allow for fast, saltatory conduction. The nodes of Ranvier are flanked by paranodes and juxtaparanodes; the myelinated parts are called internodes. Myelin encircles the axons and consists primarily of lipids (70–80% [63]) and to a lesser degree of (glyco)proteins, of which P0 (MP0 or myelin protein zero), myelin basic protein (MBP) and periaxin are the most prevalent [64].

Myelin is organized in lamellae, compacted sheaths of myelin apposed to each other. This results in alternating phospholipid and protein layers, forming the major dense line (MDL) and intraperiod line (IPL), respectively. Compact myelin is interrupted by Schmidt–Lanterman incisures: characteristic funnel-shaped structures providing oblique cytosolic channels through compact myelin and thus forming a connection of cytoplasma between the myelin membranes juxtaposed to the axon (adaxonal membranes) and juxtaposed to the basal lamina of the nerve (abaxonal membranes). Each non-compacted membrane is called a mesaxonal membrane. The myelinated peripheral nerve configuration is summarized in Figure 1.

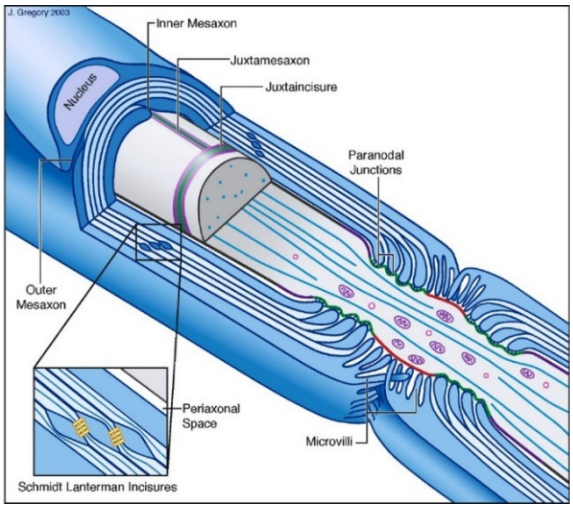

Figure 1. Morphology of myelinated PNS nerve, borrowed from Salzer with permission from Elsevier [65].

PNP as a result of IgM gammopathy may be caused by different mechanisms that trigger a malfunctioning of the nerve [66]. The monoclonal IgM may act as an auto-reactive or toxic antibody. This antibody, in the majority of cases, has a target antigen [67–73] of which the prototype is anti-MAG but may also cause disease without an antigen, as seen in POEMS syndrome, which is related to cytokine release [74]. Myelin contains components that may act as antigens in several chronic inflammatory neuropathies and some of these antigens are targets for IgM antibodies [26].

Other mechanisms include deposits of the M-protein, or fragments of the M-protein, within various parts of the nerve (such as in IgM deposition disease or amyloid light chain amyloidosis, covered in the article by Sarosiek et al. in this issue). Moreover, the IgM M-protein can cause vasculitis (with or without cryoglobulinemia [75] resulting in ischemic damage to the nerve). This ischemic damage may also be caused by the direct blocking of blood vessels by cryoglobulins (covered in the article by Khwaja et al. in this issue) or the intrinsic increased viscosity of the blood because of the size of the IgM molecules [76]. Alternatively, the clonal B-cells may directly infiltrate the nerve, as is the case with neurolymphomatosis.

3.3.1. IgM M-Protein Related Polyneuropathies and Corresponding Phenotypes

Molecules in the peripheral nerve are capable of acting as antigens for the M-proteins being produced by IgM gammopathies (Table 1).

Table 1. Possible antigens for M-proteins in the peripheral nerve. HNK1: human natural killer 1 carbohydrate epitope. SGPG: sulfated glucuronyl paragloboside. MAG: myelin-associated glycoprotein. MP0: myelin protein zero. Disialosyl epitope: specifically, the NeuAc(α2-8)NeuAc(α2-3)-Gal configuration. Sulfatide: galactosylceramide-3-*O*-sulfate.

Target Molecule	**Associated PNP**	**References**
HNK1 (present on SGPG, MAG, MP0 and other glycoproteins)	Anti-MAG PNP	[77–79]
Disialosyl epitope	B-series anti-ganglioside PNP (GD1b, GD3, GT1b and GQ1b)	[80,81]
Terminal Galβ(1–3)GalNAc structure	Anti-GM1/-GD1b/-asialo-GM1 ganglioside PNP	[82,83]
Sulfatide	Anti-sulfatide PNP	[82–85]

Table 1. *Cont.*

Target Molecule	Associated PNP	References
Combination sulfatide/galactocerebroside	Anti-sulfatide PNP	[86]
Internal sialylated epitope	Anti-GM1/-GM2 PNP	[87]
Chondroitin sulfate C	Anti-chondroitin sulfate C PNP	[88]

This group of IgM gammopathy-associated PNPs, where the M-protein acts as an autoantibody, contains phenotypically, immunologically and electrophysiologically heterogeneous neuropathies [89]. Despite this heterogeneity, the majority of these neuropathies manifest as a chronic, slowly progressive demyelinating PNP [20,27,90–92].

Katz et al. showed that 60% of patients with an acquired demyelinating neuropathy and distal phenotype (DADS neuropathy) had an IgM M-protein, and 67% of these patients had anti-MAG antibodies [93]. Matà et al. showed in a cohort of 30 IgM gammopathy anti-MAG neuropathy patients that all of them cohered to the DADS phenotype [89]. Of all PNPs associated with IgM gammopathy, approximately 50% consist of PNP with anti-MAG antibodies [90,94,95], although this percentage might differ and might be up to 70% [96] or even 85% [86].

To detect the antibody activity of M-proteins (for instance with the HNK1 epitope in anti-MAG PNP), different techniques may be used [97–99]. While initially the Western blot method was widely used, approximately 15 years ago an enzyme-linked immunosorbent assay (ELISA) for MAG was developed that proved more sensitive compared to the Western blot [96], albeit less specific. The most used anti-MAG ELISA kit is from Bühlmann and measures the titer in Bühlmann titer units (BTU). While the initial lower limit for a positive test was >1000, studies suggest that a higher value of >7000 [100] gives a higher specificity and accuracy [26].

Although the entire group is heterogeneous, the IgM anti-MAG PNP patients are clinically and electrophysiologically more homogeneous, although differences can be seen [94,101] possibly related to lower anti-MAG titers [102]. Clinically, they classically manifest as a chronic, slowly progressive, predominantly sensory (atactic) PNP [73,89–92,94,101,103–105], regularly accompanied by a tremor [106–108]. Although the progression is usually slow, up to 24% and 50% of patients with anti-MAG IgM antibodies are disabled at 10 and 15 years after the onset of neuropathy, respectively [109]. At the most severe disease stage, with a mean follow-up of 8.4 years, 22.4% were found to be significantly disabled (Overall Neuropathy Limitations Scale > 3) [101].

Electrophysiologically, there is nearly always the presence of nerve conduction slowing indicating a demyelinating neuropathy, either with or without axonal degeneration [91,92,110–112] with distal conduction slowing increasing with nerve length [113,114]. The uncommon absence of demyelinating features in anti-MAG PNP is associated with a better prognosis regarding disability and progression, compared to demyelinating patterns in nerve conduction studies (NCS) [105]. Compared to controls, NCS of anti-MAG neuropathy showed statistically significant prolonged DML (distal motor latency) and reduced MCV (motor conduction velocity), SCV (sensory conduction velocity), CMAP (compound motor action potential) and SNAP (compound sensory nerve action potential) [115], indicative of distal demyelination. Anti-MAG neuropathy patients show a reduced terminal latency index (TLI) [114] and may have a reduced TLI of the median nerve more often compared to anti-MAG-negative patients [115]. This may be due to a higher susceptibility to nerve compression (in the wrist) in anti-MAG neuropathy since similar frequencies between anti-MAG-positive and negative patients of TLI < 0.25 were found in other nerves. The susceptibility to nerve compression has been suggested before [116]. Motor conduction slowing without conduction blocks remains stable over longer periods, whereas lower limb motor and sensory potentials frequently become unrecordable [117].

3.3.2. IgM Anti-MAG Antibody Polyneuropathy

In 1980, Latov et al. showed that in the setting of an IgM monoclonal gammopathy, in some cases a particular protein component on the peripheral nerve acts as an antigen and might be part of the pathophysiology of these PNPs [22,26]. Braun et al. [68] provided evidence that this protein is the myelin-associated glycoprotein (MAG).

MAG is a minor component of the peripheral nervous system myelin, accounting for less than 1% of the total protein weight [64]. It is a 100-kDa transmembrane adhesion protein of myelin-containing Schwann cell or glia cell membranes (in the CNS). MAG is located in the adaxonal membrane and on apposing myelin membranes in the non-compact myelin compartments, such as the Schmidt–Lanterman incisures and the paranodal loops [118,119].

Although the precise pathways are not known, there is evidence of bidirectional signaling between Schwann or glia cells and axon [120], concerning myelin maintenance and axon configuration. The fact that MAG knock-out mice develop a chronic axonopathy (with a decreased axonal diameter and progressive axonal degeneration [121,122]) and mild signs of demyelination on NCS [123] suggests that MAG promotes axonal stability, survival and maximal radial caliber and is thus needed for the maintenance of normal myelinated nerves [124].

MAG contains five extracellular immunoglobulin-like domains, a single transmembrane domain and a cytoplasmic domain [124]. MAG is a member of the immunoglobulin superfamily adhesion molecules [125], and because it binds sialic acid it also is a SIGLEC (sialic acid-binding immunoglobulin-like lectin) [126] and as such is named Siglec4a. SIGLECs recognize sialic acid groups on other molecules, and so does MAG. Sialic acid-containing glycosphingolipids are called gangliosides [127] and are abundant in the PNS and CNS. MAG recognizes the NeuAcα2$\rightarrow$3Galβ1$\rightarrow$3GalNAc (3-O) sialic acid [125], which is present on the GD1a and GT1b gangliosides, among others. By binding to axonal gangliosides, MAG maintains a defined spacing between the axon membrane and the adaxonal membrane of the Schwann cell [128].

In IgM anti-MAG PNP, IgM immunoglobulins cause disease by binding to the HNK1 carbohydrate epitope of MAG, which is shared with SGPG, MP0 and other proteins in peripheral nerves [79]. This has been shown by purifying MAG using deglycosylation, with MAG not causing reactivity afterward [77]. Biopsy studies show primary segmental demyelination, remyelination and IgM deposition on myelin sheaths [129], associated with the widening of myelin lamellae (WML) [130–134] and a decrease in neurofilament spacing [135], with axonal degeneration and tomaculous appearance (i.e., focal thickening [136]) of myelinated fibers [132]. There are multiple lines of evidence for the hypothesis that anti-MAG antibodies are the cause of these effects.

The deposition of IgM is associated with sites of MAG localization [131], mainly the Schmidt–Lanterman incisures and paranodal loops, but also additional HNK1-positive components of the basal lamina. Paranodal regions show an altered morphology, presumably because of IgM deposition on the terminal loops impairing paranodal function [137]. Dermal myelinated nerve fibers have diffuse deposits of anti-IgM antibodies, with increasing frequency distally compared to proximally in the limbs [138]. The IgM deposits colocalize with the aforementioned anti-MAG sites. Although MAG is also present in the adaxonal membrane, histological studies do not show IgM deposition at the membrane, most likely because the IgM immunoglobulins are unable to access these sites.

The fact that systemic transfusion of chickens with monoclonal IgM anti-MAG antibodies produced peripheral demyelination with a similar widening of the myelin lamellae, demyelination, remyelination and IgM deposition [139] strengthens the hypothesis that anti-MAG antibodies induce the demyelinating PNP. Similarly, intraneural injections of serum from patients with anti-MAG IgM PNP, supplemented with additional complements, produced an extensive inflammatory, macrophage-mediated demyelination of feline peripheral nerve, although pathological examination differed from human findings [140]. Moreover, immunization of cats with SGPG-induced anti-SGPG antibodies caused a sensory PNP

clinically resembling the sensory ataxia of patients with monoclonal IgM anti-MAG/SGPG antibodies [141]. This has been shown in rats as well [142].

The widening of myelin lamellae may be one of the main mechanisms of demyelination in IgM anti-MAG PNP and is considered to be caused by the direct binding of IgM to the myelin membrane, with a positive correlation between the widening of the lamellae and demyelination [132], and the colocalization of IgM deposits and the finding of widening of the lamellae [132,143]. The fact that the frequency of these histological changes was correlated with anti-MAG titers suggests a causal role for IgM anti-MAG.

Histological studies suggest a role for the complement system in the pathogenesis of demyelination in IgM anti-MAG PNP, with the colocalization of sites with the widening of myelin lamellae and deposition of complement factors (C1q, C3d and C5) [132,134,144]. Deposits of both IgM and C3d were colocalized in the paranodal region, which suggests that the IgM antibody might injure myelin through activation of the complement pathway [132]. When classical and lectin pathways of complement activation are measured, there is no increase within anti-MAG patients [145]. Similarly, serum C3b and C4b were not elevated in MAG patients, nor were contactin-1 or neurofilament light chain (indicating axonal and paranodal damage) [146]. These findings might be the result of a sub-threshold effect due to extremely localized complement activation and particularly slow axonal damage. The exact influence of the complement system on IgM anti-MAG-induced demyelination is not known and needs further research, especially in light of the emerging potent complement inhibitors.

Interestingly, the $MYD88^{L265P}$ mutation is highly prevalent (approximately 60%) in patients with IgM M-protein anti-MAG-associated PNP [55,147]. The prevalence of CXCR4 mutations in this group is approximately 10%, although this might be an underestimate since only the $CXCL4^{S338X}$ mutation was analyzed [55]. The implication of the high frequency of these mutations is that the pathophysiology of anti-MAG PNP patients is close to WM and that patients therefore might be investigated and treated in this light [23].

3.4. Current Therapy for IgM Gammopathy Mediated Polyneuropathy

Evidence of pathological effects of IgM monoclonal proteins acting as antibodies (e.g., anti-MAG), led to the notion that lowering the M-protein titer would reduce the pathological and clinical effects. In the case of IgM anti-MAG PNP, clinical improvement is indeed associated with a relative decrease in anti-MAG titer, while a stable titer is not associated with improvement and a transient increase in anti-MAG titer is associated with acute worsening [148]. Since IgM M-protein-associated PNPs are slowly progressive and do not resolve without treatment [91,149], targeted treatment must be considered early to prevent axonal damage which might be irreversible. While the presence of an associated PNP is not a justification for treatment per se, steady deterioration of neurological findings with a disability may be a viable reason [66].

A decrease in IgM M-protein, or the amount of damage the M-protein does, can be achieved by different techniques. These include scavenging the M-protein, decreasing production by attacking the clonal B-cell population, preventing the M-protein from binding/attacking the target antigen or decreasing the damage done by the M-protein. In Table 2, we sum up these techniques with past and current treatment options for IgM monoclonal gammopathy anti-MAG PNP. In the next section, we will cover novel and possible future treatments. We used studies with the largest number of cases, and if possible we used RCTs. Treatment options in italic have not been proven effective.

Table 2. Tried and current treatment options for IgM anti-MAG PNP.

Technique	Intervention	Design	Study Arms	Number of Patients	Outcome	Authors
Scavenging M-protein	Plasma exchange (PE)	Prospective double-blind RCT. Follow-up 3 weeks	PE vs. sham exchange	19 (11 IgM) vs. 20 (10 IgM). No information on MAG status	Significant improvement in motor score in IgG and IgA paraprotein patients, but not for IgM paraprotein patients	Dyck et al., 1991. [150]
		Prospective, open-label RCT. Follow-up 12 months	PE + chlorambucil vs. chlorambucil	22 vs. 23 (16 & 17 antimyelin Abs, respectively)	No difference in clinical outcome	Oksenhendler et al., 1995. [151]
		Retrospective case series	PE	6 (all anti-MAG)	1 patient subjective improvement, 1 patient objective improvement but became unresponsive to PE later in disease course	Ellie et al., 1996. [91]
		Retrospective case series	PE PE + chlorambucil	5 2 (all anti-MAG)	2/5 patients with PE alone improved, 2/2 patients with PE + chlorambucil improved on functional impairment scale. Effect duration not mentioned	Nobile-Orazio et al., 2000. [109]
		Retrospective case series	PE	20 (all anti-MAG)	8 patients had at least temporal neurological improvement on MRC sum scale and neurological impairment scale	Gorson et al., 2001. [152]
		Pro- and retrospective, uncontrolled open-label case series. Follow-up 6–12 months	PE	24 (all anti-MAG)	4 patients had a significant clinical improvement (ONLS and/or modified functional impairment scale score) after 6 months, 1 after 12 months	Svahn et al., 2018. [101]
		Retrospective case series	PE (in acute worsening)	4 (all anti-MAG)	4 patients improved on ONLS score and subjectively after 3 to 6 PEs	Baron et al., 2017. [153]
	Selective apheresis	Prospective case series. Follow-up 12 months	Selective apheresis	1 IgM (2 IgG). No information on MAG status.	Sensory and motor response	Siciliano et al., 1994. [154]

Table 2. *Cont.*

Technique	Intervention	Design	Study Arms	Number of Patients	Outcome	Authors
Decreasing M-protein production by targeting B-cell	Rituximab (RTx)	Prospective, double-blind RCT. Follow-up 8 months	RTx vs. placebo	13 vs. 13 (all anti-MAG)	No significant improvement in primary outcome, but significant improvement in secondary outcome measures (e.g., 10 m walk test)	Dalakas et al., 2009. [155]
		Prospective, double-blind RCT. Follow-up 12 months	RTx vs. placebo	26 vs. 28 (all anti-MAG)	No significant improvement in primary outcome, but significant improvement in secondary outcome measures (e.g., INCAT disability scale)	Léger et al., 2013. [156]
		Pro- and retrospective, uncontrolled open-label case series. Follow-up 6–12 months	RTx	92 (all anti-MAG)	29 patients had a significant clinical improvement (ONLS and/or modified functional impairment scale score), 27 remained stable	Svahn et al., 2018. [101]
		Retrospective case series	RTx	25 IgM MGUS (23 anti-MAG), 8 WM (all anti-MAG)	18 of 33 patients clinically significant improvement (INCAT, INCAT sensory sum score, MRC sum score). MGUS statistically significant, WM not reached	Campagnolo et al., 2017. [157]
	Cyclo-phosphamide	Prospective, double-blind RCT, 2nd phase cross-over study. Follow-up 1st phase 6 months, 2nd phase 24 months	Cyclophos-phamide + prednisone vs. placebo	16 vs. 19 (all anti-MAG)	No difference in primary outcome (Rivermead mobility index). Some secondary outcomes (e.g., MRC sum score, sensory sum score) improved significantly more than placebo after 24 months	Niermeijer et al. 2007. [158]
		Prospective, uncontrolled open-label case series. Follow-up mean 28 months (range 18–30)	Cyclophos-phamide	9 (all anti-MAG)	7 patients significantly improved in muscle strength and modified ranking scale, 2 remained stable	Hamidou et al., 2005. [159]

Table 2. *Cont.*

Technique	Intervention	Design	Study Arms	Number of Patients	Outcome	Authors
	Fludarabine	Prospective uncontrolled open-label case series. Follow-up mean 14.5 months (range 4–28)	Fludarabine	4 (2 anti-MAG)	4 patients significantly improved in motor and sensory neurological functioning and MRC sum score increase	Wilson et al., 1999. [160]
		Prospective uncontrolled open label case series. Follow-up 12 months	Fludarabine	16 (6 anti-MAG)	5 patients (all anti-MAG) significantly improved (1 point on median ranking scale), others were stable. Similar findings with Rivermead mobility index and MRC sum score	Niermeijer et al., 2006. [161]
	Cladribine	Case report	Cladribine + IVIG	1 (anti-MAG-positive)	Significant motor and sensory improvement (albeit after second IVIG trial)	Ghosh et al., 2002. [162]
	Chlorambucil	Retrospective case series	Chlorambucil	2 (both anti-MAG)	No significant difference in clinical outcome	Gorson et al., 2001. [152]
		Pro- and retrospective, uncontrolled open-label case series. Follow-up 6–12 months	Chlorambucil	33 (all anti-MAG)	1 patient had a clinically significant improvement (ONLS and/or modified functional impairment scale score), 8 remained stable	Svahn et al., 2018. [101]
	Melphalan	Prospective, uncontrolled open-label case series. Follow-up unknown	Melphalan + chlorambucil	1 (anti-peripheral nerve myelin Ab's)	No significant difference in clinical outcome	Ernerudh et al., 1992. [163]

Table 2. *Cont.*

Technique	Intervention	Design	Study Arms	Number of Patients	Outcome	Authors
Decreasing damage done by M-protein by immunosuppression or -modulation	Intravenous immunoglobulins (IVIG)	Randomized double-blind crossover trial. Follow-up 6 months (3 months for 1st treatment, 3 months for 2nd treatment)	IVIG vs. placebo	11 vs. 11 (9 anti-MAG)	2 patients had a short (<3 months) clinically significant improvement in neurological functions	Dalakas et al., 1996. [164]
		Randomized double-blind crossover trial. Follow-up 4 weeks	IVIG vs. placebo	11 vs. 11 (11 anti-MAG)	Significant clinical improvement after 4 weeks (INCAT score and 10 m walk test). Secondary outcomes significantly increased as well. No percentages of patients given. No data after follow-up	Comi et al., 2002. [165]
		Pro- and retrospective, uncontrolled open-label case series. Follow-up 6–12 months	IVIG	68 (all anti-MAG)	Significant clinical improvement 19 after 6 months, 3 after 12 months	Svahn et al., 2018. [101]
	Interferon alpha-2a (IFNα-2a)	Prospective, double-blind RCT. Follow-up 6 months	*IFNα-2a* vs. placebo	12 vs. 12 (all anti-MAG)	No significant difference in clinical outcome	Mariette et al., 2000. [166]
	Dexamethasone (pulsed high dose)	Prospective, uncontrolled open-label case series, follow-up mean 19 months	Dexamethasone	6 (5 IgM anti-MAG, 1 IgG)	2 patients improved significantly, 4 had serious adverse events	Notermans et al., 1997. [167]
	Prednisone	Retrospective case series	Prednisone	6 (all anti-MAG)	No significant difference in clinical outcome	Nobile-Orazio et al., 2000. [109]
		Retrospective case series	Prednisone	8 (all anti-MAG)	No significant difference in clinical outcome	Gorson et al., 2001. [152]
		Pro- and retrospective, uncontrolled open-label case series. Follow-up 6–12 months	Oral prednisone IV prednisone	14 7 (all anti-MAG)	No significant clinical difference after 6 months, 3 patients significantly improved 12 months after oral prednisone	Svahn et al., 2018. [101]
	Azathioprine	Retrospective case series	Azathioprine	2 (all anti-MAG)	No significant difference in clinical outcome	Gorson et al., 2001. [152]
	Mycophenolate	Retrospective case series	Mycophenolate	8 (4 anti-MAG)	No significant difference in clinical outcome	Gorson et al., 2004. [168]

Only a few studies on these treatment regimens were randomized controlled trials (RCTs) [169]. Many studies had a short follow-up period, had few participants and were different in design compared to each other. They often evaluate combinations of treatment with other combinations, instead of a placebo. Furthermore, there was no uniformity in selected outcome measures and outcome measures were mostly of the ordinal scale instead of the interval scale, being inadequate and insensitive as a measurement of response [170]. This might have contributed to trials with negative outcomes [171]. Rasch methodology-built outcome measures may offer better responsiveness in future trials [170].

Although two RCTs showed no significant improvement after plasma exchange [150,151], a temporal improvement cannot be ruled out [91,101,109,152,172], especially after a rapid clinical worsening [153]. A temporal improvement after IVIG in some patients was demonstrated in two RCTs [164,165], although a sustained effect was generally not shown in a large retro- and prospective study [101]. Prednisone is regarded as not effective, as are other immunomodulatory drugs except IVIG. Dexamethasone showed effects but caused a high degree of side effects such as severe mood disturbances classified as serious adverse events [167]. Immunomodulatory drugs may, however, improve the effects of other treatments [169]. Currently, the best technique seems to decrease M-protein production by directly targeting B-cells. While cyclophosphamide [158,159] and fludarabine [160,161] showed some effect, these therapies have considerable toxicity.

The most promising results regarding sustained treatment effects were found when using rituximab [169], shown through a meta-analysis of two RCTs [155,156]. Rituximab is a chimeric anti-CD20 monoclonal antibody that targets CD20-positive B-cells from pre-B-cells to memory B-cells [173]. Anti-CD20 activity is accomplished by several mechanisms, including complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) [174]. ADCC is induced by NK cells and macrophages and is dependent on genetic polymorphisms in IgG Fcγ receptor II and III (FcγR II/III) [175]. Rituximab was first shown to be effective in IgM MGUS-associated PNP (anti-GM1 and anti-MAG) in 1999 [176]. An improvement is found in a portion of patients after approximately one year (circa 30–55% [101,157,177]), with an effect in sensory neuropathic tests, anti-MAG titers, total IgM and patient clinical impression of change, although some may not be clinically significant.

Since rituximab only has an effect on a portion of patients, it is interesting and helpful to know if there are correlations between patient characteristics and response to treatment. There is a positive correlation between an anti-MAG ELISA titer of $\geq$10 000 BTU and response to treatment [101]. Rituximab seems to have less effect on functional outcomes in patients with a longer disease course [157,178,179]. Clinically, proximal weakness of the lower limbs seems to predict significant treatment response, although the number of patients was small [179]. Patients with more profound axonal damage have a tendency to have an inferior response to rituximab treatment [180], which can be explained by a longer disease course. Furthermore, a certain FcγR polymorphism (FcγRIIIA-V/V158) was associated with (better) improvement in outcomes in a study with IgM PNP patients, of which 67% had anti-MAG antibodies [181]. This suggests different receptor binding properties of patients with this specific genotype, with subsequent better recruitment of effector cells. The effect of rituximab is similar in IgM MGUS anti-MAG and WM anti-MAG patients, with 36% (9/25) and 37.5% (3/8) of patients responding on the used neurological scales, respectively [157].

Sporadically, treatment of IgM anti-MAG PNP with rituximab can cause a paradoxical acute and severe worsening of clinical features [182]. The reason for this flare-up phenomenon is not known. A rapid rise in total IgM has been reported before in the light of WM treatment with rituximab [183,184], and this could include IgM anti-MAG antibodies, thus causing the worsening of clinical features. This rise in total IgM was, however, only seen in a portion of patients with an acute worsening after rituximab treatment and can therefore not explain all cases [182]. Other mechanisms that may be of influence on the transient worsening include an increase in pro-inflammatory cytokines and a higher

permeability of the blood–brain or blood–nerve barrier to antibodies (such as anti-MAG), complement or cytokines [185].

Similar to current practice in WM [186], where rituximab combined with chemotherapy yields superior responses compared to rituximab monotherapy, rituximab might be more effective in treating IgM M-protein anti-MAG PNP if combined with chemotherapies such as cyclophosphamide [187], fludarabine [188] and bendamustine [189].

The addition of these agents may elicit an earlier response compared to rituximab monotherapy. Moreover, patients that do not respond to rituximab monotherapy might respond to rituximab combined with chemotherapy [190]. This study by Hospital et al. [190] was reproduced by Nivet et al. [191] and showed a larger neurological response rate (modified Rankin scale) with rituximab combined with chemotherapy at different measuring moments (at 1 year; 46% vs. 18%), compared to rituximab monotherapy. Both therapies were initiated at similar moments after disease onset. The study being retrospective, however, likely caused selection bias, with rituximab monotherapy patients being less disabled and thus less able to have a large improvement. Moreover, these regimens give an increased risk of prolonged immunosuppression and myeloid neoplasms [186]. However, in some cases, such as rapidly deteriorating patients with IgM anti-MAG M-protein autoantibodies, rituximab combined with chemotherapy can be considered.

Current guidelines for WM give suggestions for the treatment of WM-associated PNP which can be used in clinical practice [186,192,193]. Considering the proposed shared etiology of disorders, these therapies seem viable for IgM MGUS anti-MAG PNP patients as well. Moreover, BTK inhibitors can be considered, such as ibrutinib. Since these are not yet investigated in large trials, much less in RCTs, we will cover these therapies in the next section.

3.5. Novel Therapy Options

Advances in attacking the M-protein-producing B-cells have been made through specific characteristics of B-cells. These techniques are increasingly used in WM patients (covered by Kapoor and Abeykoon in this issue). The $MYD88^{L265P}$ mutation makes the B-cells susceptible to BTK inhibition. This has been shown with ibrutinib, a first-generation BTK inhibitor, in WM and also in IgM gammopathy anti-MAG PNP [51,52]. This response was positively influenced by the $MYD88^{L265P}$ mutation and was negatively influenced by CXCR4 mutations. Treon et al. showed a high and durable response rate in WM and furthermore showed that IgM-related peripheral polyneuropathy improved in five of nine patients and stayed stable in the remaining four [51]. Castellani et al. showed both a subjective and objective neurological improvement (by means of sensory, motor and ataxia scales) in three anti-MAG patients with the $MYD88^{L265P}$ mutation with a concomitant decrease in M-protein and IgM levels, but not of MAG-titers [52]. Larger studies are needed to confirm a significant improvement in neurological parameters in IgM gammopathy-associated PNP.

In recent years, second- and third-generation BTK inhibitors have been developed, aiming to minimize the side effects of ibrutinib and reduce resistance to ibrutinib by more selectively targeting BTK. The second-generation BTK inhibitors bind to BTK covalently and irreversibly, similar to ibrutinib, and include acalabrutinib, zanabrutinib and tirabrutinib [194]. Third-generation BTK inhibitors bind BTK reversibly and are versatile in the binding site, aiming to overcome resistance. These agents are currently still being tested in clinical trials, including pirtobrutinib [195]. In the near future, we will conduct a multicenter, open-label, phase II study in patients with IgM MGUS and anti-MAG antibodies to analyze the treatment effects of zanubrutinib in combination with rituximab on neurological and hematological outcomes (MAGNAZ trial) [196].

In the field of WM treatment, many novel options are being developed. These include BCL2 inhibitors such as venetoclax [197], anti-CXCR4 monoclonal antibodies (ulocuplumab) [198], next-generation proteasome inhibitors [199] and next-generation anti-CD20 agents, such as ofatumumab and obinutuzumab [200]. Obinutuzumab causes enhanced

B-cell-depleting activity compared to rituximab [201] and may be effective in treating (rituximab non-responding) IgM gammopathy anti-MAG polyneuropathy [202,203].

Briani et al. published a case of CLL with IgM-kappa monoclonal protein with anti-MAG antibody activity without MYD88 or CXCL4 mutations. There was a sensorimotor demyelinating polyneuropathy present. The patient had only a minor improvement with rituximab with cyclophosphamide. Since BTK inhibitor response might be low due to the lack of an MYD88 mutation, venetoclax was given in a dose-increasing regimen, combined with rituximab. Venetoclax may improve BTK inhibition and, as such, can improve response rates of BTK inhibitors used to treat anti-MAG PNP [197]. There was a decrease in total IgM, anti-MAG titer, and importantly, the neurological symptomatology. Being only one case report, additional observations and controlled studies are needed to form conclusions [204].

Considering the notion that IgM anti-MAG PNP needs complement activation to elicit damage to the nerve and myelin sheath, complement activation inhibiting therapy could be an interesting way to prevent IgM anti-MAG antibodies from causing damage. Complement activation plays a role in the pathophysiology of several neurological disorders, including myasthenia gravis [205], Guillain–Barré syndrome [206], CIDP [207] and MMN [208].

Since the complement activation cascade consists of many steps and pathways [209], there are several points in this cascade at which therapies can intervene. Therapies acting on C1 (e.g., Cinryze [210]), C2 (e.g., ARGX-117 [211]), C3 (the compstatin family of C3 inhibitors [212]), C5 (e.g., eculizumab [213]) and other components of the complement system are being investigated for a variety of (neurological) disorders wherein complement activation plays a role [214]. To our knowledge, up to now there have been no clinical trials conducted that evaluated direct complement-inhibiting therapies in gammopathy-associated polyneuropathy.

Analogous to plasma exchange and plasmapheresis, the circulating antibodies could be removed by novel techniques as well. Since the M-protein acts as a de facto autoantibody, an autoantibody competitor decoy may be used to scavenge the harmful IgM M-proteins by acting as the actual antigen [215]. In this fashion, glycopolymers mimicking the HNK1 epitope have been designed to selectively decoy the circulating HNK1 epitope targeting antibody-acting M-protein [216]. This poly(phenyl disodium 3-O-sulfo-β-d-glucopyranuronate)-(1→3)-β-d-galactopyranoside (PPSGG, also called PN-1007) glycopolymer quickly removed the anti-HNK1 IgM immunoglobulin ex vivo [217]. A clinical trial was set up to evaluate this effect and its safety in a clinical setting (NCT04568174) but was terminated early. Glycopolymers acting as a decoy can elicit a potentially dangerous complement-mediated reaction called CARPA (complement activation-related pseudoallergy), which may be a reason not to try this technique [218].

In conclusion, in recent years there have been many developments in treating IgM gammopathies and, subsequently, the associated (anti-MAG) PNP as well. Similarly, in other polyneuropathies and chronic neurological disorders, new treatment options may be effective in treating IgM (anti-MAG) PNP too. While there have not been controlled trials yet to confirm the efficacy and clinical significance of treatment effects, small case reports and case series show promising results and warrant larger studies. In Table 3, we sum up the novel therapy options.

Table 3. Novel treatment options for IgM anti-MAG PNP.

Technique	Treatment	Anti-MAG Literature	Effect on Anti-MAG
Decreasing M-protein production by targeting B-cell	BTK inhibitors (e.g., ibrutinib, zanubrutinib, acalabrutinib)	Castellani et al., 2020. Prospective case series, follow-up 9–12 months [52]	Clinical improvement of 3/3 WM anti-MAG patients (sensory, motor and ataxia scales)
	BCL2 inhibitors (Venetoclax)	Briani et al., 2022. Case report [204]	Clinical improvement in CLL anti-MAG patient.
	Anti-BCL2 monoclonal antibody (ulocuplumab)		
	Next-generation anti-CD20 monoclonal antibodies (e.g., ofatumumab and obinutuzumab)	Rakocevic et al., 2018. Retrospective IgM MGUS anti-MAG case series (N = 2) [202] Briani et al., 2019. Retrospective CLL IgM anti-MAG case series (N = 2) [203]	Rakocevic et al. reported no clinical improvement, but decrease in total IgM and anti-MAG titer Briani et al. reported both
	Proteasome inhibitors (e.g., carfilzomib and ixazomib)		
Decreasing damage by M-protein by immunosuppression or -modulation	Complement inhibitors (e.g., Cinryze, ARGX-117, compstatin family C3 inhibitors, and eculizumab)		
Preventing the M-protein from binding/attacking target antigen	Autoantibody competitor decoys or antigen mimics (e.g., PPSGG)		

4. Conclusions

With increasing age, the chances of developing either MGUS or polyneuropathy increase as well. In some cases, this is no coincidence. Particularly in IgM gammopathies, it is important to identify when polyneuropathy is caused by the IgM M-protein. In approximately half of these cases, IgM targets MAG. This results in chronic polyneuropathy with slowly progressive, predominantly sensory neurological deficits and distally demyelinating features in nerve conduction studies. Despite the disease being chronic and developing slowly, it can cause considerable impairment. Treatment options have been limited for a long time, with a temporizing effect of intravenous immunoglobulins in some patients and a more sustained effect of rituximab, but in only 30 to 55 percent of patients. An increase in our knowledge concerning genetic mutations in WM, IgM MGUS and IgM anti-MAG polyneuropathy patients, particularly the $MYD88^{L265P}$ mutation, has led to the development of novel targeted treatment options such as BTK inhibitors in these settings. Similarly, due to the increasing knowledge about the pathophysiology of anti-MAG polyneuropathy, new treatment options are emerging. Since anti-MAG polyneuropathy is a rare disease with diverse symptomatology, large trials with good outcome measures are a challenge. However, promising results of novel therapy options in recent case series warrant larger studies to confirm potential good treatment options in this difficult-to-treat disease.

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