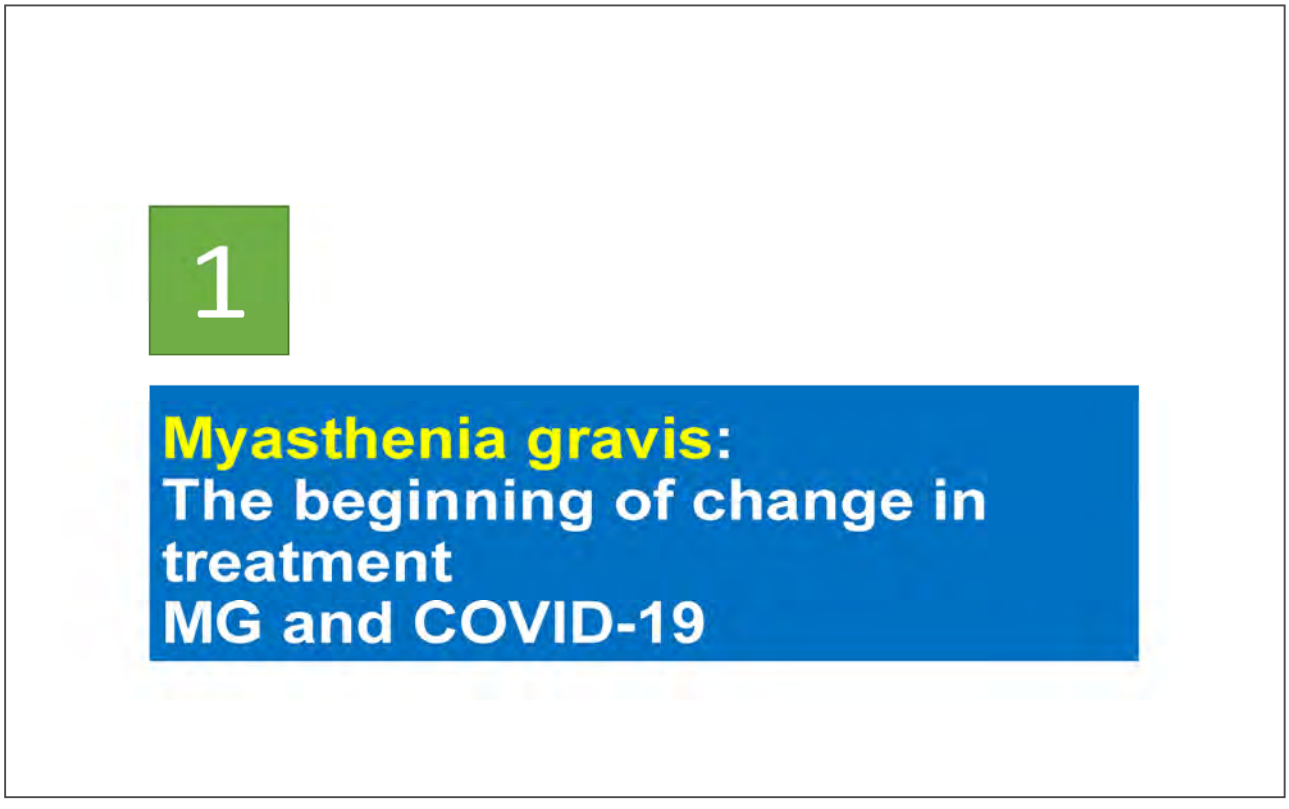
Peripheral

석 흥 열
계명의대 동산의료원



International Consensus Guidance for Management of Myasthenia Gravis

2020 Update

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Keywords

Immune checkpoint inhibitors
Rituximab
Eculizumab

Immune checkpoint inhibitors

Table 1 Drugs to Avoid or Use With Caution in MG[a]

Drug	Comment
Aminoglycoside antibiotics (e.g., gentamycin, neomycin, and tobramycin)	Used for gram-negative bacterial infections. May worsen MG. Use cautiously if no alternative treatment available.
Beta-blockers	Commonly prescribed for hypertension, heart disease, and migraine but potentially dangerous in MG. May worsen MG. Use cautiously.
Botulinum toxin	Presynaptic neuromuscular junction blocker. Avoid use.
Chloroquine and hydroxychloroquine	Used to treat/prevent malaria and for certain autoimmune diseases. May precipitate de novo MG or worsen preexisting MG. Use only if necessary and observe for worsening.
Corticosteroids	A standard treatment for MG but may cause transient worsening within the first 2 weeks. Monitor carefully for this possibility.
Desferrioxamine (deferoxamine)	Chelating agent used for hemochromatosis. May worsen MG.
D-Penicillamine	Used for Wilson disease and rarely for rheumatoid arthritis. Strongly associated with causing MG. Avoid use.
Fluoroquinolone antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin)	Commonly prescribed broad-spectrum antibiotics that are associated with worsening MG. The US FDA has designated a "black-box" warning for these agents in MG. Use cautiously, if at all.
Immune checkpoint inhibitors (e.g., ipilimumab, pembrolizumab, atezolizumab, and nivolumab)	Used for certain cancers. Can precipitate de novo MG or worsen preexisting MG. Use with caution as determined by oncologic status.

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Immune checkpoint inhibitors

Recommendations

1. The risk of MG and other immune-mediated neurologic illnesses should be discussed with patients who are candidates for ICIs (median 9, range 5–9).
2. At this time, there is no evidence to either support or refute the utility of AChR antibody testing in patients without MG before starting ICIs (median 8, range 7–9).
3. MG associated with ICIs is generally severe, with a high rate of respiratory crises (median 8, range 5–9).
4. Preexisting MG does not constitute an absolute contraindication to the use of ICIs, at least in patients with well-controlled disease (MM status or better). However, in these patients:
   - It may be prudent to avoid combined therapy (anti–CTLA-4 plus anti-PD-1/PD-L1 monoclonal antibodies), given the higher potential for severe irAEs.
   - Close clinical monitoring, particularly of respiratory and bulbar function, is mandatory.
   - Although the therapeutic response to ICIs seems to be less satisfactory in patients receiving immunosuppressants, MG treatment should be maintained and may even be restarted in patients whose MG is in remission before treatment with ICIs (median 8, range 5–9).
5. Early aggressive treatment with high-dose steroids in combination with plasma exchange or IVIg may be required in patients who develop overt MG while on ICIs. The decision to withdraw ICIs is determined by the oncologic status (median 8, range 7–9) (table e-9, doi:10.5061/dryad.

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Rituximab and Eculizumab

Recommendations

Recommendation 1 is unchanged from the 2016 consensus guidance.[1]

1. Rituximab should be considered as an early therapeutic option in patients with MuSK-Ab+ MG who have an unsatisfactory response to initial immunotherapy (median 9, range 4–9).
2. The efficacy of RTX in refractory AChR-Ab+ MG is uncertain. It is an option if patients fail or do not tolerate other IS agents (median 8, range 4–9) (tables e-2 and e-7, doi:10.5061/dryad.6hdr7sqxx).

Recommendations

1. Eculizumab should be considered in the treatment of severe, refractory, AChR-Ab+ generalized MG (median 9, range 2–9).
2. The role of eculizumab in the treatment of MG is likely to evolve over time. Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals (median 9, range 5–9).
3. Recommendations of the Advisory Committee on Immunization Practices or other local guidelines regarding immunization against meningococcal meningitis should be followed before treatment with eculizumab (median 9, range 8–9).
4. Future research should include assessment of the duration of eculizumab therapy necessary to achieve and maintain treatment goals, its efficacy in other MG populations (MG with thymoma and seronegative MG), and in other stages of disease (MG crises, exacerbations, and early therapy in nonrefractory AChR-Ab+ MG) (median 8, range 4–9) (table e-2, doi:10.5061/dryad.6hdr7sqxx).

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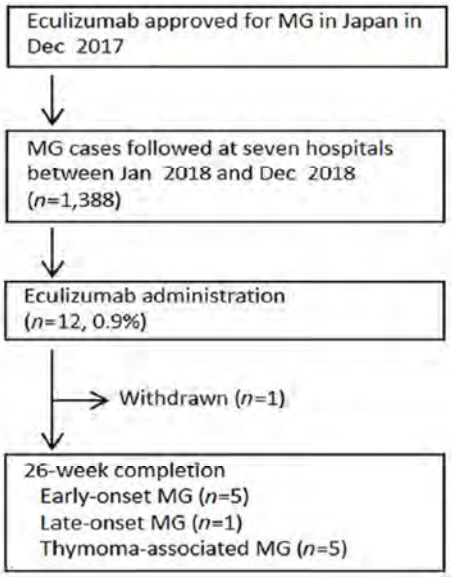
Sum score to define refractory MG

SCORE CATEGORY	SCORE ITEM	SCORING
Present MGFA score	MGFA III	5
	MGFA IV or V[1]	10
Inefficacy of treatment (failure to reach a MGFA II status)	Azathioprine, at least for 12 months	5
	Mycophenolate, at least for 12 months	5
	All other conventional immunosuppressants, at least for 12 months[2]	5
	Rituximab, cumulative dosage at least 2 g and at least for 3 months	8
	Steroids: prednisolone 1 mg/kg body weight for 8 weeks, or equivalent	5
	Plasma exchange or immunoadsorption, 5 sessions at least	8
Treatment cessation due to side effects	Azathioprine	3
	Mycophenolate	4
	Rituximab	5
	Others[2]	4
ICU stay	Longer than 42 days[1]	10
1 If both apply resulting points are reduced to 15!		
2 May apply only once irrespective of the number of substances tried		
Sum score	Scoring of at least 20 defines treatment refractory	

Schroeter et al. J Cent Nerv Syst Dis. 2021;13:1179573521989151

Suitable indications of eculizumab



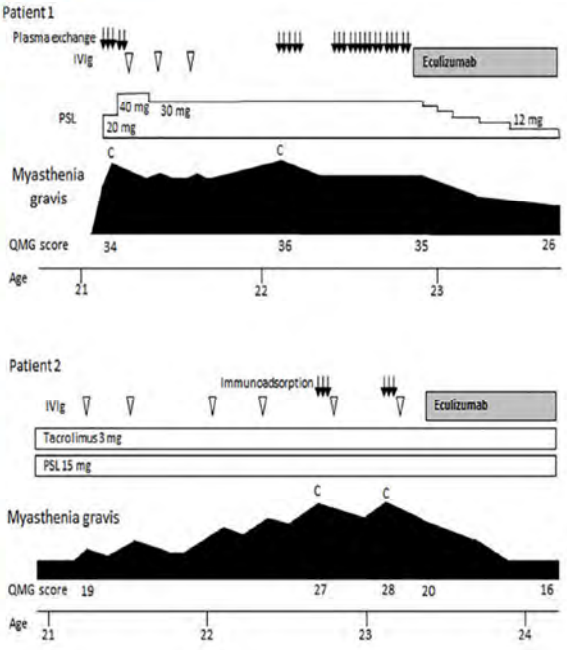
REGAIN Criteria

- Older than 18 years
- Anti-acetylcholine-positive
- MG ADL score of 6 or higher
- Unresponsive to 2 immunosuppressive drugs
- Unresponsive to immunosuppressive drug and rescue therapy
- **MGFA classification II, III, IV**
- **Excluded if they had a history of thymoma**

Oyama et al. Ther Adv Neurol Disord. 2020;13:1-9

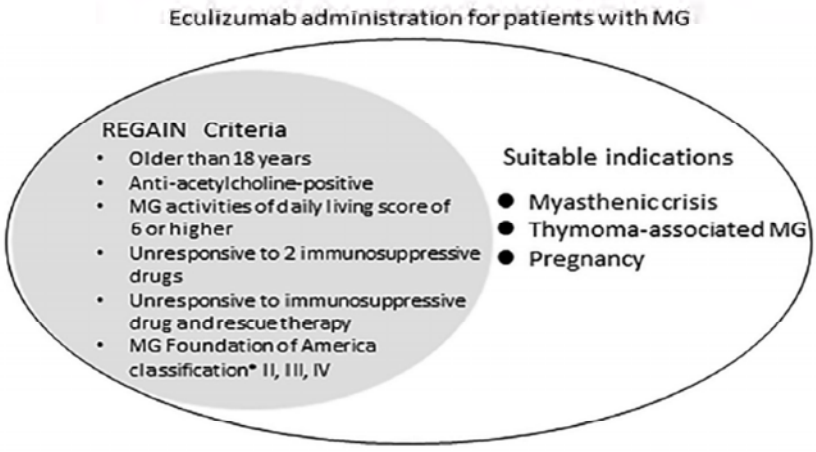
MG crisis

Patient/ age/sex	Onset age	Type	MGFA class	QMG score	MG-ADL score	Anti-AChR (nM)
1/22/F	21	EOMG	V	35	17	80
2/23/F	17	EOMG	V	20	10	12
3/33/F	12	EOMG	V	17	9	29
4/33/F	31	EOMG	IIIa	19	17	0.8
5/36/M	29	EOMG	IIIa	17	13	280
6/40/F	19	TMG	V	18	5	120
7/53/F	46	TMG	V	31	15	44
8/55/M	49	TMG	V	12	6	26
9/55/M	50	LOMG	IIIa	9	10	14
10/61/F	49	TMG	IVb	16	12	21
11/67/F	66	TMG	V	11	5	23



Patient	Follow-up period (months)	Thymus histology	Clinical symptoms	Times of myasthenic crisis	Postinterventional status
1	33	Not performed	Neck and limb weakness, dyspnea, ptosis	2	Improved
2	76	Hyperplasia	Nasal voice, dysphagia, dyspnea	3	Improved
3	254	Hyperplasia	Ptosis, diplopia, dyspnea	1	Minimal manifestations
4	33	Not performed	Dyspnea, leg weakness, dysarthria	0	Improved
5	86	Atrophy	Neck and limb weakness, diplopia, ptosis	0	Minimal manifestations
6	248	Thymoma (type B3, stage III)	Neck weakness, dysphagia, ptosis	3	Minimal manifestations
7	102	Thymoma (type B1, stage I)	Arm weakness, ptosis, diplopia	1	Improved
8	76	Thymoma (type B2, stage II)	Dyspnea, diplopia, ptosis	1	Minimal manifestations
9	67	Not performed	Dysarthria, ptosis, diplopia, limb weakness	0	Minimal manifestations
10	153	Thymoma (type AB, stage II)	Dysarthria, dysphagia, limb weakness	0	Minimal manifestations
11	19	Thymoma (type A, stage I)	Facial muscle weakness, dysphagia, nasal voice	1	Minimal manifestations

Suitable indications of eculizumab



Oyama et al. Ther Adv Neurol Disord. 2020;13:1-9

Rituximab: where do we stand?

- **What, if any, improvement does the drug hold over other conventional therapies for MG?**
  - MuSK Ab+ patients respond earlier than the AchR Ab+ patients
  - The typical onset of beneficial effect is within a few months, with peak effect reported around 4 to 5 months.
  - Most patients experience sustained clinical improvement/remission that can last several months to a few years after the induction dose.
  - Periodic infusions are required to maintain efficacy, typically every 6 to 9 months, though frequency is variable.
- **What impact, if any, could the treatment have on current treatment strategies for MG?**
- **How likely are physicians to prescribe the drug for MG?**
- **What data is still needed?**

Zaeem et al. Expert Opin Biol Ther. 2021 Feb 10

	Ocular	Anti-AchR Ab	Anti-MuSK Ab	Seronegative
1st line	Prednisone			
Steroid Sparing Agents				
1st line	Azathioprine	Azathioprine	Rituximab*	Azathioprine
2nd line	Cellcept	Rituximab	Azathioprine	Rituximab
	?Rituximab	Cellcept	Cellcept	Cellcept
Refractory MG*				
1st line	IVIG			
	PLEX			
	Rituximab			
2nd line	No robust data	Cyclosporine		
		Tacrolimus		
3rd line	No robust data	Eculizumab		
		Methotrexate		
		Cyclophosphamide		

Zaeem et al. Expert Opin Biol Ther. 2021 Feb 10

Emerging drugs for MG

Drug	Target	Mechanism of action	Administration	Mg study status	Main side effects
Eculizumab	C5	C5 inhibition	IV	Approved (USA, Europe, Japan)	Infection by encapsulated bacteria, headache, nasopharyngitis
Ravulizumab	C5	High-affinity C5 inhibition	IV	Phase III clinical trial ongoing	Similar to eculizumab
Zilucoplan	C5	C5 inhibition	SC	Phase III clinical trial ongoing	Potential risk of infection by encapsulated bacteria
Efgartigimod	FcRn	Prevention of FcRn-mediated IgG recycling	IV	Phase III clinical trial ongoing	Headache, reduction of monocyte count
Rozanolixizumab	FcRn	Prevention of FcRn-mediated IgG recycling	SC	Phase III clinical trial ongoing	Headache
Nipocalimab (M281)	FcRn	Prevention of FcRn-mediated IgG recycling	IV	Phase II clinical trial completed, results not published	Potential risk of infection
Rituximab	CD-20 B cells	B cells depletion	IV	Phase III clinical trial ongoing	Infections, allergic infusion reaction, reactivation of herpes zoster, PML
Belimumab	BAFF factor	Prevention of B cells differentiation into antibody-secreting cells	IV	Phase II clinical trial completed	Flu, nausea, one case of sepsis-induced death
Bortezomib	Proteasome	Plasma cells apoptosis by inhibition of proteasome	SC	Phase II clinical trial completed	Sensorimotor polyneuropathy
Etanercept	TNFα	TNFα inhibition	SC	No	Infection and autoimmune phenomena (including MG onset/worsening)
Infliximab	TNFα	TNFα inhibition	IV	No	Similar to etanercept
Adalimumab	TNFα	TNFα inhibition	SC	No	Similar to etanercept
Tocilizumab	IL-6 receptor	Blocking of a switch from suppressive Treg to pathogenic Th17 cells	IV	No	Good safety

Rodolico et al. Neurol Sci. 2021;42(4):1367-1375

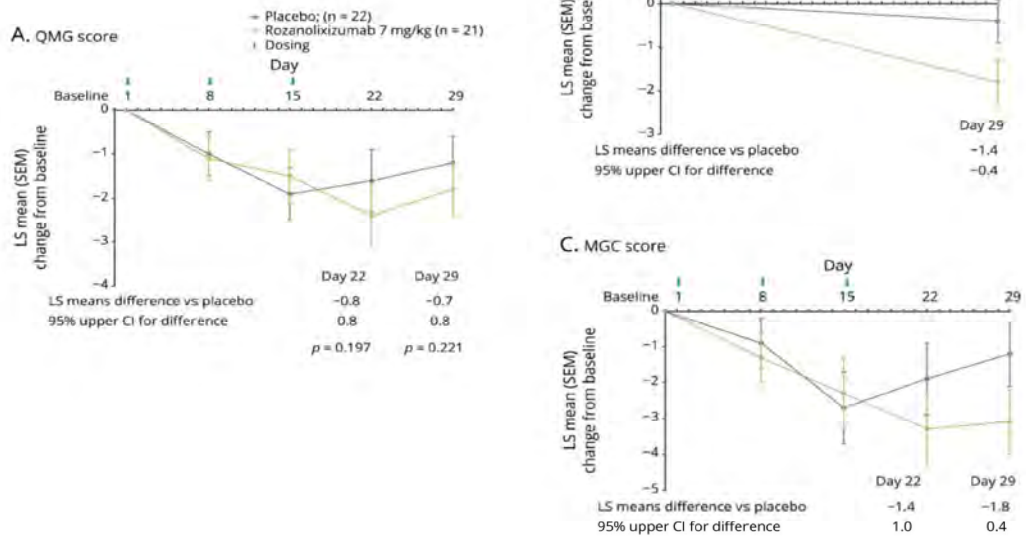
Efficacy and Safety of Rozanolixizumab in Moderate to Severe Generalized Myasthenia Gravis

A Phase 2 Randomized Control Trial

Neurology® 2021;96:e853-e865.

- ≥ 18 years of age
- gMG with evidence of elevated autoantibodies (AChR or MuSK)
- In the opinion of the investigator, IVIg or PLEX might be considered as a treatment option
- QMGscore of ≥11 at baseline
- Serum total IgG concentration of >6 g/L

Rozanolixizumab n=21, Placebo n=22



Clinical Effects of the Self-administered Subcutaneous Complement Inhibitor Zilucoplan in Patients With Moderate to Severe Generalized Myasthenia Gravis

Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial

JAMA Neurol. 2020;77(5):582-592.

- 18 to 85 years
- MG(MGFA Class II-IVa)
- Presence of AChR-Ab
- QMG score of at least 12 points

- Placebo (n = 15)
- Zilucoplan: 0.1 mg/kg (n = 15), 0.3 mg/kg (n = 14)

Figure 2. Change From Baseline Over 12 Weeks for 0.3-mg/kg Zilucoplan vs Placebo in Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Activities of Daily Living (MG-ADL), Myasthenia Gravis Quality-of-Life Revised Scale (MG-QoL15r), and Myasthenia Gravis Composite (MGC)