Update on Neuromuscular Disorders

석 흥 열
계명의대

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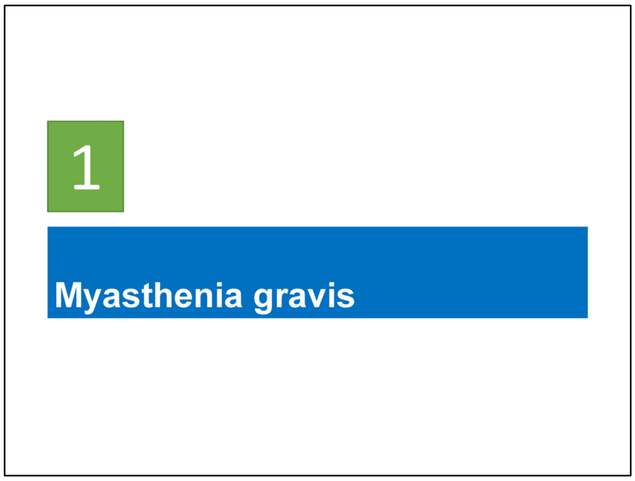

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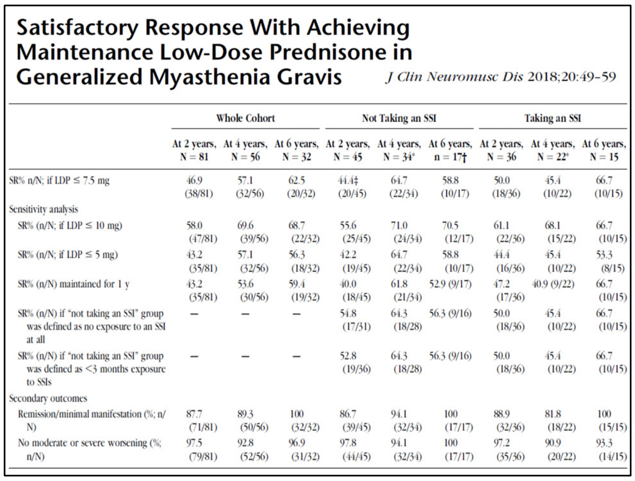
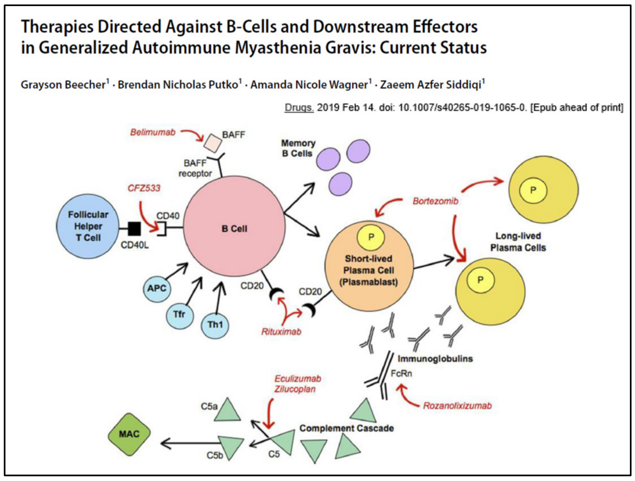
Myasthenia gravis



Satisfactory Response With Achieving Maintenance Low-Dose Prednisone in Generalized Myasthenia Gravis

J Clin Neuromusc Dis 2018;20:49–59

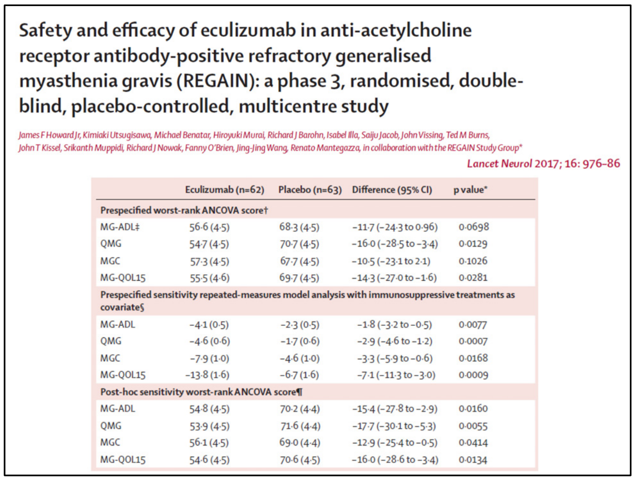
	Whole Cohort			Not Taking an SSI			Taking an SSI		
	At 2 years, N = 81	At 4 years, N = 56	At 6 years, N = 32	At 2 years, N = 45	At 4 years, N = 34*	At 6 years, n = 17†	At 2 years, N = 36	At 4 years, N = 22*	At 6 years, N = 15
SR% n/N; if LDP ≤ 7.5 mg	46.9 (38/81)	57.1 (32/56)	62.5 (20/32)	44.4‡ (20/45)	64.7 (22/34)	58.8 (10/17)	50.0 (18/36)	45.4 (10/22)	66.7 (10/15)
Sensitivity analysis									
SR% (n/N; if LDP ≤ 10 mg)	58.0 (47/81)	69.6 (39/56)	68.7 (22/32)	55.6 (25/45)	71.0 (24/34)	70.5 (12/17)	61.1 (22/36)	68.1 (15/22)	66.7 (10/15)
SR% (n/N; if LDP ≤ 5 mg)	43.2 (35/81)	57.1 (32/56)	56.3 (18/32)	42.2 (19/45)	64.7 (22/34)	58.8 (10/17)	44.4 (16/36)	45.4 (10/22)	53.3 (8/15)
SR% (n/N) maintained for 1 y	43.2 (35/81)	53.6 (30/56)	59.4 (19/32)	40.0 (18/45)	61.8 (21/34)	52.9 (9/17)	47.2 (17/36)	40.9 (9/22)	66.7 (10/15)
SR% (n/N) if "not taking an SSI" group was defined as no exposure to an SSI at all	—	—	—	54.8 (17/31)	64.3 (18/28)	56.3 (9/16)	50.0 (18/36)	45.4 (10/22)	66.7 (10/15)
SR% (n/N) if "not taking an SSI" group was defined as <3 months exposure to SSIs	—	—	—	52.8 (19/36)	64.3 (18/28)	56.3 (9/16)	50.0 (18/36)	45.4 (10/22)	66.7 (10/15)
Secondary outcomes									
Remission/minimal manifestation (%; n/N)	87.7 (71/81)	89.3 (50/56)	100 (32/32)	86.7 (39/45)	94.1 (32/34)	100 (17/17)	88.9 (32/36)	81.8 (18/22)	100 (15/15)
No moderate or severe worsening (%; n/N)	97.5 (79/81)	92.8 (52/56)	96.9 (31/32)	97.8 (44/45)	94.1 (32/34)	100 (17/17)	97.2 (35/36)	90.9 (20/22)	93.3 (14/15)



Therapies Directed Against B-Cells and Downstream Effectors in Generalized Autoimmune Myasthenia Gravis: Current Status

Grayson Beecher[1] · Brendan Nicholas Putko[1] · Amanda Nicole Wagner[1] · Zaeem Azfer Siddiqi[1]

Drugs. 2019 Feb 14. doi: 10.1007/s40265-019-1065-0. [Epub ahead of print]

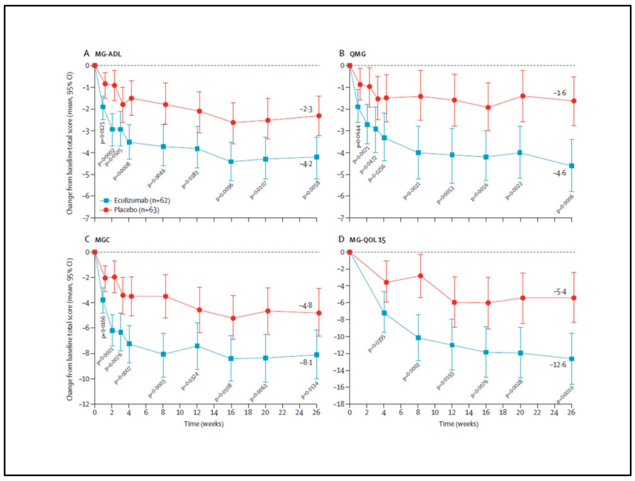


Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

*James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group**

Lancet Neurol 2017; 16: 976–86

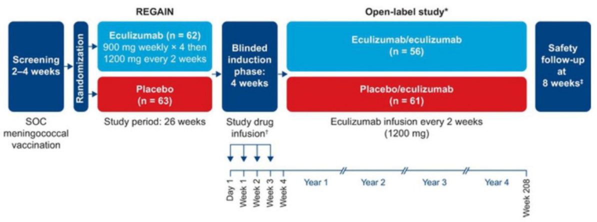
	Eculizumab (n=62)	Placebo (n=63)	Difference (95% CI)	p value*
Prespecified worst-rank ANCOVA score†				
MG-ADL‡	56·6 (4·5)	68·3 (4·5)	−11·7 (−24·3 to 0·96)	0·0698
QMG	54·7 (4·5)	70·7 (4·5)	−16·0 (−28·5 to −3·4)	0·0129
MGC	57·3 (4·5)	67·7 (4·5)	−10·5 (−23·1 to 2·1)	0·1026
MG-QOL15	55·5 (4·6)	69·7 (4·5)	−14·3 (−27·0 to −1·6)	0·0281
Prespecified sensitivity repeated-measures model analysis with immunosuppressive treatments as covariate§				
MG-ADL	−4·1 (0·5)	−2·3 (0·5)	−1·8 (−3·2 to −0·5)	0·0077
QMG	−4·6 (0·6)	−1·7 (0·6)	−2·9 (−4·6 to −1·2)	0·0007
MGC	−7·9 (1·0)	−4·6 (1·0)	−3·3 (−5·9 to −0·6)	0·0168
MG-QOL15	−13·8 (1·6)	−6·7 (1·6)	−7·1 (−11·3 to −3·0)	0·0009
Post-hoc sensitivity worst-rank ANCOVA score¶				
MG-ADL	54·8 (4·5)	70·2 (4·4)	−15·4 (−27·8 to −2·9)	0·0160
QMG	53·9 (4·5)	71·6 (4·4)	−17·7 (−30·1 to −5·3)	0·0055
MGC	56·1 (4·5)	69·0 (4·4)	−12·9 (−25·4 to −0·5)	0·0414
MG-QOL15	54·6 (4·5)	70·6 (4·5)	−16·0 (−28·6 to −3·4)	0·0134



Long-term safety and efficacy of eculizumab in generalized myasthenia gravis

Srikanth Muppidi MD

Muscle Nerve. 2019 Feb 14. doi: 10.1002/mus.26447. [Epub ahead of print]



REGAIN

Open-label study*

Screening 2–4 weeks

Randomization

Eculizumab (n = 62)
900 mg weekly × 4 then
1200 mg every 2 weeks

Placebo
(n = 63)

Blinded induction phase: 4 weeks

Eculizumab/eculizumab
(n = 56)

Placebo/eculizumab
(n = 61)

Safety follow-up at 8 weeks‡

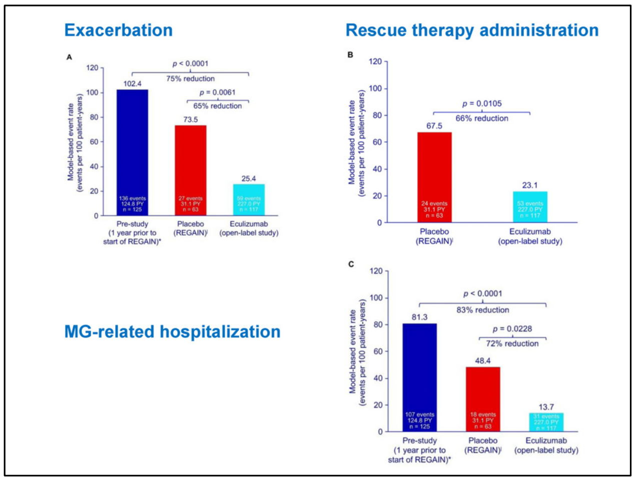
SOC meningococcal vaccination

Study period: 26 weeks

Study drug infusion†

Eculizumab infusion every 2 weeks (1200 mg)

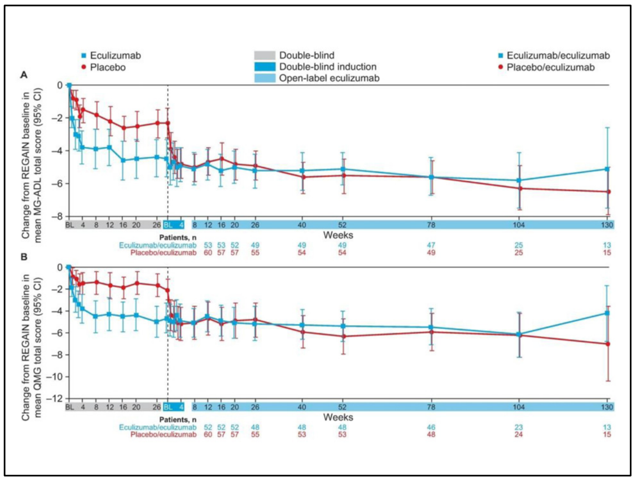
Day 1
Week 1
Week 2
Week 3
Week 4
Year 1
Year 2
Year 3
Year 4
Week 208

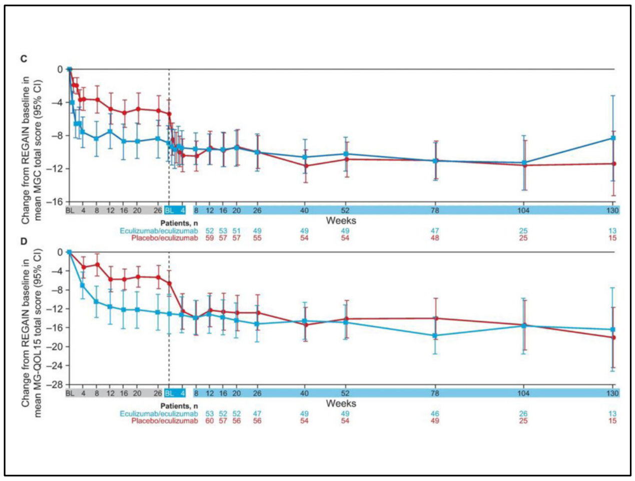


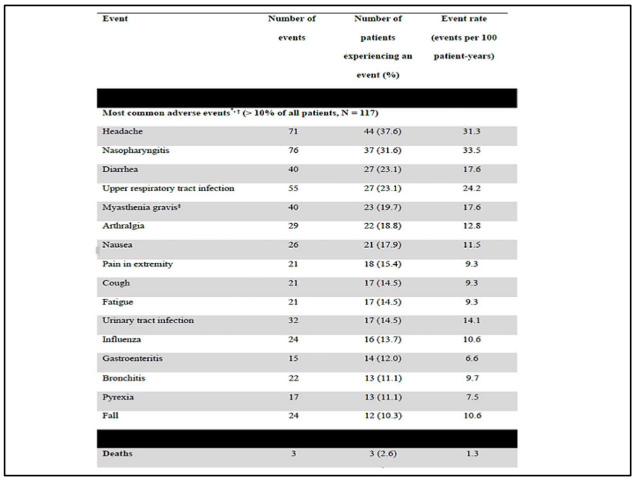
Exacerbation

Rescue therapy administration

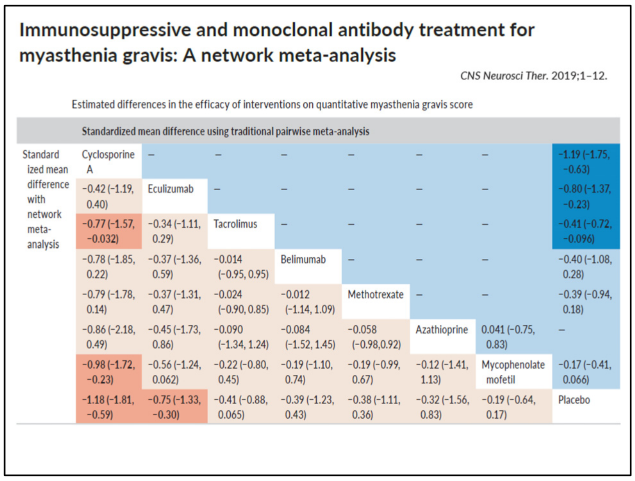
MG-related hospitalization







Event	Number of events	Number of patients experiencing an event (%)	Event rate (events per 100 patient-years)
Most common adverse events*,† (> 10% of all patients, N = 117)			
Headache	71	44 (37.6)	31.3
Nasopharyngitis	76	37 (31.6)	33.5
Diarrhea	40	27 (23.1)	17.6
Upper respiratory tract infection	55	27 (23.1)	24.2
Myasthenia gravis‡	40	23 (19.7)	17.6
Arthralgia	29	22 (18.8)	12.8
Nausea	26	21 (17.9)	11.5
Pain in extremity	21	18 (15.4)	9.3
Cough	21	17 (14.5)	9.3
Fatigue	21	17 (14.5)	9.3
Urinary tract infection	32	17 (14.5)	14.1
Influenza	24	16 (13.7)	10.6
Gastroenteritis	15	14 (12.0)	6.6
Bronchitis	22	13 (11.1)	9.7
Pyrexia	17	13 (11.1)	7.5
Fall	24	12 (10.3)	10.6
Deaths	3	3 (2.6)	1.3

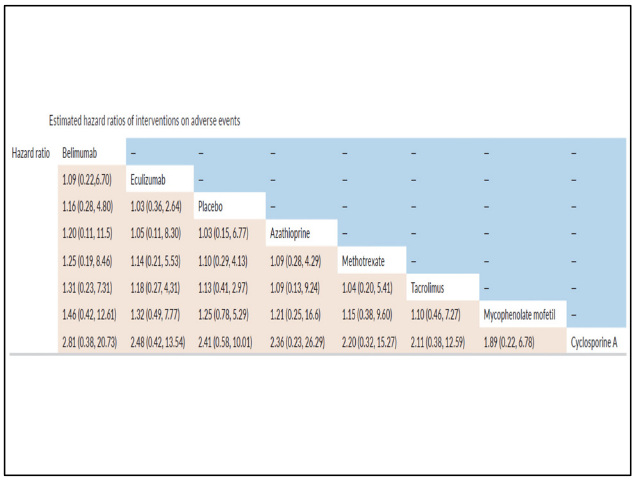


Immunosuppressive and monoclonal antibody treatment for myasthenia gravis: A network meta-analysis

CNS Neurosci Ther. 2019;1–12.

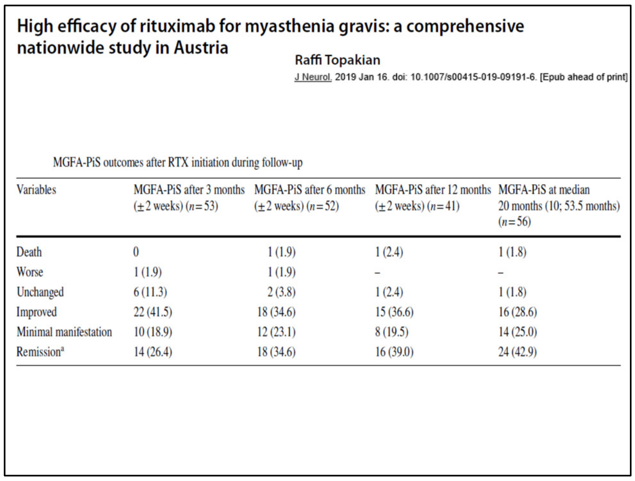
Estimated differences in the efficacy of interventions on quantitative myasthenia gravis score

	Standardized mean difference using traditional pairwise meta-analysis							
Standardized mean difference with network meta-analysis	Cyclosporine A	–	–	–	–	–	–	−1.19 (−1.75, −0.63)
	−0.42 (−1.19, 0.40)	Eculizumab	–	–	–	–	–	−0.80 (−1.37, −0.23)
	−0.77 (−1.57, −0.032)	−0.34 (−1.11, 0.29)	Tacrolimus	–	–	–	–	−0.41 (−0.72, −0.096)
	−0.78 (−1.85, 0.22)	−0.37 (−1.36, 0.59)	−0.014 (−0.95, 0.95)	Belimumab	–	–	–	−0.40 (−1.08, 0.28)
	−0.79 (−1.78, 0.14)	−0.37 (−1.31, 0.47)	−0.024 (−0.90, 0.85)	−0.012 (−1.14, 1.09)	Methotrexate	–	–	−0.39 (−0.94, 0.18)
	−0.86 (−2.18, 0.49)	−0.45 (−1.73, 0.86)	−0.090 (−1.34, 1.24)	−0.084 (−1.52, 1.45)	−0.058 (−0.98,0.92)	Azathioprine	0.041 (−0.75, 0.83)	–
	−0.98 (−1.72, −0.23)	−0.56 (−1.24, 0.062)	−0.22 (−0.80, 0.45)	−0.19 (−1.10, 0.74)	−0.19 (−0.99, 0.67)	−0.12 (−1.41, 1.13)	Mycophenolate mofetil	−0.17 (−0.41, 0.066)
	−1.18 (−1.81, −0.59)	−0.75 (−1.33, −0.30)	−0.41 (−0.88, 0.065)	−0.39 (−1.23, 0.43)	−0.38 (−1.11, 0.36)	−0.32 (−1.56, 0.83)	−0.19 (−0.64, 0.17)	Placebo



Estimated hazard ratios of interventions on adverse events

Hazard ratio	Belimumab	–	–	–	–	–	–	–
	1.09 (0.22,6.70)	Eculizumab	–	–	–	–	–	–
	1.16 (0.28, 4.80)	1.03 (0.36, 2.64)	Placebo	–	–	–	–	–
	1.20 (0.11, 11.5)	1.05 (0.11, 8.30)	1.03 (0.15, 6.77)	Azathioprine	–	–	–	–
	1.25 (0.19, 8.46)	1.14 (0.21, 5.53)	1.10 (0.29, 4.13)	1.09 (0.28, 4.29)	Methotrexate	–	–	–
	1.31 (0.23, 7.31)	1.18 (0.27, 4,31)	1.13 (0.41, 2.97)	1.09 (0.13, 9.24)	1.04 (0.20, 5.41)	Tacrolimus	–	–
	1.46 (0.42, 12.61)	1.32 (0.49, 7.77)	1.25 (0.78, 5.29)	1.21 (0.25, 16.6)	1.15 (0.38, 9.60)	1.10 (0.46, 7.27)	Mycophenolate mofetil	–
	2.81 (0.38, 20.73)	2.48 (0.42, 13.54)	2.41 (0.58, 10.01)	2.36 (0.23, 26.29)	2.20 (0.32, 15.27)	2.11 (0.38, 12.59)	1.89 (0.22, 6.78)	Cyclosporine A



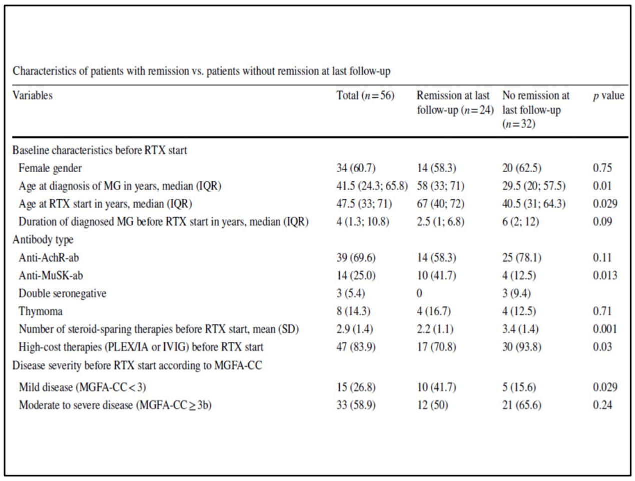
High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria

Raffi Topakian

J Neurol. 2019 Jan 16. doi: 10.1007/s00415-019-09191-6. [Epub ahead of print]

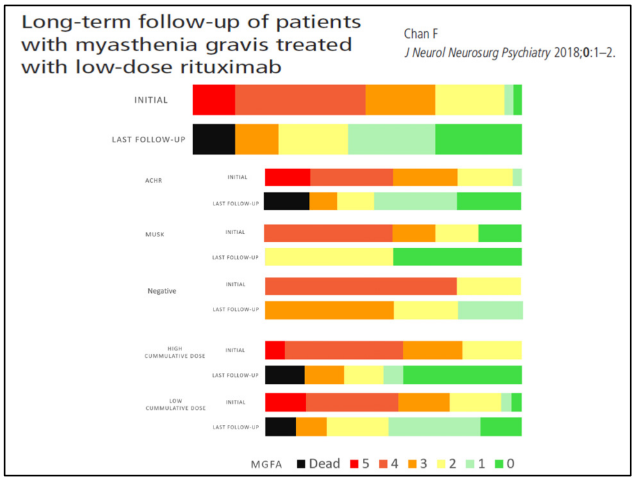
MGFA-PiS outcomes after RTX initiation during follow-up

Variables	MGFA-PiS after 3 months (±2 weeks) (*n*=53)	MGFA-PiS after 6 months (±2 weeks) (*n*=52)	MGFA-PiS after 12 months (±2 weeks) (*n*=41)	MGFA-PiS at median 20 months (10; 53.5 months) (*n*=56)
Death	0	1 (1.9)	1 (2.4)	1 (1.8)
Worse	1 (1.9)	1 (1.9)	–	–
Unchanged	6 (11.3)	2 (3.8)	1 (2.4)	1 (1.8)
Improved	22 (41.5)	18 (34.6)	15 (36.6)	16 (28.6)
Minimal manifestation	10 (18.9)	12 (23.1)	8 (19.5)	14 (25.0)
Remission[a]	14 (26.4)	18 (34.6)	16 (39.0)	24 (42.9)



Characteristics of patients with remission vs. patients without remission at last follow-up

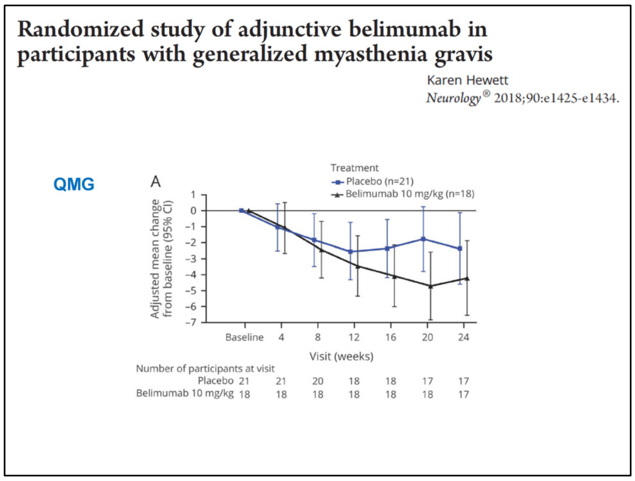
Variables	Total (*n*=56)	Remission at last follow-up (*n*=24)	No remission at last follow-up (*n*=32)	*p* value
Baseline characteristics before RTX start				
Female gender	34 (60.7)	14 (58.3)	20 (62.5)	0.75
Age at diagnosis of MG in years, median (IQR)	41.5 (24.3; 65.8)	58 (33; 71)	29.5 (20; 57.5)	0.01
Age at RTX start in years, median (IQR)	47.5 (33; 71)	67 (40; 72)	40.5 (31; 64.3)	0.029
Duration of diagnosed MG before RTX start in years, median (IQR)	4 (1.3; 10.8)	2.5 (1; 6.8)	6 (2; 12)	0.09
Antibody type				
Anti-AchR-ab	39 (69.6)	14 (58.3)	25 (78.1)	0.11
Anti-MuSK-ab	14 (25.0)	10 (41.7)	4 (12.5)	0.013
Double seronegative	3 (5.4)	0	3 (9.4)	
Thymoma	8 (14.3)	4 (16.7)	4 (12.5)	0.71
Number of steroid-sparing therapies before RTX start, mean (SD)	2.9 (1.4)	2.2 (1.1)	3.4 (1.4)	0.001
High-cost therapies (PLEX/IA or IVIG) before RTX start	47 (83.9)	17 (70.8)	30 (93.8)	0.03
Disease severity before RTX start according to MGFA-CC				
Mild disease (MGFA-CC < 3)	15 (26.8)	10 (41.7)	5 (15.6)	0.029
Moderate to severe disease (MGFA-CC ≥ 3b)	33 (58.9)	12 (50)	21 (65.6)	0.24



Long-term follow-up of patients with myasthenia gravis treated with low-dose rituximab

Chan F

J Neurol Neurosurg Psychiatry 2018;**0**:1–2.



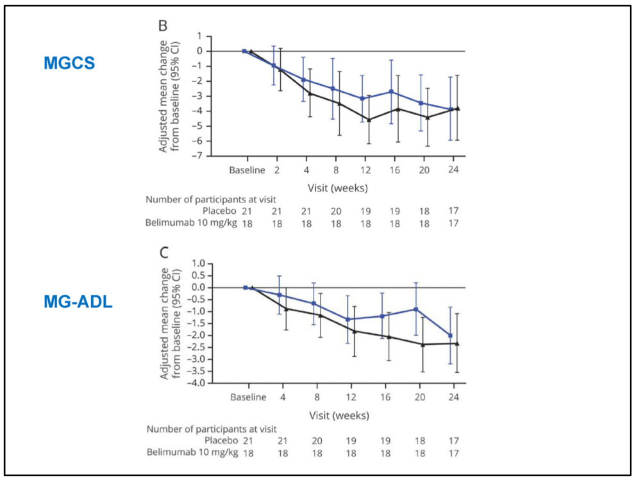
Randomized study of adjunctive belimumab in participants with generalized myasthenia gravis

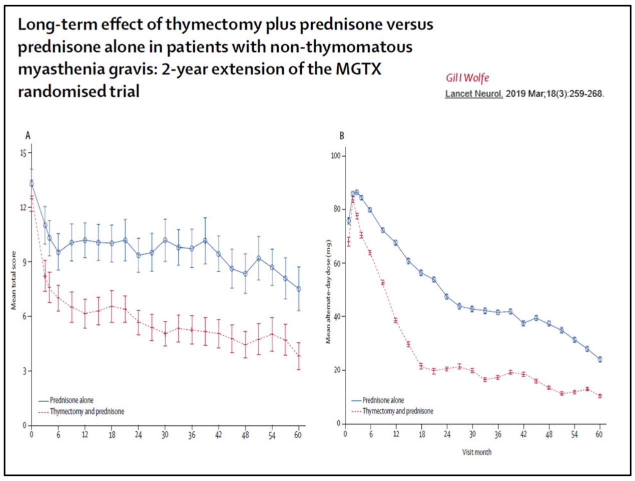
Karen Hewett

Neurology® 2018;90:e1425-e1434.

Number of participants at visit

	Baseline	4	8	12	16	20	24
Placebo	21	21	20	18	18	17	17
Belimumab 10 mg/kg	18	18	18	18	18	18	17

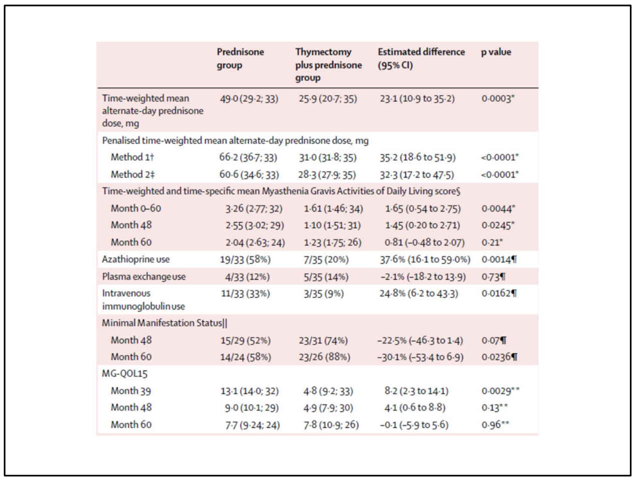




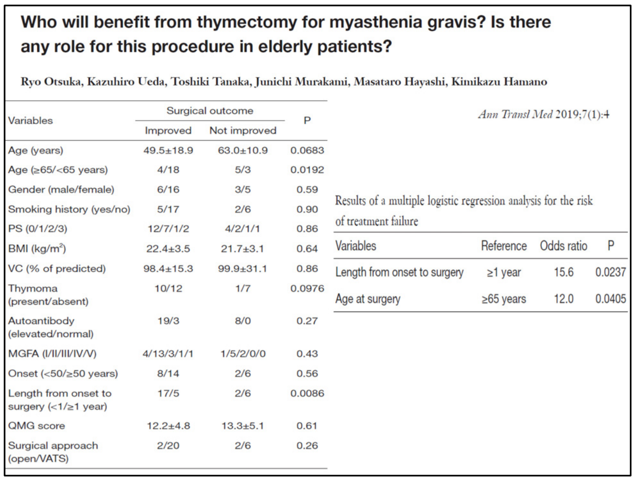
Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial

Gil I Wolfe

Lancet Neurol. 2019 Mar;18(3):259-268.



	Prednisone group	Thymectomy plus prednisone group	Estimated difference (95% CI)	p value
Time-weighted mean alternate-day prednisone dose, mg	49·0 (29·2; 33)	25·9 (20·7; 35)	23·1 (10·9 to 35·2)	0·0003*
Penalised time-weighted mean alternate-day prednisone dose, mg				
Method 1†	66·2 (36·7; 33)	31·0 (31·8; 35)	35·2 (18·6 to 51·9)	<0·0001*
Method 2‡	60·6 (34·6; 33)	28·3 (27·9; 35)	32·3 (17·2 to 47·5)	<0·0001*
Time-weighted and time-specific mean Myasthenia Gravis Activities of Daily Living score§				
Month 0–60	3·26 (2·77; 32)	1·61 (1·46; 34)	1·65 (0·54 to 2·75)	0·0044*
Month 48	2·55 (3·02; 29)	1·10 (1·51; 31)	1·45 (0·20 to 2·71)	0·0245*
Month 60	2·04 (2·63; 24)	1·23 (1·75; 26)	0·81 (–0·48 to 2·07)	0·21*
Azathioprine use	19/33 (58%)	7/35 (20%)	37·6% (16·1 to 59·0%)	0·0014¶
Plasma exchange use	4/33 (12%)	5/35 (14%)	–2·1% (–18·2 to 13·9)	0·73¶
Intravenous immunoglobulin use	11/33 (33%)	3/35 (9%)	24·8% (6·2 to 43·3)	0·0162¶
Minimal Manifestation Status‖				
Month 48	15/29 (52%)	23/31 (74%)	–22·5% (–46·3 to 1·4)	0·07¶
Month 60	14/24 (58%)	23/26 (88%)	–30·1% (–53·4 to 6·9)	0·0236¶
MG-QOL15				
Month 39	13·1 (14·0; 32)	4·8 (9·2; 33)	8·2 (2·3 to 14·1)	0·0029**
Month 48	9·0 (10·1; 29)	4·9 (7·9; 30)	4·1 (0·6 to 8·8)	0·13**
Month 60	7·7 (9·24; 24)	7·8 (10·9; 26)	–0·1 (–5·9 to 5·6)	0·96**



Who will benefit from thymectomy for myasthenia gravis? Is there any role for this procedure in elderly patients?

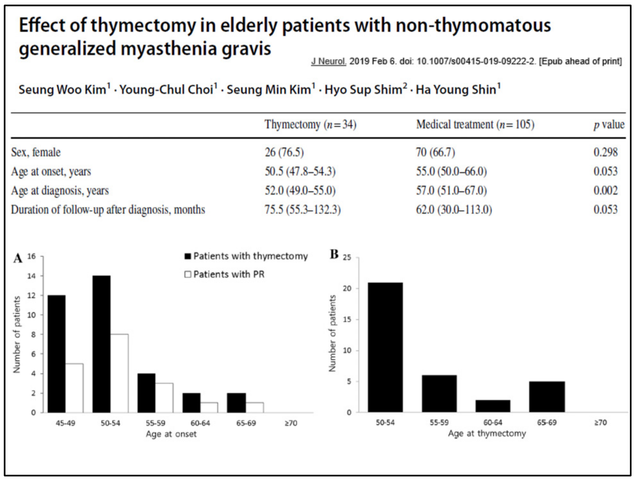
Ryo Otsuka, Kazuhiro Ueda, Toshiki Tanaka, Junichi Murakami, Masataro Hayashi, Kimikazu Hamano

Ann Transl Med 2019;7(1):4

Variables	Surgical outcome		P
	Improved	Not improved	
Age (years)	49.5±18.9	63.0±10.9	0.0683
Age (≥65/<65 years)	4/18	5/3	0.0192
Gender (male/female)	6/16	3/5	0.59
Smoking history (yes/no)	5/17	2/6	0.90
PS (0/1/2/3)	12/7/1/2	4/2/1/1	0.86
BMI (kg/m^2)	22.4±3.5	21.7±3.1	0.64
VC (% of predicted)	98.4±15.3	99.9±31.1	0.86
Thymoma (present/absent)	10/12	1/7	0.0976
Autoantibody (elevated/normal)	19/3	8/0	0.27
MGFA (I/II/III/IV/V)	4/13/3/1/1	1/5/2/0/0	0.43
Onset (<50/≥50 years)	8/14	2/6	0.56
Length from onset to surgery (<1/≥1 year)	17/5	2/6	0.0086
QMG score	12.2±4.8	13.3±5.1	0.61
Surgical approach (open/VATS)	2/20	2/6	0.26

Results of a multiple logistic regression analysis for the risk of treatment failure

Variables	Reference	Odds ratio	P
Length from onset to surgery	≥1 year	15.6	0.0237
Age at surgery	≥65 years	12.0	0.0405



Effect of thymectomy in elderly patients with non-thymomatous generalized myasthenia gravis

J Neurol. 2019 Feb 6. doi: 10.1007/s00415-019-09222-2. [Epub ahead of print]

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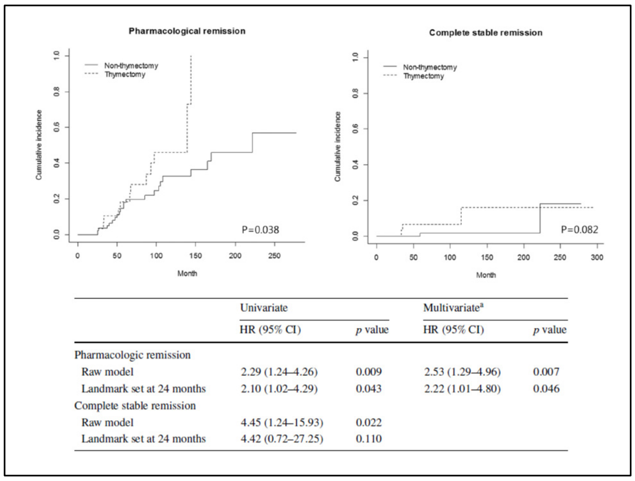
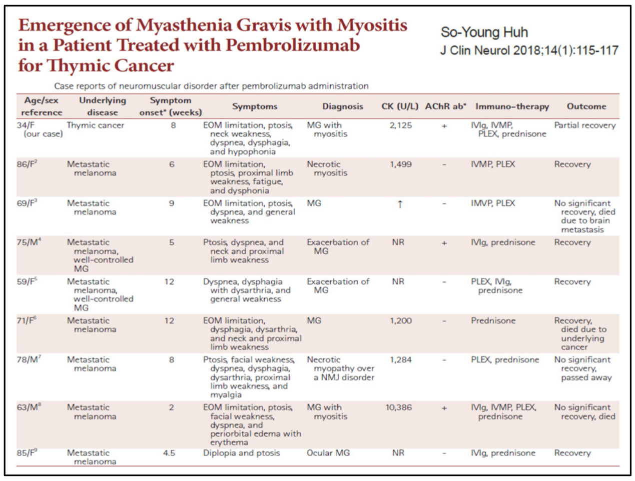
	Thymectomy ($n=34$)	Medical treatment ($n=105$)	*p* value
Sex, female	26 (76.5)	70 (66.7)	0.298
Age at onset, years	50.5 (47.8–54.3)	55.0 (50.0–66.0)	0.053
Age at diagnosis, years	52.0 (49.0–55.0)	57.0 (51.0–67.0)	0.002
Duration of follow-up after diagnosis, months	75.5 (55.3–132.3)	62.0 (30.0–113.0)	0.053



	Univariate		Multivariate[a]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Pharmacologic remission				
Raw model	2.29 (1.24–4.26)	0.009	2.53 (1.29–4.96)	0.007
Landmark set at 24 months	2.10 (1.02–4.29)	0.043	2.22 (1.01–4.80)	0.046
Complete stable remission				
Raw model	4.45 (1.24–15.93)	0.022		
Landmark set at 24 months	4.42 (0.72–27.25)	0.110		

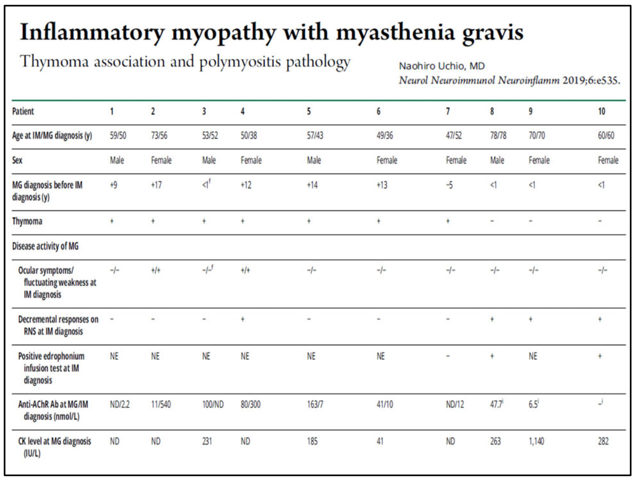


Emergence of Myasthenia Gravis with Myositis in a Patient Treated with Pembrolizumab for Thymic Cancer

So-Young Huh
J Clin Neurol 2018;14(1):115-117

Case reports of neuromuscular disorder after pembrolizumab administration

Age/sex reference	Underlying disease	Symptom onset* (weeks)	Symptoms	Diagnosis	CK (U/L)	AChR ab*	Immuno–therapy	Outcome
34/F (our case)	Thymic cancer	8	EOM limitation, ptosis, neck weakness, dyspnea, dysphagia, and hypophonia	MG with myositis	2,125	+	IVIg, IVMP, PLEX, prednisone	Partial recovery
86/F[2]	Metastatic melanoma	6	EOM limitation, ptosis, proximal limb weakness, fatigue, and dysphonia	Necrotic myositis	1,499	-	IVMP, PLEX	Recovery
69/F[3]	Metastatic melanoma	9	EOM limitation, ptosis, dyspnea, and general weakness	MG	↑	-	IMVP, PLEX	No significant recovery, died due to brain metastasis
75/M[4]	Metastatic melanoma, well-controlled MG	5	Ptosis, dyspnea, and neck and proximal limb weakness	Exacerbation of MG	NR	+	IVIg, prednisone	Recovery
59/F[5]	Metastatic melanoma, well-controlled MG	12	Dyspnea, dysphagia with dysarthria, and general weakness	Exacerbation of MG	NR	-	PLEX, IVIg, prednisone	Recovery
71/F[6]	Metastatic melanoma	12	EOM limitation, dysphagia, dysarthria, and neck and proximal limb weakness	MG	1,200	-	Prednisone	Recovery, died due to underlying cancer
78/M[7]	Metastatic melanoma	8	Ptosis, facial weakness, dyspnea, dysphagia, dysarthria, proximal limb weakness, and myalgia	Necrotic myopathy over a NMJ disorder	1,284	-	PLEX, prednisone	No significant recovery, passed away
63/M[8]	Metastatic melanoma	2	EOM limitation, ptosis, facial weakness, dyspnea, and periorbital edema with erythema	MG with myositis	10,386	+	IVIg, IVMP, PLEX, prednisone	No significant recovery, died
85/F[9]	Metastatic melanoma	4.5	Diplopia and ptosis	Ocular MG	NR	-	IVIg, prednisone	Recovery

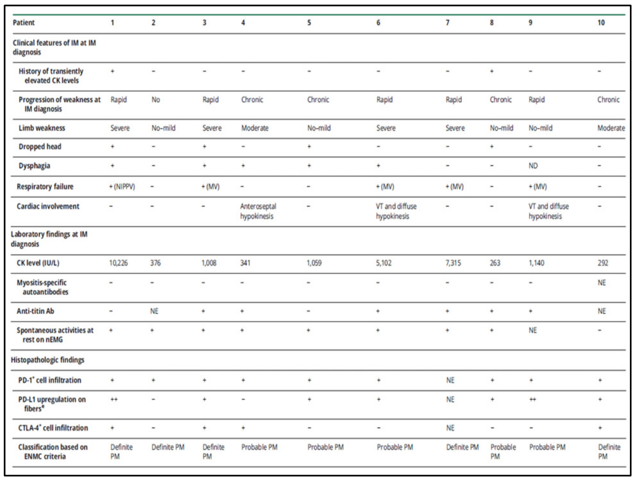


Inflammatory myopathy with myasthenia gravis

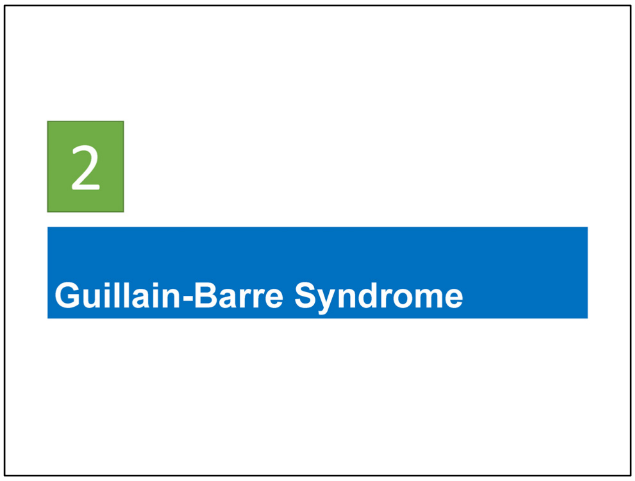
Thymoma association and polymyositis pathology

Naohiro Uchio, MD
Neurol Neuroimmunol Neuroinflamm 2019;6:e535.

Patient	1	2	3	4	5	6	7	8	9	10
Age at IM/MG diagnosis (y)	59/50	73/56	53/52	50/38	57/43	49/36	47/52	78/78	70/70	60/60
Sex	Male	Female	Male	Female	Male	Female	Female	Male	Female	Female
MG diagnosis before IM diagnosis (y)	+9	+17	<1[f]	+12	+14	+13	–5	<1	<1	<1
Thymoma	+	+	+	+	+	+	+	-	-	-
Disease activity of MG										
Ocular symptoms/ fluctuating weakness at IM diagnosis	–/–	+/+	–/–[f]	+/+	–/–	–/–	–/–	–/–	–/–	–/–
Decremental responses on RNS at IM diagnosis	-	-	-	+	-	-	-	+	+	+
Positive edrophonium infusion test at IM diagnosis	NE	NE	NE	NE	NE	NE	-	+	NE	+
Anti-AChR Ab at MG/IM diagnosis (nmol/L)	ND/2.2	11/540	100/ND	80/300	163/7	41/10	ND/12	47.7[i]	6.5[i]	–[i]
CK level at MG diagnosis (IU/L)	ND	ND	231	ND	185	41	ND	263	1,140	282

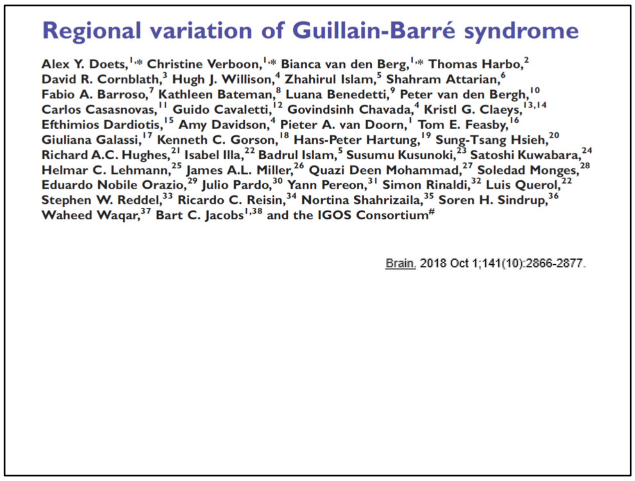


Patient	1	2	3	4	5	6	7	8	9	10
Clinical features of IM at IM diagnosis										
History of transiently elevated CK levels	+	-	-	-	-	-	-	+	-	-
Progression of weakness at IM diagnosis	Rapid	No	Rapid	Chronic	Chronic	Rapid	Rapid	Chronic	Rapid	Chronic
Limb weakness	Severe	No-mild	Severe	Moderate	No-mild	Severe	Severe	No-mild	No-mild	Moderate
Dropped head	+	-	+	-	+	-	-	+	-	-
Dysphagia	+	-	+	+	+	+	-	-	ND	-
Respiratory failure	+ (NIPPV)	-	+ (MV)	-	-	+ (MV)	+ (MV)	-	+ (MV)	-
Cardiac involvement	-	-	-	Anteroseptal hypokinesis	-	VT and diffuse hypokinesis	-	-	VT and diffuse hypokinesis	-
Laboratory findings at IM diagnosis										
CK level (IU/L)	10,226	376	1,008	341	1,059	5,102	7,315	263	1,140	292
Myositis-specific autoantibodies	-	-	-	-	-	-	-	-	-	NE
Anti-titin Ab	-	NE	+	+	-	+	+	+	+	NE
Spontaneous activities at rest on nEMG	+	+	+	+	+	+	+	+	NE	-
Histopathologic findings										
PD-1^{+} cell infiltration	+	+	+	+	+	+	NE	+	+	+
PD-L1 upregulation on fibers[e]	++	-	+	-	+	+	NE	+	++	+
CTLA-4^{+} cell infiltration	+	-	+	+	-	-	NE	-	-	+
Classification based on ENMC criteria	Definite PM	Definite PM	Definite PM	Probable PM	Probable PM	Probable PM	Definite PM	Probable PM	Probable PM	Definite PM



2

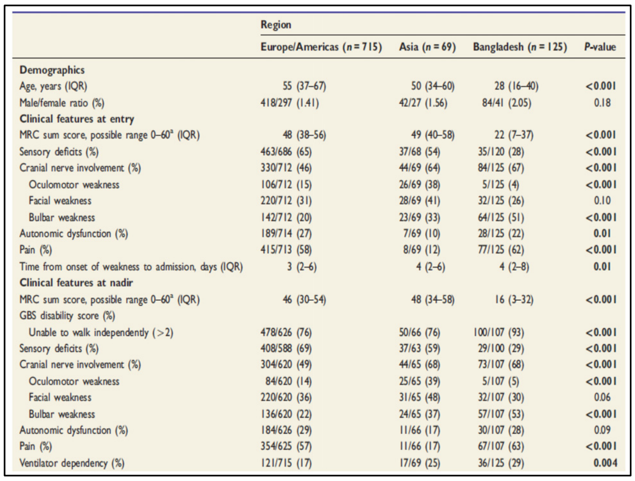
Guillain-Barre Syndrome



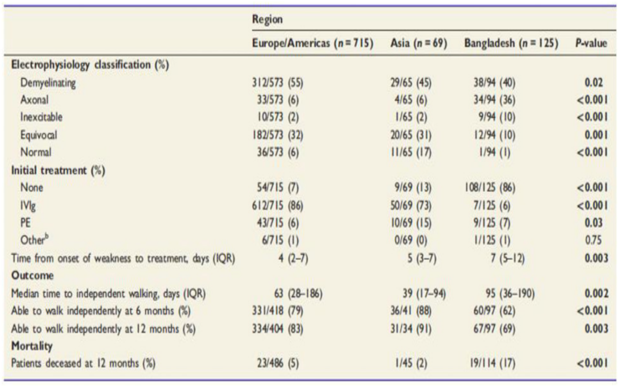
Regional variation of Guillain-Barré syndrome

Alex Y. Doets,[1,*] Christine Verboon,[1,*] Bianca van den Berg,[1,*] Thomas Harbo,[2] David R. Cornblath,[3] Hugh J. Willison,[4] Zhahirul Islam,[5] Shahram Attarian,[6] Fabio A. Barroso,[7] Kathleen Bateman,[8] Luana Benedetti,[9] Peter van den Bergh,[10] Carlos Casasnovas,[11] Guido Cavaletti,[12] Govindsinh Chavada,[4] Kristl G. Claeys,[13,14] Efthimios Dardiotis,[15] Amy Davidson,[4] Pieter A. van Doorn,[1] Tom E. Feasby,[16] Giuliana Galassi,[17] Kenneth C. Gorson,[18] Hans-Peter Hartung,[19] Sung-Tsang Hsieh,[20] Richard A.C. Hughes,[21] Isabel Illa,[22] Badrul Islam,[5] Susumu Kusunoki,[23] Satoshi Kuwabara,[24] Helmar C. Lehmann,[25] James A.L. Miller,[26] Quazi Deen Mohammad,[27] Soledad Monges,[28] Eduardo Nobile Orazio,[29] Julio Pardo,[30] Yann Pereon,[31] Simon Rinaldi,[32] Luis Querol,[22] Stephen W. Reddel,[33] Ricardo C. Reisin,[34] Nortina Shahrizaila,[35] Soren H. Sindrup,[36] Waheed Waqar,[37] Bart C. Jacobs[1,38] and the IGOS Consortium[#]

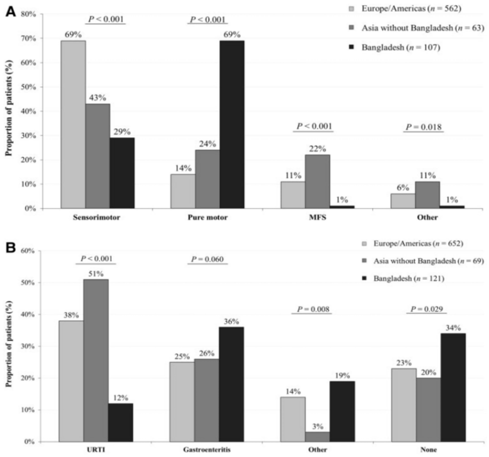
Brain. 2018 Oct 1;141(10):2866-2877.



	Region			
	Europe/Americas ($n = 715$)	Asia ($n = 69$)	Bangladesh ($n = 125$)	*P*-value
Demographics				
Age, years (IQR)	55 (37–67)	50 (34–60)	28 (16–40)	**<0.001**
Male/female ratio (%)	418/297 (1.41)	42/27 (1.56)	84/41 (2.05)	0.18
Clinical features at entry				
MRC sum score, possible range 0–60[a] (IQR)	48 (38–56)	49 (40–58)	22 (7–37)	**<0.001**
Sensory deficits (%)	463/686 (65)	37/68 (54)	35/120 (28)	**<0.001**
Cranial nerve involvement (%)	330/712 (46)	44/69 (64)	84/125 (67)	**<0.001**
Oculomotor weakness	106/712 (15)	26/69 (38)	5/125 (4)	**<0.001**
Facial weakness	220/712 (31)	28/69 (41)	32/125 (26)	0.10
Bulbar weakness	142/712 (20)	23/69 (33)	64/125 (51)	**<0.001**
Autonomic dysfunction (%)	189/714 (27)	7/69 (10)	28/125 (22)	**0.01**
Pain (%)	415/713 (58)	8/69 (12)	77/125 (62)	**<0.001**
Time from onset of weakness to admission, days (IQR)	3 (2–6)	4 (2–6)	4 (2–8)	**0.01**
Clinical features at nadir				
MRC sum score, possible range 0–60[a] (IQR)	46 (30–54)	48 (34–58)	16 (3–32)	**<0.001**
GBS disability score (%)				
Unable to walk independently (>2)	478/626 (76)	50/66 (76)	100/107 (93)	**<0.001**
Sensory deficits (%)	408/588 (69)	37/63 (59)	29/100 (29)	**<0.001**
Cranial nerve involvement (%)	304/620 (49)	44/65 (68)	73/107 (68)	**<0.001**
Oculomotor weakness	84/620 (14)	25/65 (39)	5/107 (5)	**<0.001**
Facial weakness	220/620 (36)	31/65 (48)	32/107 (30)	0.06
Bulbar weakness	136/620 (22)	24/65 (37)	57/107 (53)	**<0.001**
Autonomic dysfunction (%)	184/626 (29)	11/66 (17)	30/107 (28)	0.09
Pain (%)	354/625 (57)	11/66 (17)	67/107 (63)	**<0.001**
Ventilator dependency (%)	121/715 (17)	17/69 (25)	36/125 (29)	**0.004**



	Region			
	Europe/Americas ($n = 715$)	Asia ($n = 69$)	Bangladesh ($n = 125$)	*P*-value
Electrophysiology classification (%)				
Demyelinating	312/573 (55)	29/65 (45)	38/94 (40)	0.02
Axonal	33/573 (6)	4/65 (6)	34/94 (36)	<0.001
Inexcitable	10/573 (2)	1/65 (2)	9/94 (10)	<0.001
Equivocal	182/573 (32)	20/65 (31)	12/94 (10)	0.001
Normal	36/573 (6)	11/65 (17)	1/94 (1)	<0.001
Initial treatment (%)				
None	54/715 (7)	9/69 (13)	108/125 (86)	<0.001
IVIg	612/715 (86)	50/69 (73)	7/125 (6)	<0.001
PE	43/715 (6)	10/69 (15)	9/125 (7)	0.03
Other[b]	6/715 (1)	0/69 (0)	1/125 (1)	0.75
Time from onset of weakness to treatment, days (IQR)	4 (2–7)	5 (3–7)	7 (5–12)	0.003
Outcome				
Median time to independent walking, days (IQR)	63 (28–186)	39 (17–94)	95 (36–190)	0.002
Able to walk independently at 6 months (%)	331/418 (79)	36/41 (88)	60/97 (62)	<0.001
Able to walk independently at 12 months (%)	334/404 (83)	31/34 (91)	67/97 (69)	0.003
Mortality				
Patients deceased at 12 months (%)	23/486 (5)	1/45 (2)	19/114 (17)	<0.001



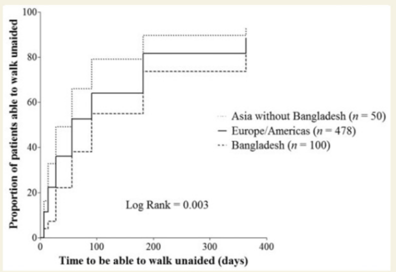
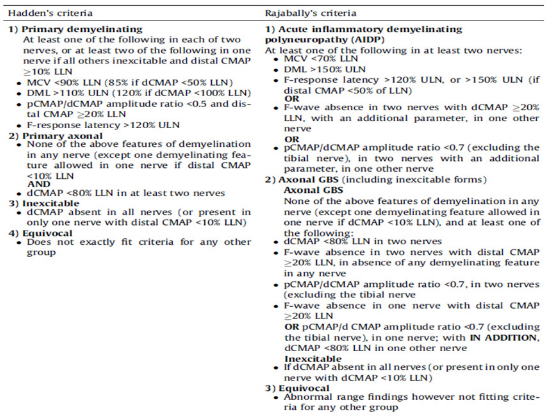


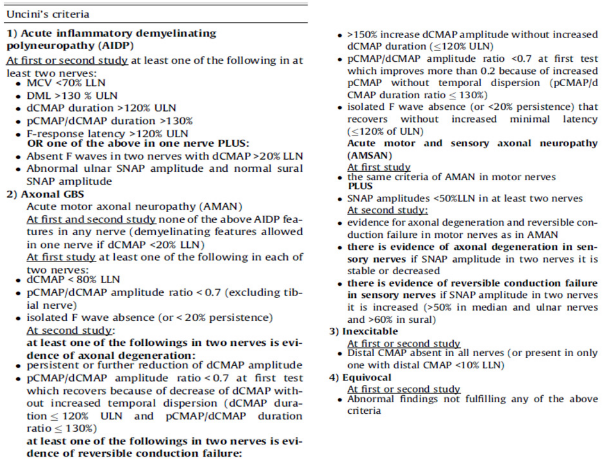
Figure 4 Kaplan-Meier analysis of time to walk unaided in different geographical areas. Kaplan-Meier analysis for patients unable to walk unaided (GBS disability score > 2) at disease nadir.

The electrodiagnosis of Guillain-Barré syndrome subtypes: Where do we stand?

Clinical Neurophysiology 129 (2018) 2586–2593



Hadden's criteria	Rajabally's criteria
1) Primary demyelinating At least one of the following in each of two nerves, or at least two of the following in one nerve if all others inexcitable and distal CMAP ≥10% LLN - MCV <90% LLN (85% if dCMAP <50% LLN) - DML >110% ULN (120% if dCMAP <100% LLN) - pCMAP/dCMAP amplitude ratio <0.5 and distal CMAP ≥20% LLN - F-response latency >120% ULN **2) Primary axonal** - None of the above features of demyelination in any nerve (except one demyelinating feature allowed in one nerve if distal CMAP <10% LLN **AND** - dCMAP <80% LLN in at least two nerves **3) Inexcitable** - dCMAP absent in all nerves (or present in only one nerve with distal CMAP <10% LLN) **4) Equivocal** - Does not exactly fit criteria for any other group	**1) Acute inflammatory demyelinating polyneuropathy (AIDP)** At least one of the following in at least two nerves: - MCV <70% LLN - DML >150% ULN - F-response latency >120% ULN, or >150% ULN (if distal CMAP <50% of LLN) **OR** - F-wave absence in two nerves with dCMAP ≥20% LLN, with an additional parameter, in one other nerve **OR** - pCMAP/dCMAP amplitude ratio <0.7 (excluding the tibial nerve), in two nerves with an additional parameter, in one other nerve **2) Axonal GBS** (including inexcitable forms) **Axonal GBS** None of the above features of demyelination in any nerve (except one demyelinating feature allowed in one nerve if dCMAP <10% LLN), and at least one of the following: - dCMAP <80% LLN in two nerves - F-wave absence in two nerves with distal CMAP ≥20% LLN, in absence of any demyelinating feature in any nerve - pCMAP/dCMAP amplitude ratio <0.7, in two nerves (excluding the tibial nerve - F-wave absence in one nerve with distal CMAP ≥20% LLN **OR** pCMAP/d CMAP amplitude ratio <0.7 (excluding the tibial nerve), in one nerve; with **IN ADDITION**, dCMAP <80% LLN in one other nerve **Inexcitable** - If dCMAP absent in all nerves (or present in only one nerve with dCMAP <10% LLN) **3) Equivocal** - Abnormal range findings however not fitting criteria for any other group



Uncini's criteria

1) Acute inflammatory demyelinating polyneuropathy (AIDP)

At first or second study at least one of the following in at least two nerves:
- MCV <70% LLN
- DML >130 % ULN
- dCMAP duration >120% ULN
- pCMAP/dCMAP duration >130%
- F-response latency >120% ULN

OR one of the above in one nerve PLUS:
- Absent F waves in two nerves with dCMAP >20% LLN
- Abnormal ulnar SNAP amplitude and normal sural SNAP amplitude

2) Axonal GBS

Acute motor axonal neuropathy (AMAN)

At first and second study none of the above AIDP features in any nerve (demyelinating features allowed in one nerve if dCMAP <20% LLN)

At first study at least one of the following in each of two nerves:
- dCMAP < 80% LLN
- pCMAP/dCMAP amplitude ratio < 0.7 (excluding tibial nerve)
- isolated F wave absence (or < 20% persistence)

At second study:

at least one of the followings in two nerves is evidence of axonal degeneration:
- persistent or further reduction of dCMAP amplitude
- pCMAP/dCMAP amplitude ratio < 0.7 at first test which recovers because of decrease of dCMAP without increased temporal dispersion (dCMAP duration ≤ 120% ULN and pCMAP/dCMAP duration ratio ≤ 130%)

at least one of the followings in two nerves is evidence of reversible conduction failure:
- >150% increase dCMAP amplitude without increased dCMAP duration (≤120% ULN)
- pCMAP/dCMAP amplitude ratio <0.7 at first test which improves more than 0.2 because of increased pCMAP without temporal dispersion (pCMAP/dCMAP duration ratio ≤ 130%)
- isolated F wave absence (or <20% persistence) that recovers without increased minimal latency (≤120% of ULN)

Acute motor and sensory axonal neuropathy (AMSAN)

At first study
- the same criteria of AMAN in motor nerves

PLUS
- SNAP amplitudes <50%LLN in at least two nerves

At second study:
- evidence for axonal degeneration and reversible conduction failure in motor nerves as in AMAN
- **there is evidence of axonal degeneration in sensory nerves** if SNAP amplitude in two nerves it is stable or decreased
- **there is evidence of reversible conduction failure in sensory nerves** if SNAP amplitude in two nerves it is increased (>50% in median and ulnar nerves and >60% in sural)

3) Inexcitable

At first or second study
- Distal CMAP absent in all nerves (or present in only one with distal CMAP <10% LLN)

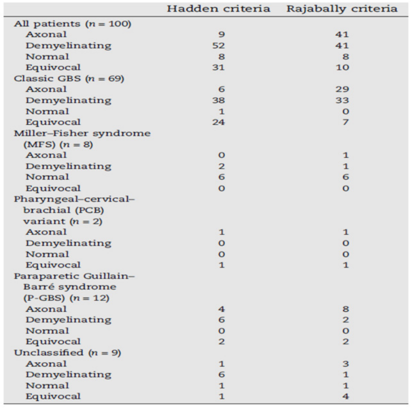
4) Equivocal

At first or second study
- Abnormal findings not fulfilling any of the above criteria

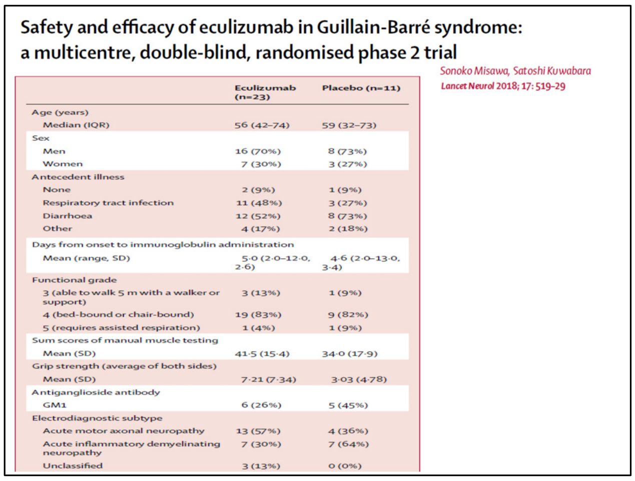
Guillain–Barré syndrome subtypes: A clinical electrophysiological study of 100 patients

A.-M. Grapperon

Rev Neurol (Paris). 2019 Jan - Feb;175(1-2):73-80.



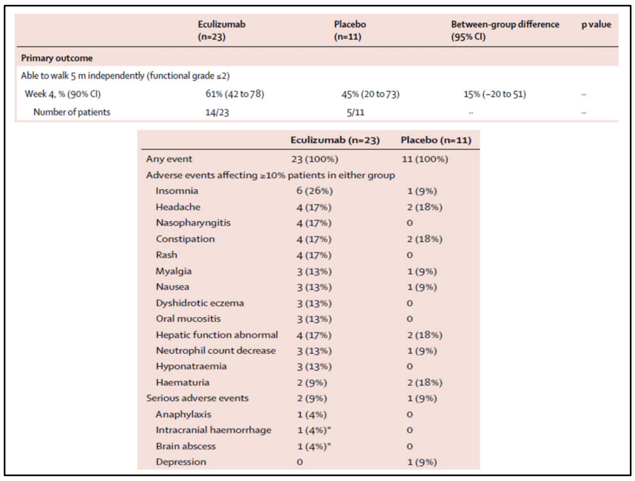
	Hadden criteria	Rajabally criteria
All patients ($n = 100$)		
Axonal	9	41
Demyelinating	52	41
Normal	8	8
Equivocal	31	10
Classic GBS ($n = 69$)		
Axonal	6	29
Demyelinating	38	33
Normal	1	0
Equivocal	24	7
Miller–Fisher syndrome (MFS) ($n = 8$)		
Axonal	0	1
Demyelinating	2	1
Normal	6	6
Equivocal	0	0
Pharyngeal–cervical–brachial (PCB) variant ($n = 2$)		
Axonal	1	1
Demyelinating	0	0
Normal	0	0
Equivocal	1	1
Paraparetic Guillain–Barré syndrome (P-GBS) ($n = 12$)		
Axonal	4	8
Demyelinating	6	2
Normal	0	0
Equivocal	2	2
Unclassified ($n = 9$)		
Axonal	1	3
Demyelinating	6	1
Normal	1	1
Equivocal	1	4



Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial

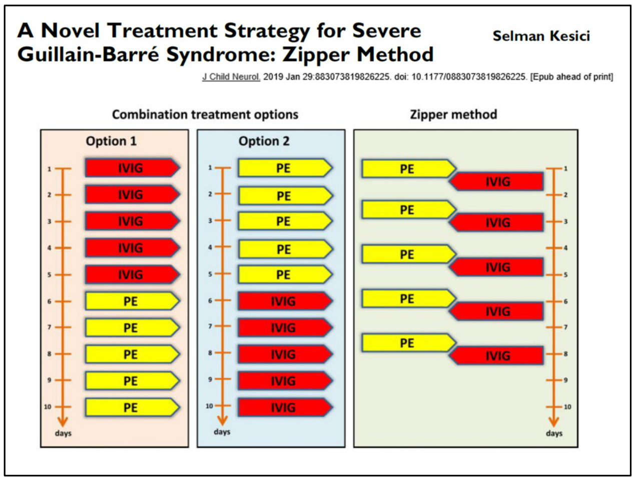
Sonoko Misawa, Satoshi Kuwabara
Lancet Neurol 2018; 17: 519–29

	Eculizumab (n=23)	Placebo (n=11)
Age (years)		
Median (IQR)	56 (42–74)	59 (32–73)
Sex		
Men	16 (70%)	8 (73%)
Women	7 (30%)	3 (27%)
Antecedent illness		
None	2 (9%)	1 (9%)
Respiratory tract infection	11 (48%)	3 (27%)
Diarrhoea	12 (52%)	8 (73%)
Other	4 (17%)	2 (18%)
Days from onset to immunoglobulin administration		
Mean (range, SD)	5·0 (2·0–12·0, 2·6)	4·6 (2·0–13·0, 3·4)
Functional grade		
3 (able to walk 5 m with a walker or support)	3 (13%)	1 (9%)
4 (bed-bound or chair-bound)	19 (83%)	9 (82%)
5 (requires assisted respiration)	1 (4%)	1 (9%)
Sum scores of manual muscle testing		
Mean (SD)	41·5 (15·4)	34·0 (17·9)
Grip strength (average of both sides)		
Mean (SD)	7·21 (7·34)	3·03 (4·78)
Antiganglioside antibody		
GM1	6 (26%)	5 (45%)
Electrodiagnostic subtype		
Acute motor axonal neuropathy	13 (57%)	4 (36%)
Acute inflammatory demyelinating neuropathy	7 (30%)	7 (64%)
Unclassified	3 (13%)	0 (0%)



	Eculizumab (n=23)	Placebo (n=11)	Between-group difference (95% CI)	p value
Primary outcome				
Able to walk 5 m independently (functional grade ≤2)				
Week 4, % (90% CI)	61% (42 to 78)	45% (20 to 73)	15% (−20 to 51)	..
Number of patients	14/23	5/11	..	..

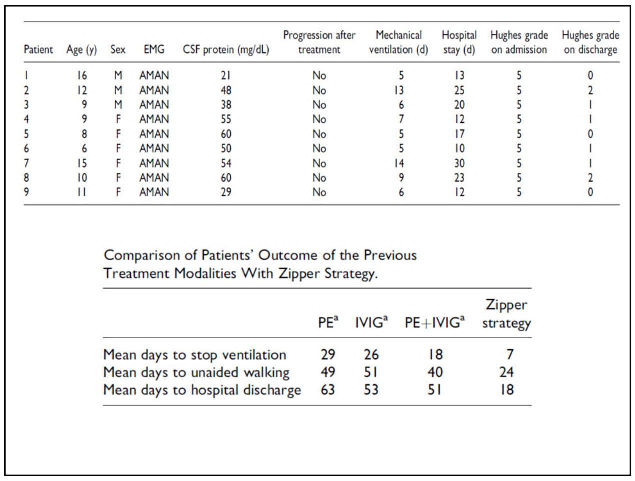
	Eculizumab (n=23)	Placebo (n=11)
Any event	23 (100%)	11 (100%)
Adverse events affecting ≥10% patients in either group		
Insomnia	6 (26%)	1 (9%)
Headache	4 (17%)	2 (18%)
Nasopharyngitis	4 (17%)	0
Constipation	4 (17%)	2 (18%)
Rash	4 (17%)	0
Myalgia	3 (13%)	1 (9%)
Nausea	3 (13%)	1 (9%)
Dyshidrotic eczema	3 (13%)	0
Oral mucositis	3 (13%)	0
Hepatic function abnormal	4 (17%)	2 (18%)
Neutrophil count decrease	3 (13%)	1 (9%)
Hyponatraemia	3 (13%)	0
Haematuria	2 (9%)	2 (18%)
Serious adverse events	2 (9%)	1 (9%)
Anaphylaxis	1 (4%)	0
Intracranial haemorrhage	1 (4%)*	0
Brain abscess	1 (4%)*	0
Depression	0	1 (9%)



A Novel Treatment Strategy for Severe Guillain-Barré Syndrome: Zipper Method

Selman Kesici

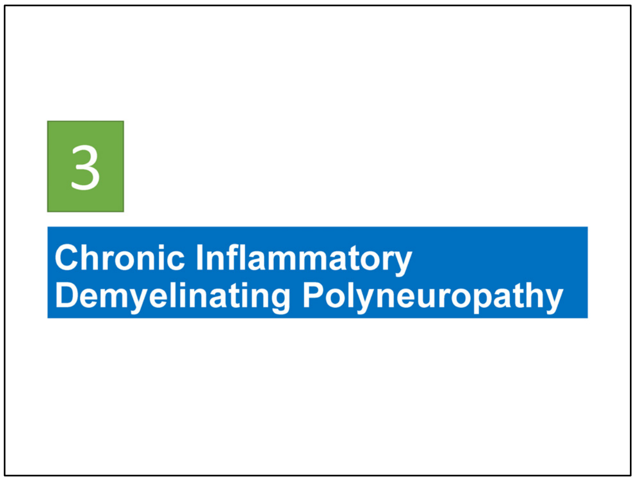
J Child Neurol. 2019 Jan 29:883073819826225. doi: 10.1177/0883073819826225. [Epub ahead of print]



Patient	Age (y)	Sex	EMG	CSF protein (mg/dL)	Progression after treatment	Mechanical ventilation (d)	Hospital stay (d)	Hughes grade on admission	Hughes grade on discharge
1	16	M	AMAN	21	No	5	13	5	0
2	12	M	AMAN	48	No	13	25	5	2
3	9	M	AMAN	38	No	6	20	5	1
4	9	F	AMAN	55	No	7	12	5	1
5	8	F	AMAN	60	No	5	17	5	0
6	6	F	AMAN	50	No	5	10	5	1
7	15	F	AMAN	54	No	14	30	5	1
8	10	F	AMAN	60	No	9	23	5	2
9	11	F	AMAN	29	No	6	12	5	0

Comparison of Patients' Outcome of the Previous Treatment Modalities With Zipper Strategy.

	PE[a]	IVIG[a]	PE+IVIG[a]	Zipper strategy
Mean days to stop ventilation	29	26	18	7
Mean days to unaided walking	49	51	40	24
Mean days to hospital discharge	63	53	51	18



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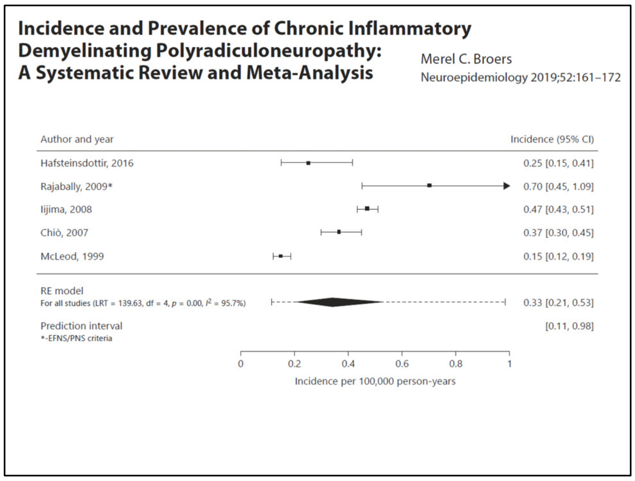
Chronic Inflammatory Demyelinating Polyneuropathy

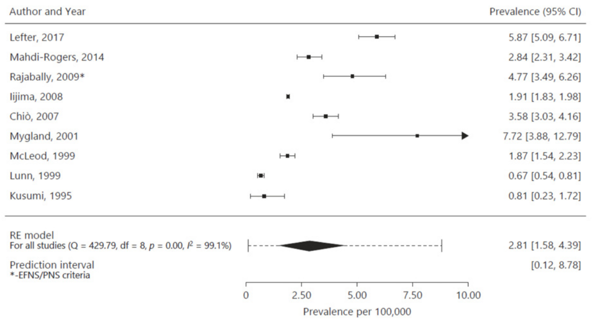


Incidence and Prevalence of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis

Merel C. Broers
Neuroepidemiology 2019;52:161–172

Author and year	Incidence (95% CI)
Hafsteinsdottir, 2016	0.25 [0.15, 0.41]
Rajabally, 2009*	0.70 [0.45, 1.09]
Iijima, 2008	0.47 [0.43, 0.51]
Chiò, 2007	0.37 [0.30, 0.45]
McLeod, 1999	0.15 [0.12, 0.19]
RE model For all studies (LRT = 139.63, df = 4, p = 0.00, I^2 = 95.7%)	0.33 [0.21, 0.53]
Prediction interval	[0.11, 0.98]

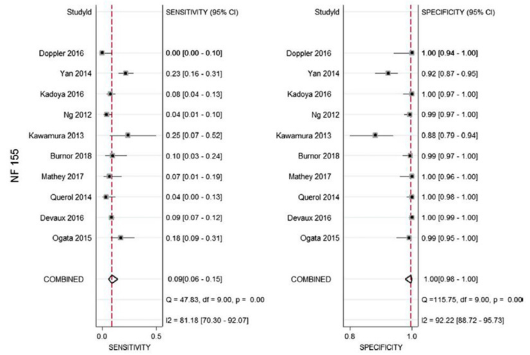
*-EFNS/PNS criteria

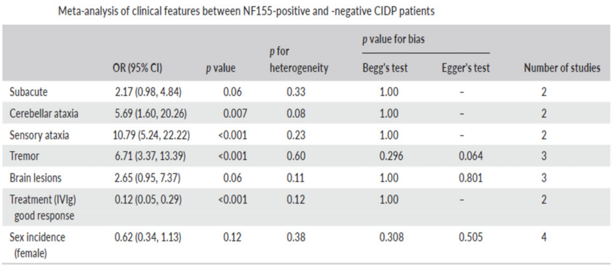


Association of neurofascin IgG4 and atypical chronic inflammatory demyelinating polyneuropathy: A systematic review and meta-analysis

Wenyu Hu

Brain and Behavior. 2018;8:e01115.





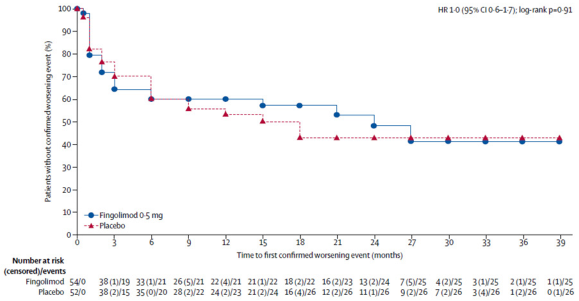
Meta-analysis of clinical features between NF155-positive and -negative CIDP patients

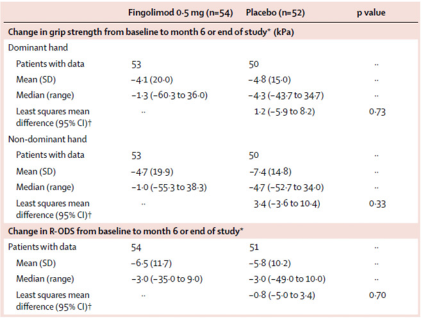
	OR (95% CI)	*p* value	*p* for heterogeneity	*p* value for bias: Begg's test	*p* value for bias: Egger's test	Number of studies
Subacute	2.17 (0.98, 4.84)	0.06	0.33	1.00	-	2
Cerebellar ataxia	5.69 (1.60, 20.26)	0.007	0.08	1.00	-	2
Sensory ataxia	10.79 (5.24, 22.22)	<0.001	0.23	1.00	-	2
Tremor	6.71 (3.37, 13.39)	<0.001	0.60	0.296	0.064	3
Brain lesions	2.65 (0.95, 7.37)	0.06	0.11	1.00	0.801	3
Treatment (IVIg) good response	0.12 (0.05, 0.29)	<0.001	0.12	1.00	-	2
Sex incidence (female)	0.62 (0.34, 1.13)	0.12	0.38	0.308	0.505	4

Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicentre, randomised controlled trial

Richard Hughes, Marinos C Dalakas, Ingemar Merkies, Norman Latov, Jean-Marc Léger, Eduardo Nobile-Orazio, Gen Sobue, Angela Genge, David Cornblath, Martin Merschhemke, Carolyn Marie Ervin, Catherine Agoropoulou, Hans-Peter Hartung

Lancet Neurol. 2018 Aug;17(8):689-698.





	Fingolimod 0·5 mg (n=54)	Placebo (n=52)	p value
Change in grip strength from baseline to month 6 or end of study* (kPa)			
Dominant hand			
Patients with data	53	50	..
Mean (SD)	−4·1 (20·0)	−4·8 (15·0)	..
Median (range)	−1·3 (−60·3 to 36·0)	−4·3 (−43·7 to 34·7)	..
Least squares mean difference (95% CI)†	..	1·2 (−5·9 to 8·2)	0·73
Non-dominant hand			
Patients with data	53	50	..
Mean (SD)	−4·7 (19·9)	−7·4 (14·8)	..
Median (range)	−1·0 (−55·3 to 38·3)	−4·7 (−52·7 to 34·0)	..
Least squares mean difference (95% CI)†	..	3·4 (−3·6 to 10·4)	0·33
Change in R-ODS from baseline to month 6 or end of study*			
Patients with data	54	51	..
Mean (SD)	−6·5 (11·7)	−5·8 (10·2)	..
Median (range)	−3·0 (−35·0 to 9·0)	−3·0 (−49·0 to 10·0)	..
Least squares mean difference (95% CI)†	..	−0·8 (−5·0 to 3·4)	0·70

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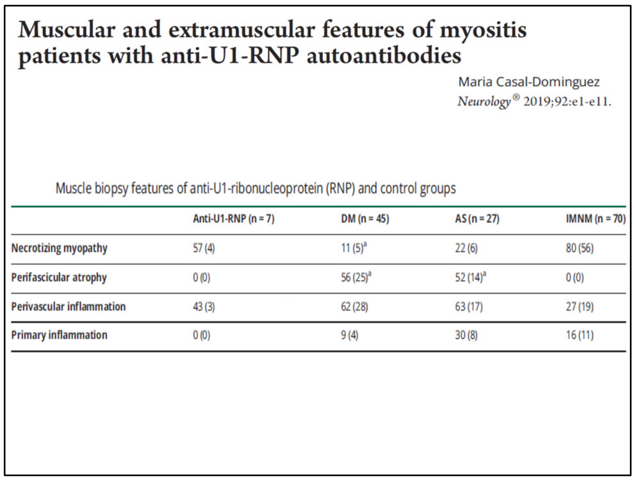
Inflammatory myopathy



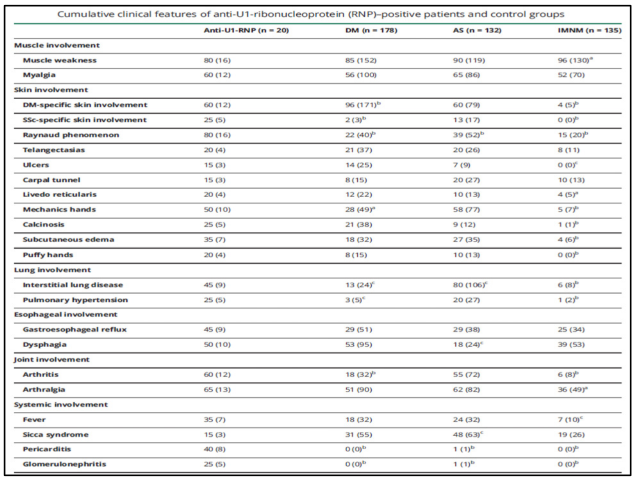
Muscular and extramuscular features of myositis patients with anti-U1-RNP autoantibodies

Maria Casal-Dominguez

Neurology® 2019;92:e1-e11.

Muscle biopsy features of anti-U1-ribonucleoprotein (RNP) and control groups

	Anti-U1-RNP (n = 7)	DM (n = 45)	AS (n = 27)	IMNM (n = 70)
Necrotizing myopathy	57 (4)	11 (5)^{a}	22 (6)	80 (56)
Perifascicular atrophy	0 (0)	56 (25)^{a}	52 (14)^{a}	0 (0)
Perivascular inflammation	43 (3)	62 (28)	63 (17)	27 (19)
Primary inflammation	0 (0)	9 (4)	30 (8)	16 (11)



Cumulative clinical features of anti-U1-ribonucleoprotein (RNP)–positive patients and control groups

	Anti-U1-RNP (n = 20)	DM (n = 178)	AS (n = 132)	IMNM (n = 135)
Muscle involvement				
Muscle weakness	80 (16)	85 (152)	90 (119)	96 (130)^{a}
Myalgia	60 (12)	56 (100)	65 (86)	52 (70)
Skin involvement				
DM-specific skin involvement	60 (12)	96 (171)^{b}	60 (79)	4 (5)^{b}
SSc-specific skin involvement	25 (5)	2 (3)^{b}	13 (17)	0 (0)^{b}
Raynaud phenomenon	80 (16)	22 (40)^{b}	39 (52)^{b}	15 (20)^{b}
Telangectasias	20 (4)	21 (37)	20 (26)	8 (11)
Ulcers	15 (3)	14 (25)	7 (9)	0 (0)^{c}
Carpal tunnel	15 (3)	8 (15)	20 (27)	10 (13)
Livedo reticularis	20 (4)	12 (22)	10 (13)	4 (5)^{a}
Mechanics hands	50 (10)	28 (49)^{a}	58 (77)	5 (7)^{b}
Calcinosis	25 (5)	21 (38)	9 (12)	1 (1)^{b}
Subcutaneous edema	35 (7)	18 (32)	27 (35)	4 (6)^{b}
Puffy hands	20 (4)	8 (15)	10 (13)	0 (0)^{b}
Lung involvement				
Interstitial lung disease	45 (9)	13 (24)^{c}	80 (106)^{c}	6 (8)^{b}
Pulmonary hypertension	25 (5)	3 (5)^{c}	20 (27)	1 (2)^{b}
Esophageal involvement				
Gastroesophageal reflux	45 (9)	29 (51)	29 (38)	25 (34)
Dysphagia	50 (10)	53 (95)	18 (24)^{c}	39 (53)
Joint involvement				
Arthritis	60 (12)	18 (32)^{b}	55 (72)	6 (8)^{b}
Arthralgia	65 (13)	51 (90)	62 (82)	36 (49)^{a}
Systemic involvement				
Fever	35 (7)	18 (32)	24 (32)	7 (10)^{c}
Sicca syndrome	15 (3)	31 (55)	48 (63)^{c}	19 (26)
Pericarditis	40 (8)	0 (0)^{b}	1 (1)^{b}	0 (0)^{b}
Glomerulonephritis	25 (5)	0 (0)^{b}	1 (1)^{b}	0 (0)^{b}