

Long-term multidisciplinary outcomes of rituximab in anti-MAG demyelinating polyneuropathy associated with IgM gammopathies

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Background. Anti-myelin-associated glycoprotein (MAG) demyelinating polyneuropathy (PNP) is driven by pathogenic IgM-producing B-cell clones and may cause progressive disability. Rituximab (RTX) is widely used, but long-term hematological disease control, neurological durability, and optimal induction remain incompletely defined.

Methods. In this single-center longitudinal study, patients with symptomatic anti-MAG PNP and an IgM gammopathy received RTX 375 mg/m² weekly and multidisciplinary hematology-neurology follow-up. Waldenström macroglobulinemia (WM) and IgM monoclonal gammopathy of undetermined significance (MGUS) were classified according to IWWM2 criteria. Baseline (T0) hematologic assessment included serum IgM, anti-MAG titers, bone-marrow histology and flow cytometry, and MYD88 L265P/CXCR4 testing; neurologic disability was assessed by modified INCAT Sensory Sum Score (mISS), INCAT disability score (INCATds), MRC sum score, patient-reported change, and serial neurophysiology. Responses were assessed ~12 months after RTX completion (T1), and 9–12 months later (T2). Neurological analysis compared standard four-dose with intensified 4+4 induction, excluding two patients receiving an incomplete 4+2 schedule.

Results. From 2017 to 2025, 47 patients were treated; median follow-up from clinical PNP onset was 86 months (range 14–209). The cohort included 34 men and 13 women; median age at RTX was 72 years (range 52–82).

29 patients had WM, 17 IgM-MGUS and one an unclassified IgM gammopathy because bone-marrow biopsy was declined. Baseline bone marrow disease burden was generally low by multiparameter flow cytometry, with median clonal B cells of 0.17% (range, 0–35; n=34) and median plasma cells of 0% (range, 0–2.34; n=35). The monoclonal component was IgM-κ in 42 patients (89%). MYD88 was available in 43/47 patients (91.5%) and mutated in 39/43 (90.7%); CXCR4 was available in 21/47 (44.7%) and mutated in 6/21 (28.6%). Seven patients had received RTX previously, whereas 40 were RTX-naïve.

RTX induced a significant serum IgM reduction, from 609.7 to 393.2 mg/dL ($p<0.001$), remaining stable at the subsequent assessment. By IWWM-11 criteria, MRR/ORR were 33.3%/72.2% at T1 and 45.5%/78.8% at T2. Among patients with evaluable absolute peripheral-blood CD19+ counts, median values were 60.5/μL at baseline (range 5–637) and 0/μL after RTX (n=12; range 0–123).

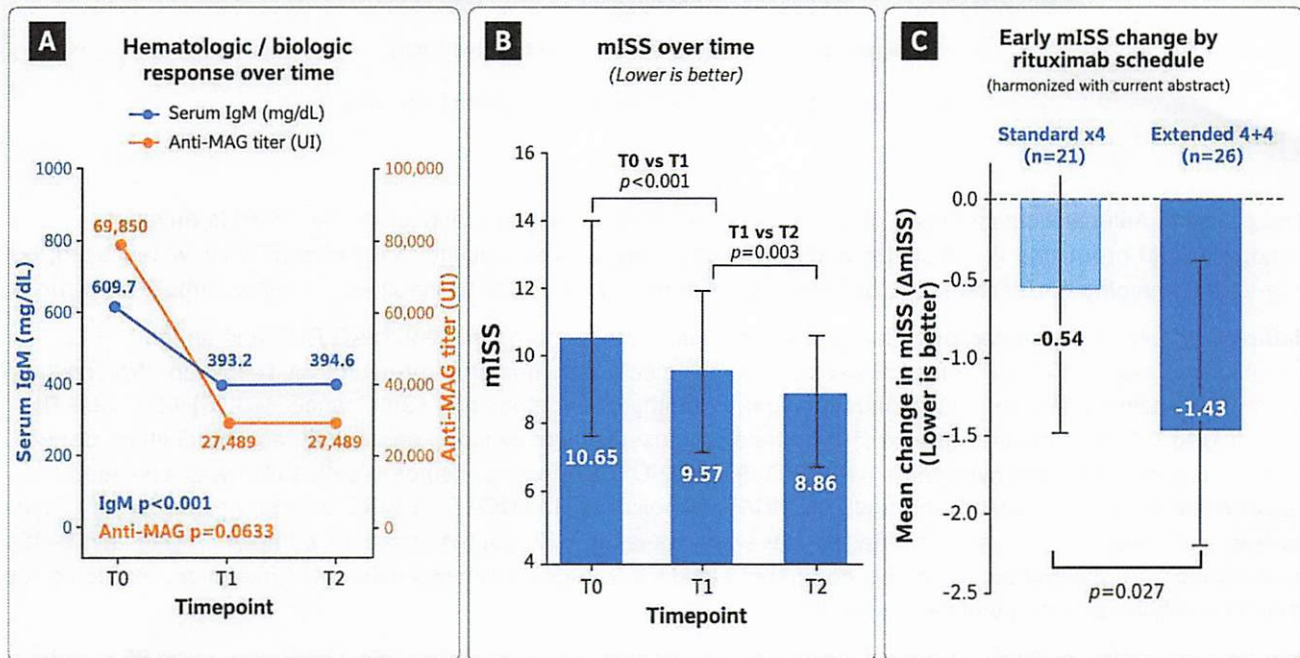
Neurologic improvement was early and sustained: mean mISS decreased from 10.65 at baseline to 9.57 at T1 and 8.86 at T2 ($p<0.001$ and $p=0.003$), while INCATds decreased from 2.30 to 2.00 and 1.98 ($p=0.014$ and $p=0.860$). Early neurophysiological improvement involved terminal latency index and ulnar distal motor latency, followed by later gains in selected CMAP/SAP amplitudes.

Intensified 4+4 induction (n=26) produced a greater early mISS improvement than standard induction (n=21) (1.43 vs 0.54 points; $p=0.027$). After a median post-RTX follow-up of 54.5 months (range 10–186), 11 patients (23.4%) received an additional RTX course for worsening PNP symptoms; retreatment was more frequent after four-dose

than eight-dose induction (8/20 vs 3/25; $p=0.03$). One patient developed systemic WM progression treated with zanubrutinib.

Conclusions. In this mature longitudinal cohort, long-term control of the IgM-producing clone with RTX was associated with durable neurological and neurophysiological benefit. Intensified induction may provide greater early sensory improvement and reduce the need for retreatment, supporting integrated hematological and neurological monitoring.

Rituximab in anti-MAG neuropathy: hematologic control and neurological improvement



mISS = modified Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score
UI = arbitrary units

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