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Case report

Time course of the autoantibody response to therapy in anti-MAG neuropathy: TWO case REPORTS

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ABSTRACT

Background: Anti-MAG neuropathy is a slowly progressive demyelinating neuropathy that can lead to disability. The neuropathy is thought to be caused by monoclonal IgM antibodies that target the Myelin Associated Glycoprotein (MAG) in peripheral nerves. Therapy is directed at lowering the autoantibody concentrations with B-cells depleting agents, most often rituximab, based on case series and uncontrolled trials reporting improvement. There are no FDA approved treatments for anti-MAG neuropathy, however, and two relatively short duration randomized controlled trials with rituximab failed to achieve their pre-specified primary endpoints. There is also little information regarding the number or duration of treatments that are required to effectively reduce the antibody concentrations.

Case presentations: We report the time course of the anti-MAG antibody response in two patients with anti-MAG neuropathy that were treated with rituximab for several years. A reduction of 50% in the anti-MAG IgM was seen after 19 and 58 months respectively, and of 70% after 74 or 104 months of treatment respectively. Titres remained low, without evidence of recurrence after the treatments were discontinued.

Conclusion: Therapy of anti-MAG neuropathy with rituximab may require repeat treatments over more than one year to achieve a significant reduction in autoantibody concentrations. These considerations should inform treatment decisions and the design of clinical trials.

1. Introduction

Anti-MAG neuropathy is a chronic demyelinating polyneuropathy that is associated with monoclonal IgM antibodies that target the Myelin Associated Glycoprotein (MAG) in the peripheral nerves. It typically presents with paresthesias and impaired sensation in the feet, and slowly progresses over years to gait ataxia and weakness in the arms and legs, with 50% becoming disabled after 15 years [1]. The neuropathy is thought to be mediated by the anti-MAG antibodies, based on evidence from clinicopathological and experimental animal studies ([2,3]).

Treatment of the neuropathy is directed at reducing the monoclonal anti-MAG antibody concentration using agents that target the autoantibody producing B-cells, most often the anti-CD20 agent rituximab [4] but also Obinutuzumab [5], with cyclophosphamide [6], Bruton's tyrosine kinase inhibitors ibrutinib or tirabrutinib ([7,8]) or the anti-BCL2 agent venetoclax [9] sometimes added. A meta-analysis of 50 mostly uncontrolled trials with 410 patients found that a significant reduction in the antibody levels is associated with a clinical response [10]. Two, double blinded, randomized placebo-controlled studies of rituximab, however, did not meet their

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pre-specified primary endpoints ([11,12]), although a meta-analysis showed low quality evidence of a benefit [13]. The studies' shortcomings were attributed to inadequate r trial design, including patient selection, length of treatment, and choice of outcome measures [14]. There is little information however regarding the number and duration of treatments required to significantly lower the autoantibody concentrations.

We would like to report our observations in 2 patients with anti-MAG neuropathy and non-malignant or monoclonal gammopathy of unknown significance (MGUS) who were treated with rituximab long term, showing that repeated treatments for more than one or 2 years may be required to reduce the antibody levels to near normal levels, and that the remission can be maintained for many years after discontinuation of the treatments.

2. Case presentations

Case 1: The patient was a 52-year-old man with numbness in the feet that progressed to the hands over several months. Electrodiagnostic studies revealed a moderately severe sensorimotor neuropathy with demyelinating features. Conduction velocities in the peroneal nerves were 24 and 22 m/s, with amplitudes 0.4 mV and 0.6 mV, and F-wave minimal latencies 64.8 ms and 73.3 ms respectively. Blood tests showed mildly elevated IgM at 267mg/dL (nl: 40 mg/dL – 230 mg/dL), with an IgMk monoclonal protein, and highly elevated IgM anti-MAG antibodies. Titres were >70,000 BTU (nl < 1000 BTU) using the Buhlmann assay that compares binding to a linear standard curve, and >1:102,400 (nl: <1:1600) at Quest Labs using serial dilution end point assay with the titre determined by the highest dilution at which binding is detected above background [2]. Bone marrow biopsy was negative for proliferative disorder. Blood tests for other acquired or hereditary causes of neuropathy were unremarkable.

He began treatment with rituximab, 375 mg/m2/week x 4 weeks, but there was no change in the antibody levels, and the neuropathy progressed. Examination showed weakness of extension of the large toes, inability to walk on the heels or toes, and absent vibratory sensation at the large toes, with mild gait instability, and adjusted INCAT disability score of 1 [15]. Cyclophosphamide was added at month 4, 1 g/m2 every month x 6 months, with continuation of the rituximab treatments 375 mg/m2 per week for 4 weeks, every 6 months. IgM concentration and anti-MAG antibody titres using the Buhlmann assay were periodically measured.

Serum IgM and anti-MAG antibody titres gradually declined, with serum IgM reaching approximately 50% of the initial values at about 19 months, and 30% at 73 months, at which time the rituximab treatments were discontinued (Fig. 1). Serum IgM levels then remained stable and anti-MAG antibody titres declined slightly over the subsequent 2 years of follow up. Serum IgG remained in the normal range, and there were no notable infections. The neuropathy also gradually improved, but with residual mild weakness of large toe extension and mild impairment of vibratory sensation at the large toes. He regained the ability to walk on his heels or toes and his gait became normal, with adjusted INCAT score of 0.

Case 2: A 64-year-old woman presented with history of paresthesias in the hands and feet for 1 year and mild gait instability. Neurological examination demonstrated normal strength, with decreased sensitivity to pinprick in the hands and feet, moderate impairment of vibratory sensation at the large toes, ankles, and fingers, and normal joint position sense. Deep tendon reflexes were absent in the arms and legs with bilateral plantar flexor responses. Romberg was positive, and she couldn't tandem walk. Gait appeared normal, with adjusted INCAT score of 0. Electrodiagnostic studies showed severe polyneuropathy with demyelinating features. Conduction velocities in the peroneal nerves were 19.1 m/s and 20.8 m/s with amplitudes 0.1 mV and 0.9 mV respectively. and left F-

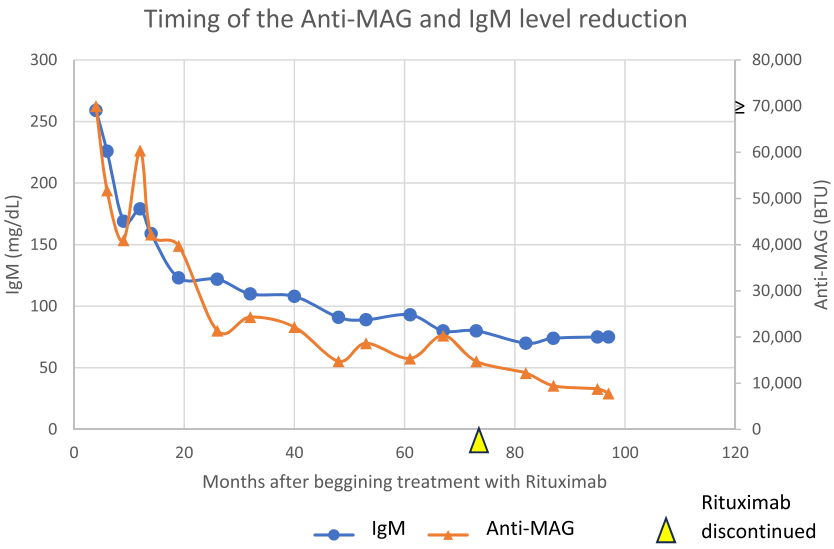

Fig. 1. Change in serum IgM ((●)) and anti-MAG IgM titres ((▲)) over time after initiation of treatment with rituximab. Antibody titres were determined by the Buhlmann assay that compares binding to a standard linear curve. Antibody levels declined by approximately 50% by month 19 and 70% by month 73, at which time the treatments were discontinued.

wave minimal latency 106.6 ms. Laboratory tests revealed IgM concentration of 225 mg/dl (nl: 40mg/dL – 230mg/dL). Serum immunofixation electrophoresis revealed an IgMk monoclonal protein. Anti- MAG antibodies were highly elevated at f > 1:102400 (nl: <1:1600) at Quest Labs using the serial dilution endpoint assay. She was treated with Rituximab 375 mg/m2 per week x 4 weeks every 6 months for 8 1/2 years, with periodic measures of the serum IgM and anti-MAG antibody titres at Quest Laboratory. Serum IgM and anti-MAG antibody titre decreased to approximately 50% of the initial value at 58 months and to 30% at 104 months, at which time the rituximab treatments were discontinued, after which they continued to slowly decrease over the subsequent 7 years without further treatment (Fig. 2). Serum IgG remained in the normal range, and there were no notable infections. Her neurological examination remained stable over the 15 years of follow-up other than loss of vibratory sensation at the large toes, with the adjusted INCAT score remaining at 0.

3. Discussion

The data from the 2 patients presented indicates that it may require multiple courses of treatment with rituximab for more than 1 or 2 years, to achieve a significant reduction in the level of anti-MAG antibodies of 50–70%. This contrasts with the single 4-week course of treatments, and follow up for 8 or 12 months, used in the 2 previously reported controlled clinical trials of rituximab ([11,12]), highlighting the need for better trial designs with longer treatment durations. The addition of agents such as cyclophosphamide as in case #1, that complement the effect of rituximab could also achieve a more rapid response.

The IgM monoclonal anti-MAG antibodies in any one patient have the same affinities, so that the titre in the Buhlmann assay would be expected to be proportional to the concentration of the serum anti-MAG IgM. The observation that the titres change in parallel to the total IgM suggests that both the monoclonal and background IgM secreting B-cells have similar susceptibilities to rituximab. Either or both measures would be suitable for following response to therapy. The serial dilution end point assay is less suitable for monitoring the response to therapy, as it is exponential rather than linear, and requires a 50% change in antibody concentration to detect a change in titre.

Both of our patients had non-malignant disease, also referred to as (MGUS), with no evidence for other lymphoproliferative disease such as macroglobulinemia, lymphoma or B-cell leukaemia which can be associated with IgM monoclonal gammopathies. The lack of relapse in antibody levels after completion of the course of treatment suggests that such patients may remain stable after significant reduction of the autoantibody levels, without requiring further treatment.

Patient # 2 had only minor neurological deficits, but treatment was initiated due to the significant

Nerve damage already present, as evidenced by the electrodiagnostic studies, to prevent further

Deterioration. Bourque et al. reported that the lower limb nerves show a marked trend to

Become inexcitable over time, consistent with the severe changes observed [16].

The inclusion of such patients in clinical trials could be problematic, as improvement would be difficult to evaluate given the mild clinical findings. In such cases, the change in anti-MAG antibody titres could serve as a biomarker to assess the therapeutic response. Patients could be followed after the anti-MAG antibody titres are reduced to near normal, to ascertain the absence of further deterioration or relapse.

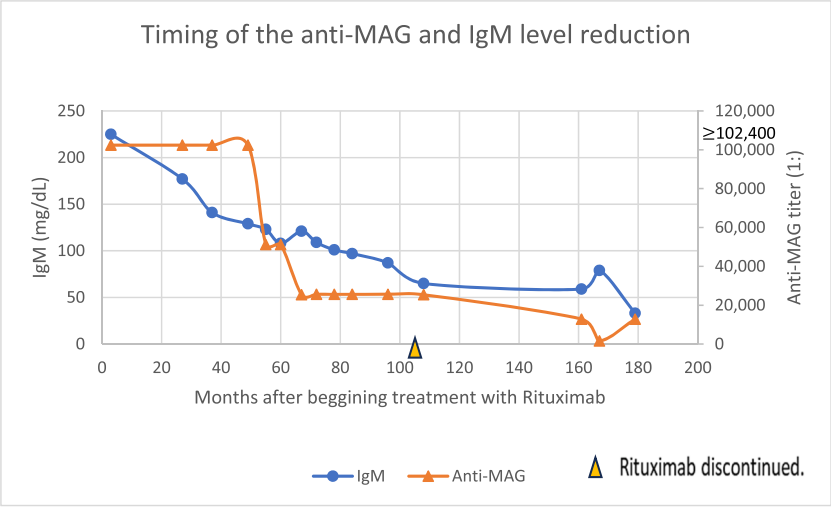

Fig. 2. Change in serum IgM ((●)) and anti-MAG IgM titres ((▲))over time after initiation of treatment. Antibody titres were measured using the serial dilution end point assay, where the titre is given as the highest dilution at which binding above background can still be detected. IgM concentration declined by 50% by month 8, and 70% by month 104, at which time the treatments were discontinued.

4. Conclusion

Patients with anti-MAG neuropathy may require multiple treatments with B-cell depleting agents such as rituximab, for more than one or two years, to achieve a significant reduction in anti-MAG antibody levels. Addition of other B-cell depleting agents may help achieve a more rapid response. In patients with mild clinical signs, where improvement is difficult to assess, the change in anti-MAG antibody titres could be used as a biomarker for response to therapy. The Buhlmann anti-MAG assay, which is a liner assay that closely parallels the change in serum IgM is more useful than the serial dilution end point assay for monitoring the response to therapy. Future clinical trials need to take into account the magnitude and time course of the antibody response in their design.

5. Ethics statement

All participants/patients (or their proxies/legal guardians) provided informed consent for the publication of their anonymized case details and images.

CRediT authorship contribution statement

Norman Latov: Writing – review & editing. **Angelica C. Cornejo:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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