Differentiating Between DADS no MAG (Variant of CIDP) and Other Distal Acquired Demyelinating Neuropathies

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Distal Acquired Demyelinating Neuropathies: Clinical Findings

- Large > small fiber sensory loss
  - Vibration, touch, JPS >> pin and temp loss
  - Distal to proximal gradient (length-dependent)
- Romberg sign
- Sensory ataxia (> 50% of cases, disabling)
- Areflexia
- Motor signs prominent in 15-20% (advanced cases)
- Cranial nerves, autonomic function spared

Dalakas MC. *Curr Treat Options Neurol.* 2010;12(2):71-83.

Distal Acquired Demyelinating Neuropathy with MAG

- Male predominance (85%)
- Older age (60-80)
- Slowly progressive
- Symptoms present for years before evaluation
- Distal, symmetrical, sensory >> motor
- Paresthesias (75%), numbness, imbalance, sensory ataxia (50%)
- Tremor (15%)

Dalakas MC. *Curr Treat Options Neurol.* 2010;12(2):71-83.

Distal Acquired Demyelinating Neuropathies: Electrodiagnostic Studies

- Prolonged distal motor latencies in most nerves
- Variable conduction velocity slowing, usually in demyelinating range
- Conduction block generally uncommon (DDx: CIDP)
- Axon loss is common
  - Reduced amplitudes, absent sensory potentials, distal denervation
  - Reflects chronicity of disorder (?)
  - Makes assessment difficult, implications for treatment response
- Rare cases (< 10%) with absent motor and sensory potentials
  - Probably limited to very advanced, end-stage cases

Ellie E, et al. *J Neurol*. 1996;243(1):34-43. Steck AJ, et al. *Curr Opin Neurol*. 2006;19(5):458-63.

Distal Acquired Demyelinating Neuropathies: Laboratory Features

- Invariable IgM paraprotein
  - Light chain kappa >> lambda
  - 75% or more related to IgM-MGUS (< 1.5 g)
  - Search for plasma cell dyscrasia; especially warranted if > 1.5 g of protein detected
- 50% of patients with IgM M-spike have MAG ab

Griffin JW. *Neurol Clin*. 1996;14(1):119-33.

Distal Acquired Demyelinating Neuropathies: Laboratory Features (cont.)

- MAG test should not be obtained in patients with IgG/IgA-MGUS
- ELISA system is standard measure for anti-MAG titer
- Western Blot more sensitive, may be positive when ELISA assay negative
- Titers < 1:6400 may not be clinically relevant
  - Reliability of laboratory should be established using appropriate methodology

Dalakas MC. *Curr Treat Options Neurol*. 2010;12(2):71-83.

Treatment of DADS no MAG (Variant of CIDP)

- DADS without a paraprotein represents an atypical form of CIDP
- Response to first-line treatment is similar to the response of typical CIDP

Nobile-Orazio E. *J Peripher Nerv Syst*. 2014;19(1):2-13. Larue S, et al. *Eur J Neurol*. 2001;18(6):899-905.

MAG Neuropathy: Treatment

- Is treatment always necessary?
- RCT thus far has not found evidence of response to therapy

Latov N. *Nat Rev Neurol*. 2014;10(8):435046. Dalakas MC. *Curr Treat Options Neurol*. 2010;12(2):71-83.

MAG Neuropathy: Treatment (cont.)

- Rituximab the “favored” treatment
- Total published rituximab experience:

  < 100 cases
- 7 with paradoxical worsening after rituximab

Stork et al. 2013; Weiss & Becker 2014.

Placebo-controlled Trial of Rituximab in IgM Anti-myelin-associated Glycoprotein Neuropathy

- **Objective**: To determine whether rituximab 375 mg/m^2 was efficacious in patients with immunoglobulin M (IgM) anti-myelin-associated glycoprotein antibody demyelinating neuropathy (IgM anti-MAG demyelinating neuropathy)
- **Methods:** 54 patients with IgM anti-MAG demyelinating neuropathy were enrolled in this randomized, double-blind, placebo-controlled trial. The inclusion criteria were inflammatory neuropathy cause and treatment (INCAT) sensory score (ISS) ≥4 and visual analogue pain scale >4 or ataxia score ≥2. The primary outcome was mean change in ISS at 12 months
- **Results:** 26 patients were randomized to a group receiving 4 weekly infusions of 375 mg/m^2 rituximab, and 28 patients were randomized to placebo. Intention-to-treat analysis, with imputation of missing ISS values by the last observation carried forward method, showed a lack of mean change in ISS at 12 months, 1.0 ± 2.7 in the rituximab group, and 1.0 ± 2.8 in the placebo group. However, changes were observed in per-protocol analysis at 12 months for the number of patients with an improvement of at least 2 points in the INCAT disability scale (P=0.027), the self-evaluation scale (P=0.016), and 2 subscores of the Short Form-36 questionnaire
- **Conclusions:** Although primary outcome measures provide no evidence to support the use of rituximab in IgM anti-MAG demyelinating neuropathy, there were improvements in several secondary outcomes in per-protocol analysis
- **Level of evidence:** This study provides Class I evidence that rituximab is ineffective in improving ISS in patients with IgM anti-MAG demyelinating neuropathy

Leger JM, et al. *Neurology*. 2013;80(24):2217-2225.

Rituximab in Anti-MAG PN

Table 5 Results for biological markers in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable	Placebo group (*n* = 27)	Rituximab group (*n* = 20)	*p* Value
Median change in B-cell count (D0-M12), % (IQR)	0.0 (−1.4; 4.0) (n′ = 15)	6.0 (3.0; 9.5) (n′ = 15)	0.002[a]
Median change in anti-MAG titer (D0-M12), g/L (IQR)[b]	0 (−9,600; 0) (n′ = 23)	13,700 (0; 38,000) (n′ = 18)	0.0015[a]
Median change in CD20 count (D0-M12), % (IQR)	−1.5 (−4.0; 0.0) (n′ = 10)	7.0 (2.5; 11.5) (n′ = 12)	0.003[a]

Abbreviations: IQR = interquartile range; MAG = myelin-associated glycoprotein; n′ = number of available data.
[a] Mann-Whitney test.
[b] Calculations carried out with a titer of 70,000 for values of 70,000 or more (censored titer).

Leger JM. *Neurology*. 2013;80(24):2217-25.

Table 3 Results for the main analysis (first row) and other analyses of inflammatory neuropathy cause and treatment sensory score in the intention-to-treat population and in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable		Placebo group (n = 28)	Rituximab group (n = 26)	p Value
Intention-to-treat population				
Between day 0 and month 12	Mean change in ISS ± SD	1.0 ± 2.8	1.0 ± 2.7	0.92[a]
	Mean percent change in ISS ± SD	10.0 ± 33.7	11.3 ± 38.3	0.90[a]
	ISS improvement ≥20% with respect to baseline, n (%)	12 (42.9)	11 (42.3)	0.97[b]
	ISS improvement ≥4, n (%)	6 (21.4)	4 (15.4)	0.73[c]
	ISS improvement ≥2, n (%)	11 (39.3)	8 (34.6)	0.72[b]
	Median change in ISS for the lower limbs (IQR)	0.0 (−1.0; 1.0)	0.0 (−1.0; 2.0)	0.39[d]
Variable		**Placebo group (n′ = 27)**	**Rituximab group (n′ = 20)**	**p Value**
Per protocol population				
Between day 0 and month 12	Mean change in ISS ± SD	1.0 ± 2.8	1.3 ± 3.0	0.68[a]
	Mean percent change in ISS ± SD	10.4 ± 34.3	15.5 ± 42.2	0.64[a]
	ISS improvement ≥20% with respect to baseline, n (%)	12 (44.4)	10 (50.0)	0.77[b]
	ISS improvement ≥4, n (%)	6 (22.2)	4 (20.0)	1.00[c]
	ISS improvement ≥2, n (%)	11 (40.7)	8 (40.0)	0.95[b]
	Median change in ISS for the lower limbs (IQR)	0 (−1.0; 1.0)	1.0 (−0.5; 3.0)	0.15[d]

Abbreviations: IQR = interquartile range; ISS = inflammatory neuropathy cause and treatment sensory score; n′ = number of available data when lower than n for the group.
[a] Student *t* test.
[b] χ^2 test.
[c] Fisher exact test.
[d] Mann-Whitney test.

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Table 4 Results for secondary analysis for clinical evaluation (change from D0 to M12), functional scores (evaluated at M12), and SF-36 scores (change from D0 to M12) in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable	Placebo group (n = 27)	Rituximab group (n = 20)	p Value
Median change in INCAT disability scale score (D0-M12) (IQR)	0.0 (−1.0; 0.0) (n′ = 27)	0.0 (−1.0; 1.0) (n′ = 20)	0.22[a]
Improvement in INCAT disability score ≥2, n (%)	0 (0.0)	4 (20.0)	0.027[b]
Improvement in INCAT disability score ≥1, n (%)	4 (14.8)	8 (40.0)	0.0503[c]
Mean change in NIS (D0-M12) ± SD	1.8 ± 5.1 (n′ = 26)	1.1 ± 6.0 (n′ = 19)	0.69[d]
Median change in MRC score (D0-M12) (IQR)	0.0 (−3.0; 0.0) (n′ = 27)	0.0 (−1.5; 1.5) (n′ = 20)	0.17[a]
Mean change in 10-meter walk time, s (D0-M12) ± SD	0.1 ± 2.7 (n′ = 24)	0.3 ± 3.2 (n′ = 18)	0.84[d]
Ataxia (2-3), n (%)	17 (65.4) (n′ = 26)	13 (65.0) (n′ = 20)	0.98[c]
Mean change in VAS score for pain ± SD	−0.07 ± 1.7 (n′ = 24)	0.61 ± 2.3 (n′ = 17)	0.28[d]
Mean functional score at M12 ± SD	14.8 ± 4.3 (n′ = 25)	12.0 ± 5.5 (n′ = 17)	0.07[d]
Self-evaluation scale at M12	(n′ = 25)	(n′ = 19)	0.016[b]
Improvement, n (%)	1 (4.0)	5 (26.3)	
Stabilization, n (%)	9 (36.0)	10 (52.6)	
No effect, n (%)	15 (60.0)	4 (21.0)	
SF-36 scores, absolute change (D0-M12)			
Physical component summary scales (mean ± SD)	−0.5 ± 4.1 (n′ = 15)	3.1 ± 6.6 (n′ = 14)	0.08[d]
Mental component summary scales (mean ± SD)	0.4 ± 9.2 (n′ = 15)	3.2 ± 8.9 (n′ = 14)	0.41[d]
SF-36 subscores, absolute change (D0-M12)			
Physical functioning (mean ± SD)	−3.9 ± 9.8 (n′ = 20)	11.6 ± 19.6 (n′ = 17)	0.0069[d]
Role-physical (median, IQR)	0.0 (0.0; 25.0) (n′ = 23)	0.0 (−25.0; 25.0) (n′ = 16)	0.76[a]
Role-emotional (median, IQR)	0.0 (−33.3; 16.7) (n′ = 24)	33.3 (0.0; 66.7) (n′ = 18)	0.02[a]
Mental health (mean ± SD)	−2.1 ± 12.8 (n′ = 24)	4.5 ± 9.9 (n′ = 17)	0.08[d]
Vitality (mean ± SD)	−1.4 ± 13.1 (n′ = 24)	2.1 ± 13.7 (n′ = 18)	0.40[d]
Social functioning (median, IQR)	0.0 (−31.2; 12.5) (n′ = 20)	12.5 (0.0; 12.5) (n′ = 18)	0.07[a]
Bodily pain (median, IQR)	0.0 (−10.5; 9.0) (n′ = 23)	9.0 (0.0; 11.0) (n′ = 17)	0.09[a]
General health (median, IQR)	0.0 (−11.0; 8.5) (n′ = 24)	5.0 (0.0; 15.0) (n′ = 17)	0.12[a]

Abbreviations: INCAT = inflammatory neuropathy cause and treatment; IQR = interquartile range; n′ = number of data available when lower than n for the group; MRC = Medical Research Council; NIS = neurologic impairment score; SF-36 = Short Form-36; VAS = visual analog pain scale.
[a] Mann-Whitney test.
[b] Fisher exact test.
[c] χ^2 test.
[d] Student *t* test.

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Therapy for MAG Neuropathy: Conclusions

- No compelling data that treatment works
  - Anecdotal evidence only
  - Indolent condition, hard to measure objective change
- Must all patients be treated?
  - No
- How to decide who should be treated
  - Functional disability (balance, gait)
  - Progression toward disability
- What treatment?

Summary: Indications for Anti-MAG Antibody Testing

- **Check anti-MAG when:**
  - Chronic progressive, large fiber sensory neuropathy, AND
  - IgM monoclonal protein detected
  - Long distal latencies

- **Anti-MAG NOT indicated when:**
  - Inherited neuropathy
  - Motor predominant pattern
  - Multifocal pattern
  - Prominent neuropathic
  - Rapid progression
  - No M-spike detected
  - Pure axonal pattern

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