




HELSE  VEST

Living with myasthenia gravis

Updates on psychosocial issues and
training

*Friday September 30 - Saturday October 1, 2022
Musholm, Denmark*

 MUSKELSVINDFONDEN

 The National Rehabilitation
Center for Neuromuscular Diseases

The need for international MG-guidelines in diagnosis and care

Nils Erik Gilhus

*University of Bergen and
Haukeland University Hospital*



Disclaimers

Nils Erik Gilhus has received consultative or speaker's honoraria from;

- Argenx
- Ra Pharma
- Alexion
- Octapharma
- UCB
- Merck
- Roche
- Immunovant
- Janssen



- International guidelines
- National guidelines
- Local guidelines
- Systematic reviews
- Reviews

What is the evidence?

Amount of benefit?

Costs?

European Journal of Neurology 2010, 17: 893-902

doi:10.1111/j.1468-1331.2010.03019.x

EFNS GUIDELINES/CME ARTICLE

Guidelines for treatment of autoimmune neuromuscular transmission disorders

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European Journal of Neurology 2014, 21: 687-693

doi:10.1111/ene.12359

EFNS/ENS GUIDELINES / CME ARTICLE

EFNS/ENS Guidelines for the treatment of ocular myasthenia

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VIEWS & REVIEWS

OPEN ACCESS

LEVEL OF RECOMMENDATION

International Consensus Guidance for Management of Myasthenia Gravis

2020 Update

Pushpa Narayanaswami, MBBS, DM, Donald B. Sanders, MD, Gil Wolfe, MD, Michael Benatar, MD, Gabriel Cea, MD, Amelia Evoli, MD, Nils Erik Gilhus, MD, Isabel Illa, MD, Nancy L. Kuntz, MD, Janice Massey, MD, Arthur Melms, MD, Hiroyuki Murai, MD, Michael Nicolle, MD, Jacqueline Palace, MD, David Richman, MD, and Jan Verschuuren, MD

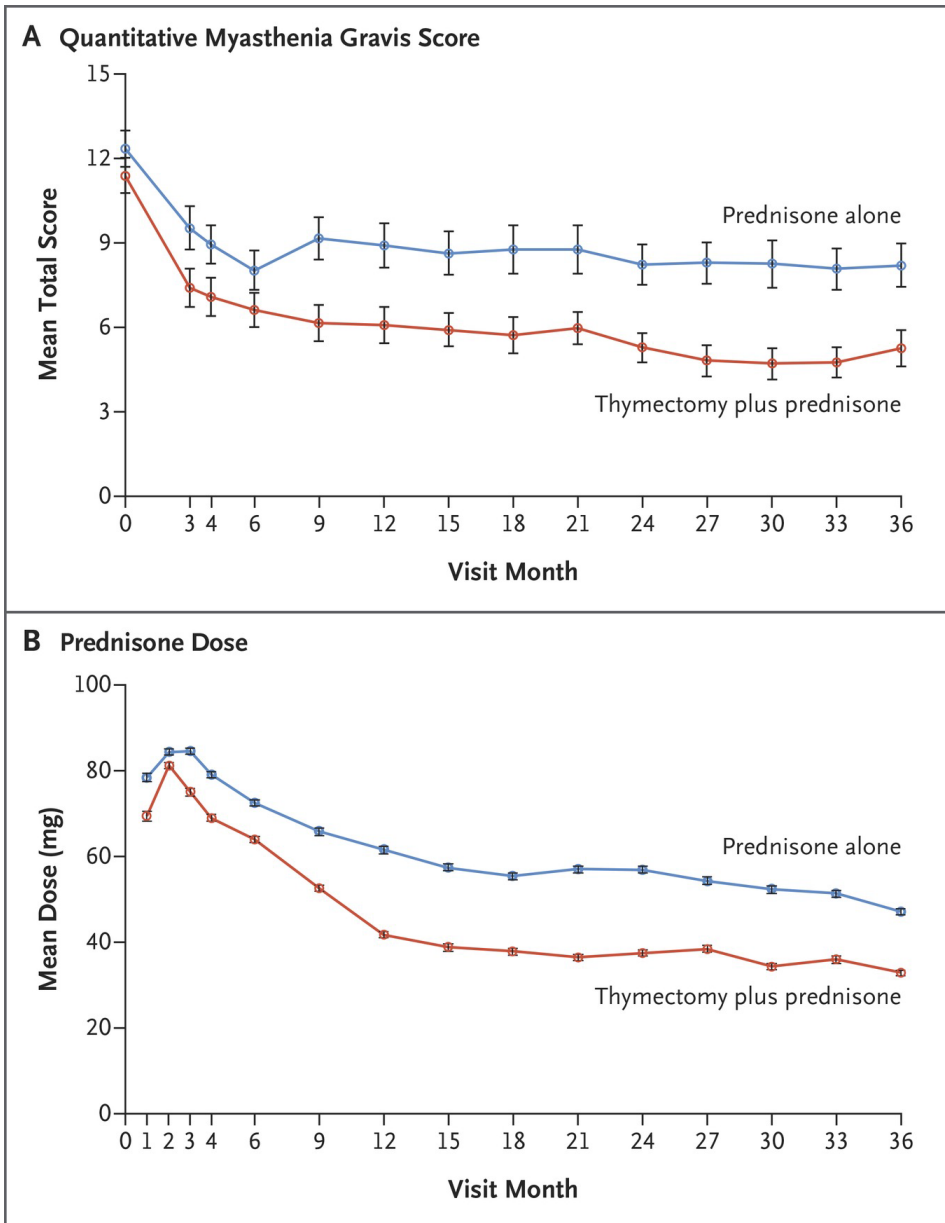
Correspondence
Dr. Narayanaswami
pnarayan@bidmc.harvard.edu

Neurology® 2021;96:114-122. doi:10.1212/WNL.00000000000011124

- Randomized controlled studies
 - Controlled studies
 - Non-controlled studies
 - Clinical cohorts
 - Epidemiological / registry-based evidence
-
- *Short-term and long-term*
 - *Real world data* (age, comorbidity, abuse, compliance, etc)
-

Thymectomy randomized and prospective trial

Wolfe et al 2016



- Generalized, non-thymoma
- 126 patients
- Thymectomy + alternate-day prednisolone
- 3-year follow-up
- Clinically and statistically significant difference

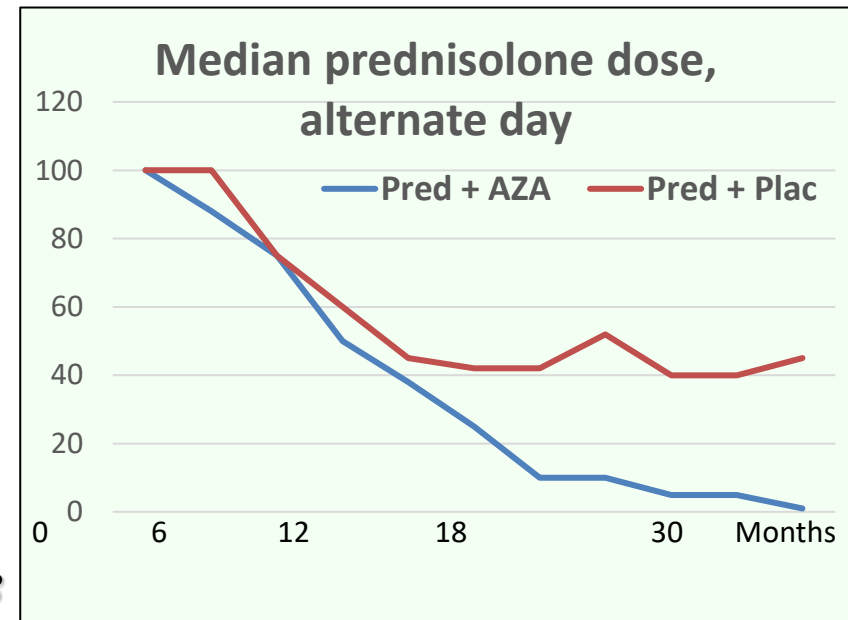
- Age ?
- Ocular only ?
- Antibody-negative ?
- Surgeon and method

Prednisolone vs. prednisolone + azathioprine

- Prednisolone dose reduced
- Relapses more frequent in prednisolone alone
- Remit failures more frequent in prednisolone alone
- Treatment failures more frequent in prednisolone alone
- Side-effects more common in prednisolone
- Very few patients (34, 18 at end)



Corticosteroid side-effects

Reduce dose



Palace et al Neurology 1998

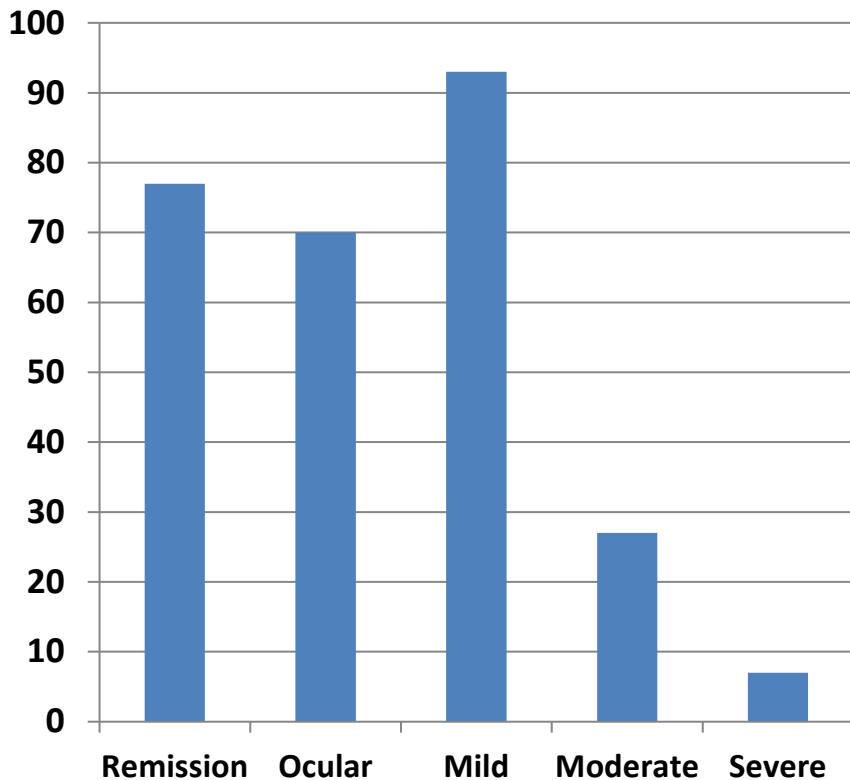
Cost-benefit

- Ra Pharma  UCB US \$ 2.5 B 2019
Complement inhibitors MG +
- Alexion  AstraZeneca US \$39 B 2021
Complement inhibitors MG +

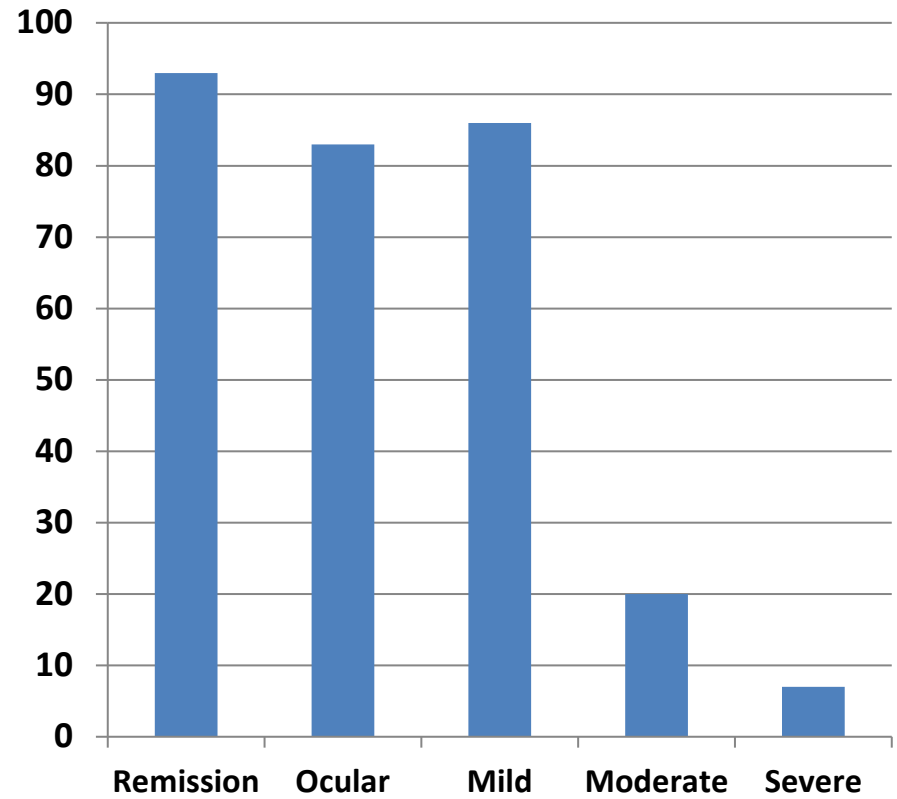
- When to start treatment ?
- **When to stop treatment ?**

MG outcome in a single centre cohort

After 2 years (no.)



Last follow-up (no.)



Be ambitious !

Andersen et al 2016 (Duke, USA)

Health-related quality of life (SF-36) in females and males with myasthenia gravis

Dutch MG vs. controls

Norwegian MG vs. controls

Dutch MG in remission vs. controls

Risk factors:

- Generalized MG
- Female
- Combined immunosuppression
- Age inconsistent

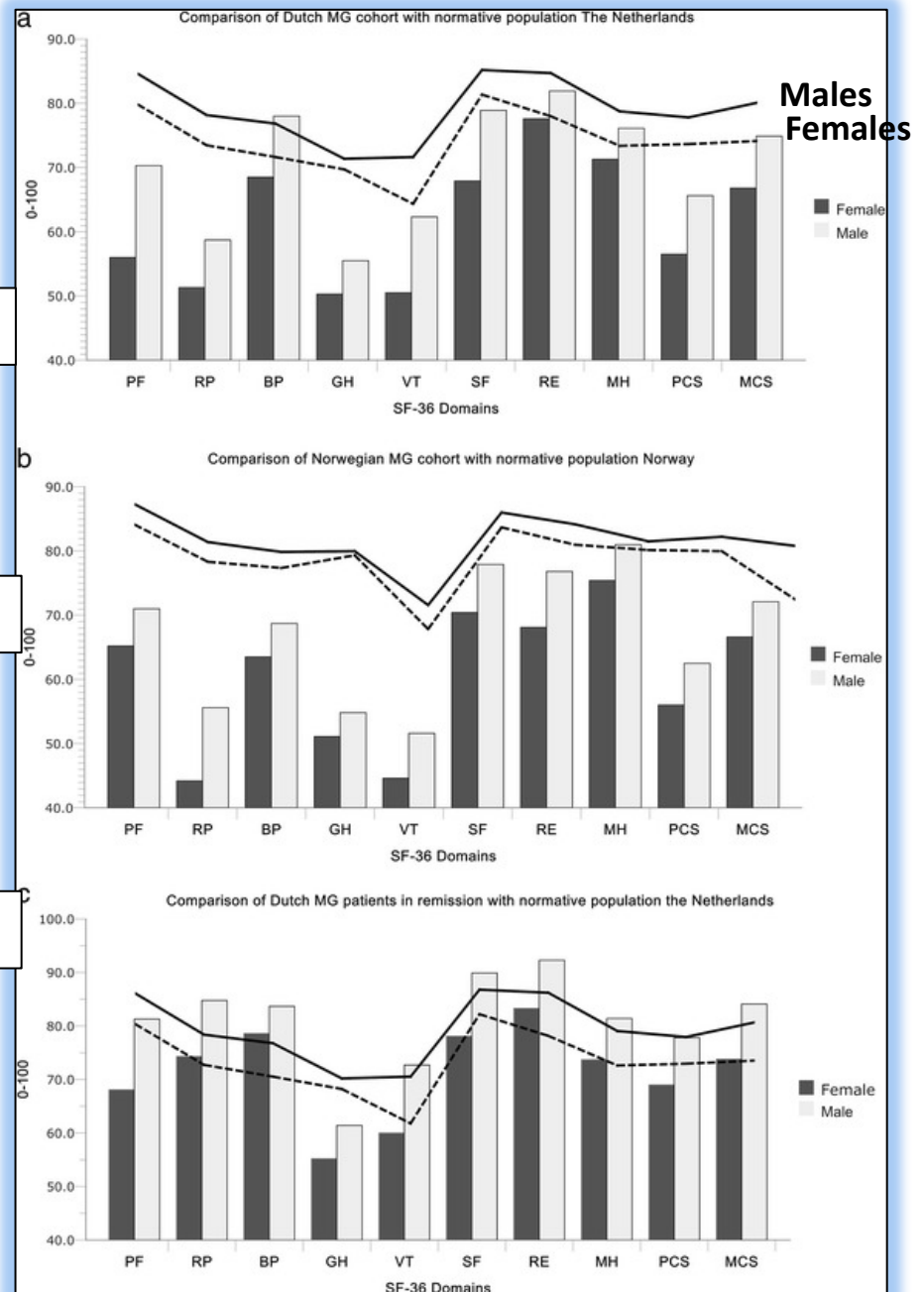


Table 2. Drugs Used Most Frequently for the Treatment of Myasthenia Gravis.

| Drug | Mode of Action | Dose | Side Effects | Risks and Contraindications |
|-----------------------------|--|---|--|--|
| Pyridostigmine | Symptomatic; acetylcholinesterase inhibition | Single dose: 10–120 mg; daily dose: 40–600 mg | Cholinergic autonomic effects | Cholinergic crisis |
| Prednisone or prednisolone | Immunomodulation | Induction dose: 40–80 mg daily; stable dose: 5–20 mg daily; alternate-day treatment is an alternative | Widespread dose-dependent glucocorticoid effects | Gastrointestinal bleeding, cushingoid appearance |
| Azathioprine | Suppression of B and T cells | 50–250 mg daily | Nausea, vomiting, tiredness, infections, night sweats | Leukopenia, liver toxicity |
| Mycophenolate mofetil | Suppression of B and T cells | 1.5–2 g daily | Nausea, vomiting, diarrhea, joint pain, infections, tiredness | Leukopenia, progressive multifocal leukoencephalopathy; contraindicated during pregnancy |
| Rituximab | Suppression of B cells | 0.5–1 g, repeated after 2 wk; can be repeated at 6-mo intervals | Nausea, infections, infusion-related problems | Progressive multifocal leukoencephalopathy |
| Methotrexate | Inhibition of folate metabolism | Gradual increase to 20 mg/wk | Nausea, infections, lung disease | Leukopenia, liver toxicity; contraindicated during pregnancy |
| Cyclosporine | Suppression of T cells and natural killer cells | 2.5–5 mg/kg of body weight daily | Nausea, hypertension, infections, hypertrichosis | Kidney toxicity |
| Tacrolimus | Suppression of T cells and natural killer cells | 3 mg daily | Nausea, infections, lung disease, hypertension, neuropsychiatric problems | Liver and kidney toxicity |
| Cyclophosphamide | Suppression of B and T cells | 1–5 mg per kg administered by intravenous infusion every 4 wk for a limited period | Nausea, vomiting, alopecia, discoloration of nails and skin, infections | Leukopenia |
| Intravenous immune globulin | Suppression of B and T cells, neutralization of autoantibodies | 2 g per kg administered over a period of 2 to 5 days | Nausea, headache, fever, hypotension or hypertension, local skin reactions | IgA deficiency, allergic reactions |

Pros and cons

Gilhus 2016



The NEW ENGLAND
JOURNAL of MEDICINE

Myasthenia gravis: do not forget the patient perspective

Nils Erik Gilhus¹, Jan J G M Verschuuren², Sandra Iren Barkås Hovland³, Huw Simmonds⁴,
Floor Groot⁵, Jacqueline Palace⁶

- Daily function
- Fatigue
- Pain
- Depression
- Speech
- Cognitive function
- Drug side-effects and safety
- Dental care
- Diet and lifestyle
- Treatment availability
- Organization of care
- Social and economic consequences

User Involvement in Myasthenia Gravis Research

Nils Erik Gilhus^{1 2}, Sandra Iren Barkås Hovland³

MG in a global perspective

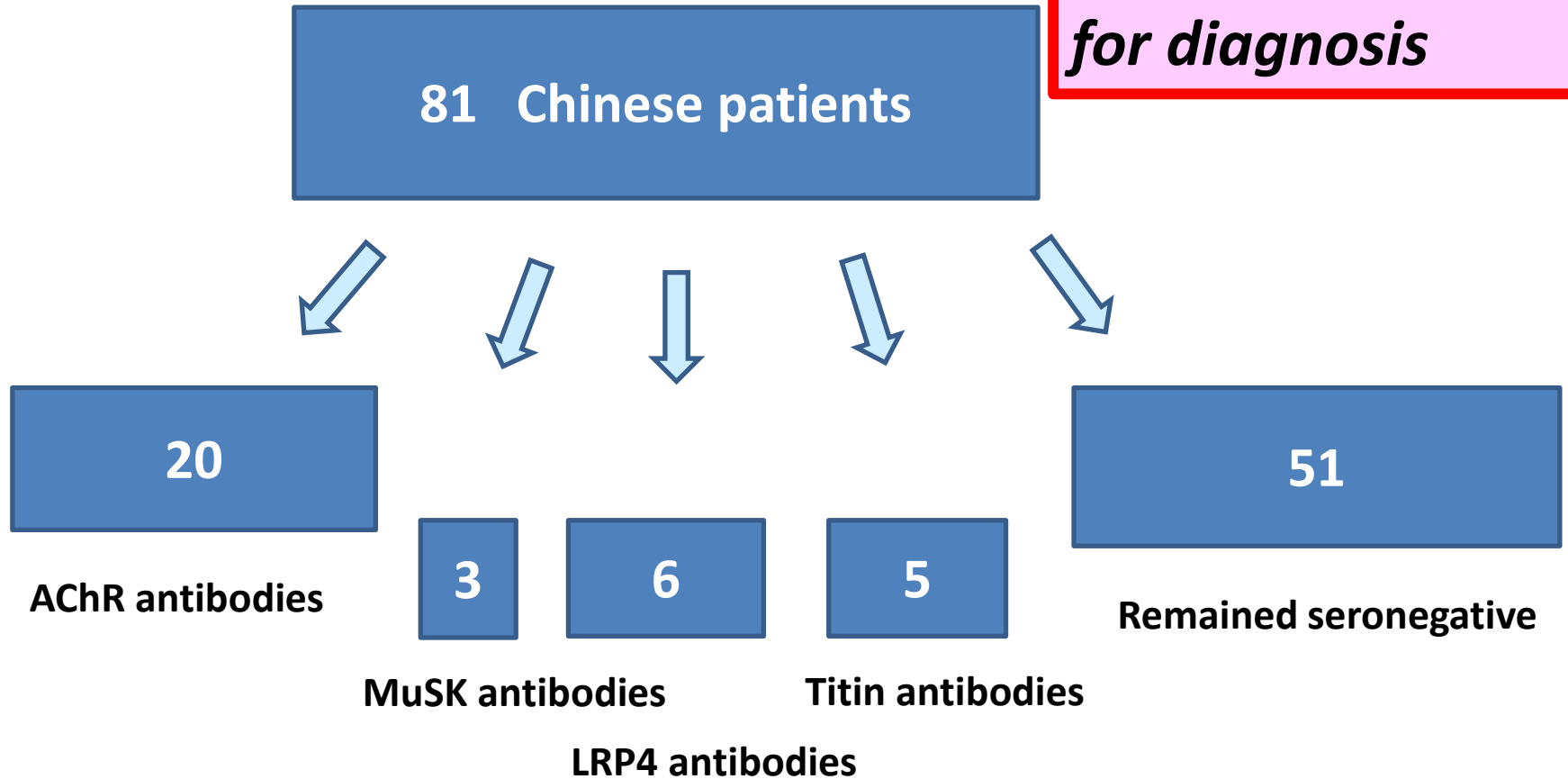
- Access to specialist care
- Optimal organization in high-income countries
- Optimal organization in low-income countries
- Access to antibody analysis
- Access to up-to-date drug treatment
- Access to intensive care
- Cost-benefit analyses
- Joint research projects



No MG antibodies in commercial tests

Sensitive testing:

***Standardized tests
needed
for diagnosis***



*Sensitive AChR-ab RIA
Sensitive AChR-ab CBA*

*Sensitive MuSK-ab CBA
Sensitive LRP4-CBA*

Sensitive titin-ab RIA

*Hong et al
Eur J Neurol 2017*

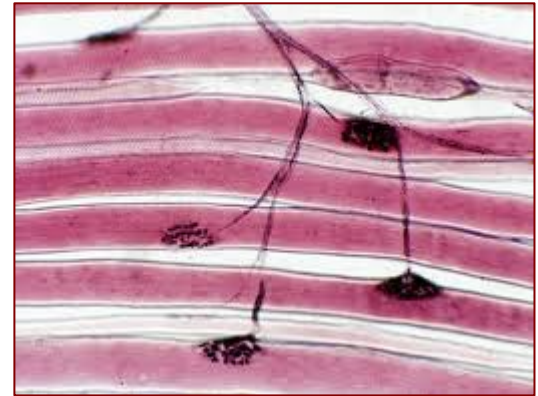
Myasthenia gravis rating scales and outcome measures

- Research
- Clinical practice
- Activities
- Performance – muscle strength
- Quality of life
- Cost-utility

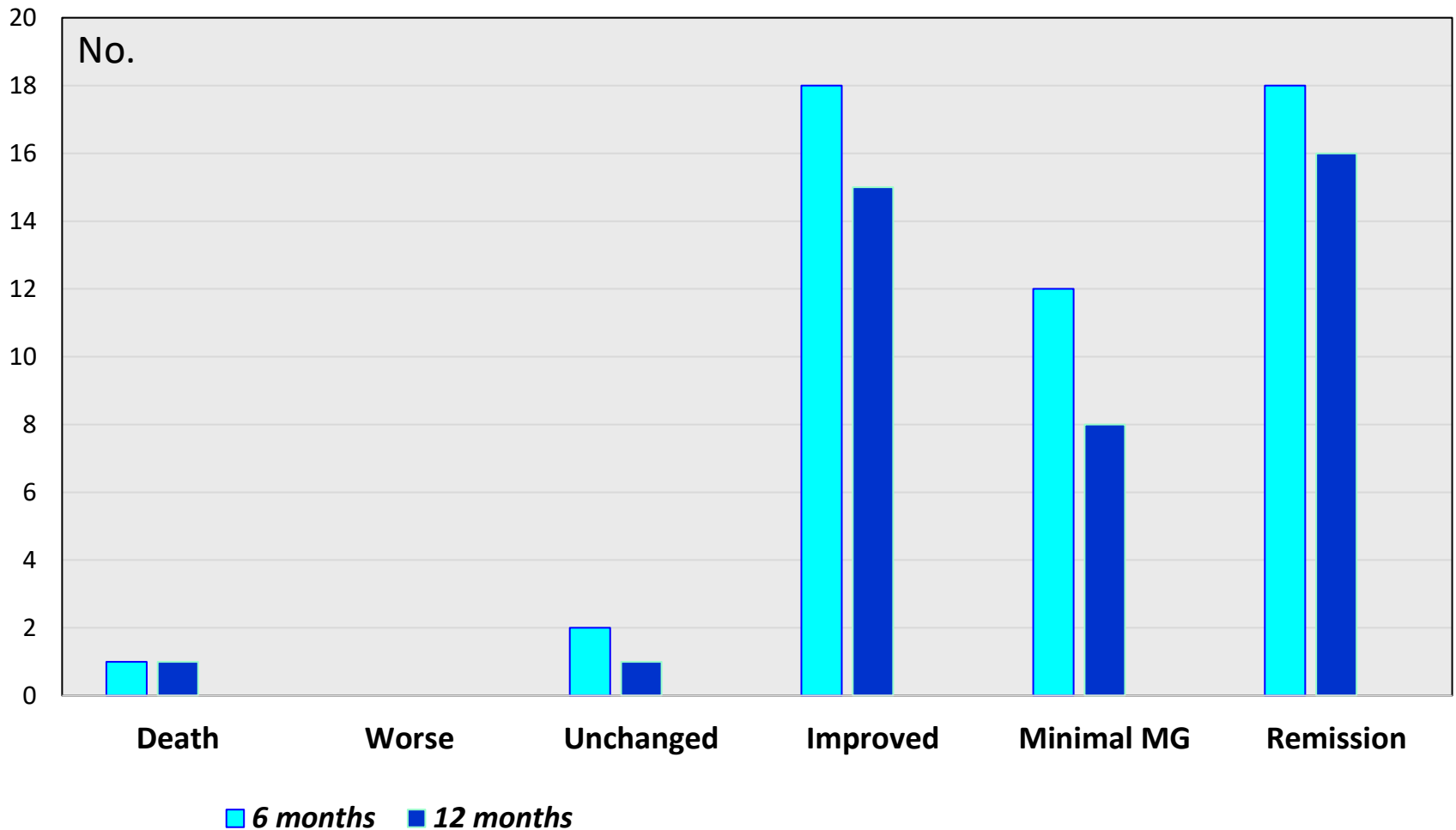
- Patient-reported data
- ADL
- Fatigue
- Patient examination
- Patient perspective

Immunosuppressive drug treatment in MG

- When to start
- Which drug
- Drug combination
- How to start
- Maximal dose
- Continuing dose
- Dose reduction
- When to stop



Rituximab for MG in Austria; a retrospective study



Rituximab in MG with AChR ab.; a meta-analysis

- 21 studies, 260 patients
- 77 % clinically improved
- 51 % minimal manifestations or better
- 71 % prednisolone \leq 10 mg daily

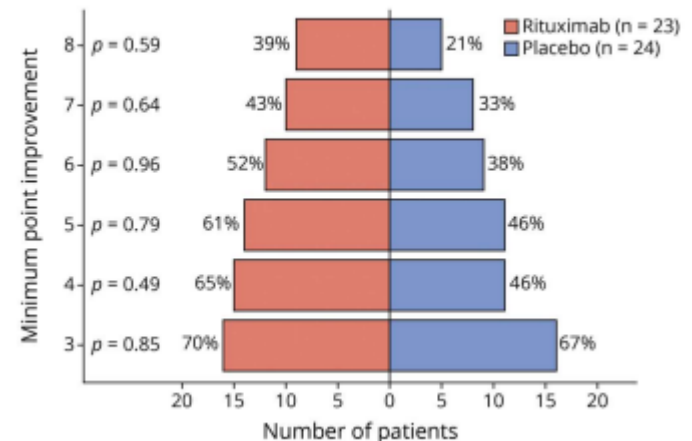
Rituximab in MG with AChR ab.; a phase 2 trial

Two cycles, 12 months observation

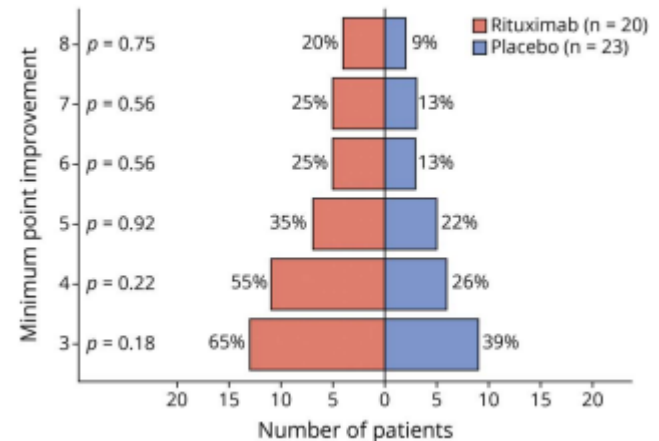
Nowak et al, Neurology 2022

- No steroid-sparing effect. >75% steroid-sparing in 15/25 vs 15/27
- MGC - 5.7 vs. - 4.0. QMG - 4.0 vs. - 1.7
- MG rescue therapy in 3/25 vs. 8/27
- AChR ab. 4.16 → 3.42 vs. 1.50 → 1.63
- MG-ADL - 2.7 vs. - 2.0
- MG-QoL - 8.0 vs. - 7.5
- Mild to moderate and stable disease

C. MGC score: Change from baseline to week 52

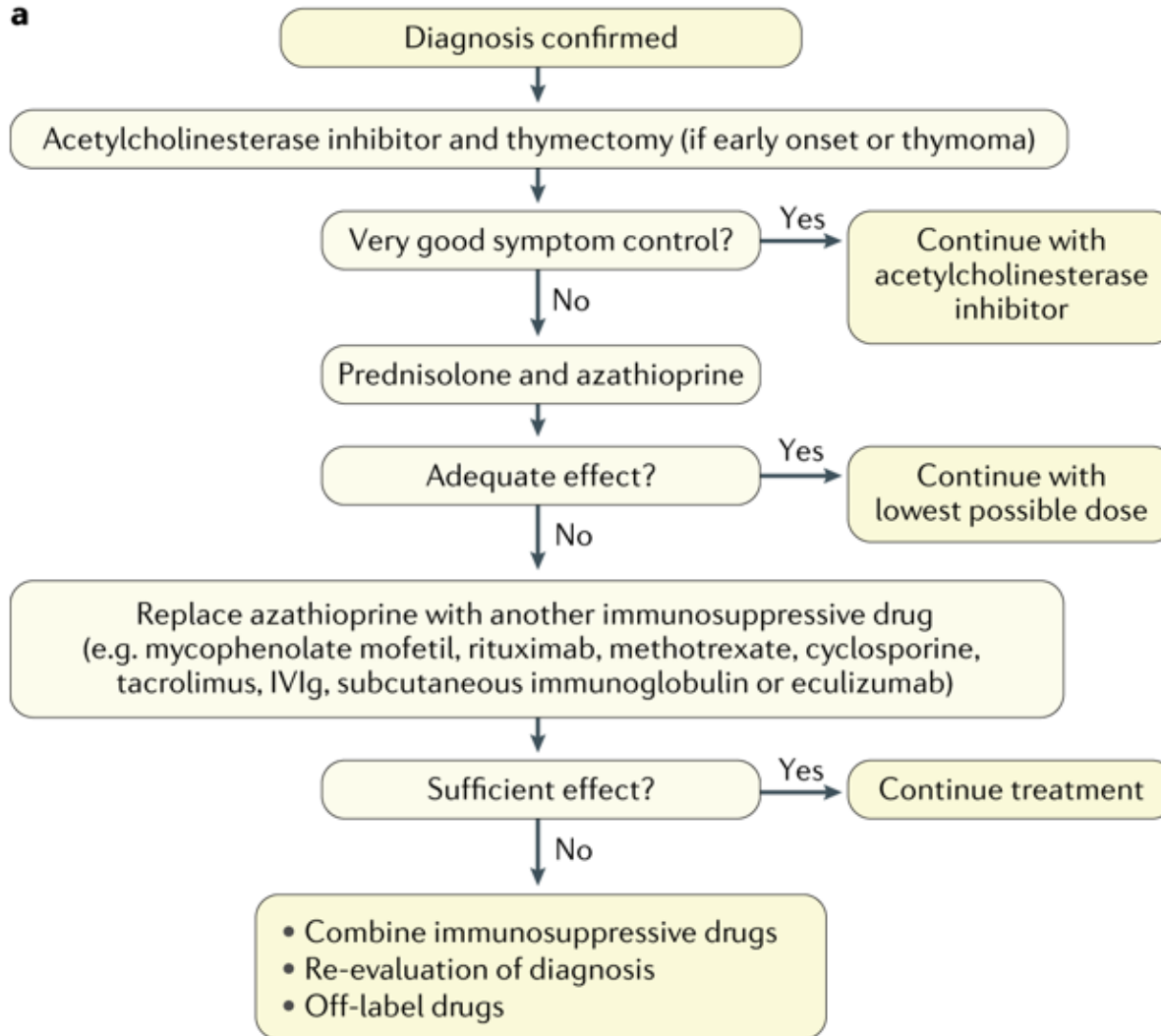


D. QMG score: Change from baseline to week 52

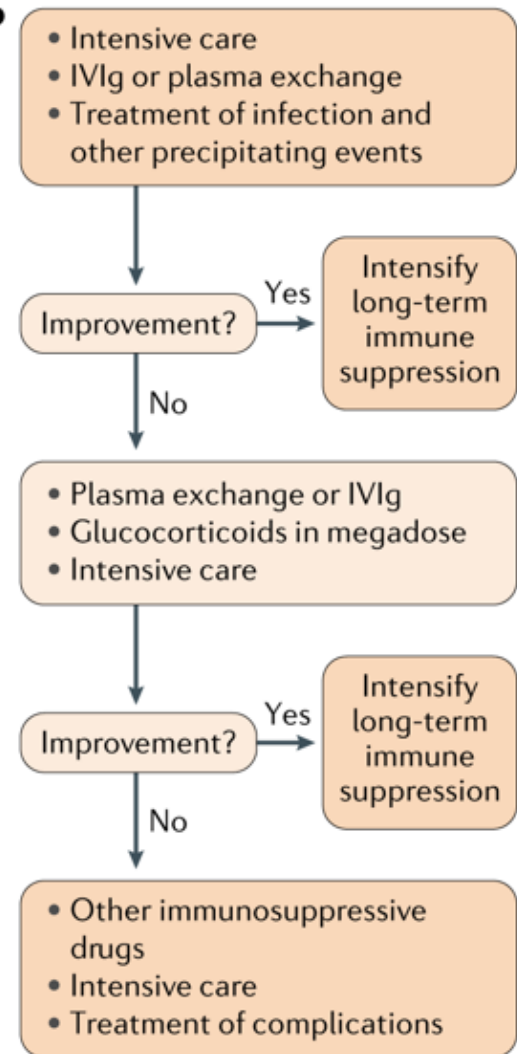


Treatment algorithms for chronic MG and acute MG exacerbations

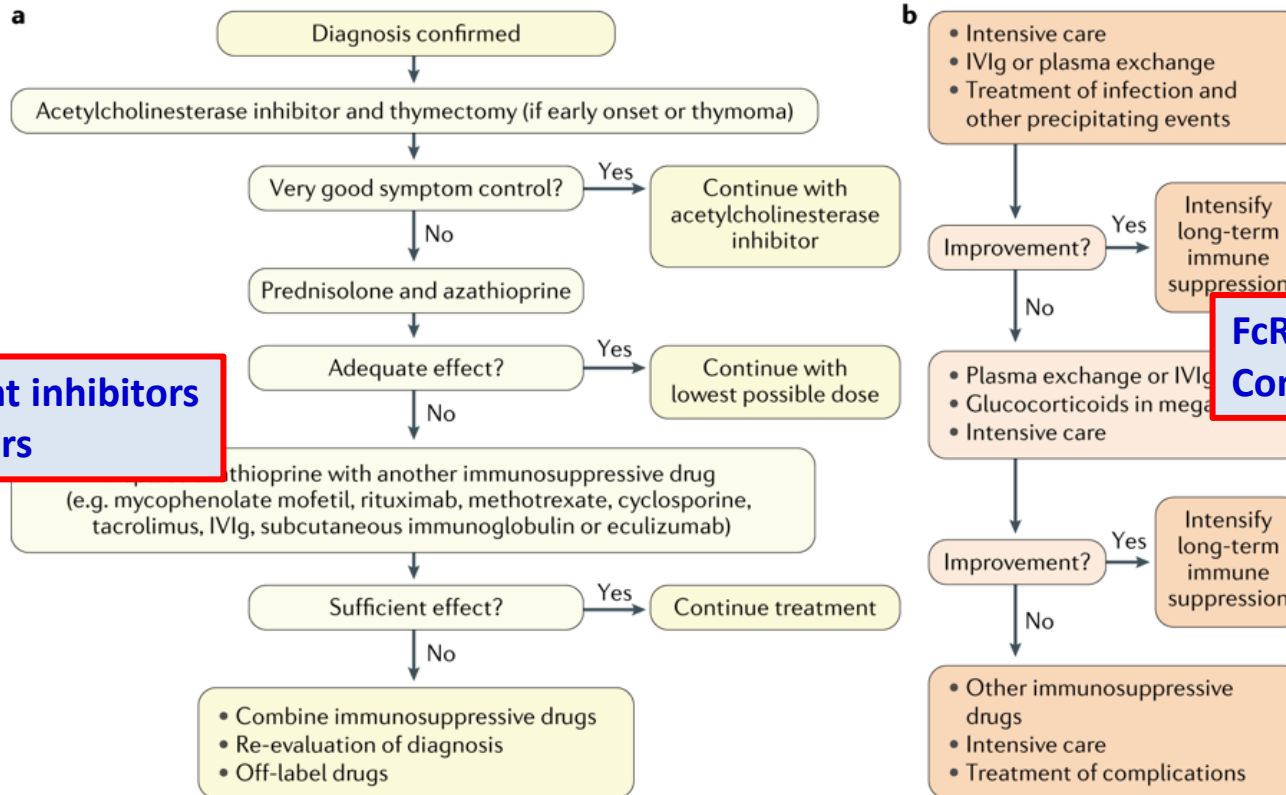
a



b



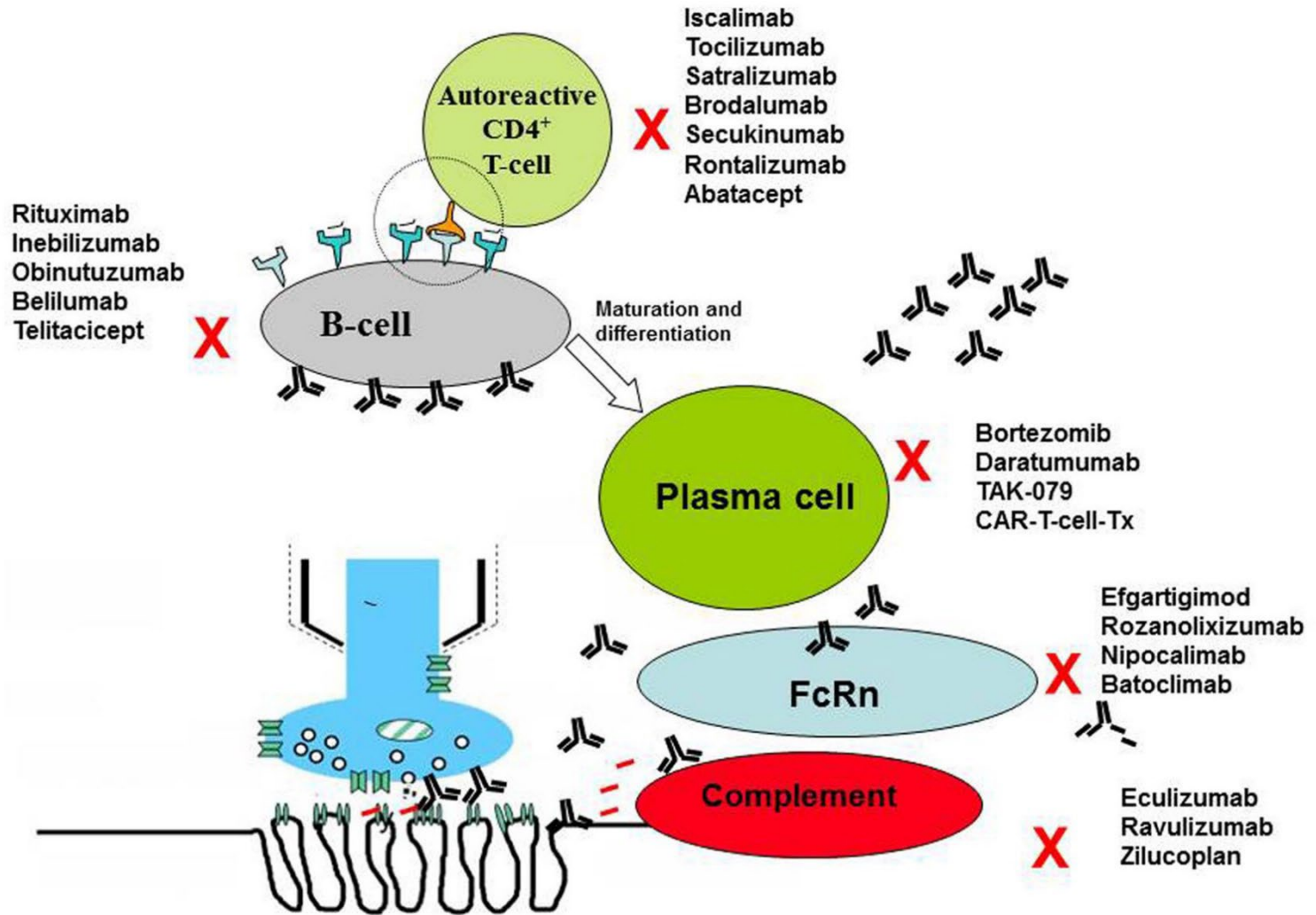
Treatment algorithms for chronic MG and acute MG exacerbations



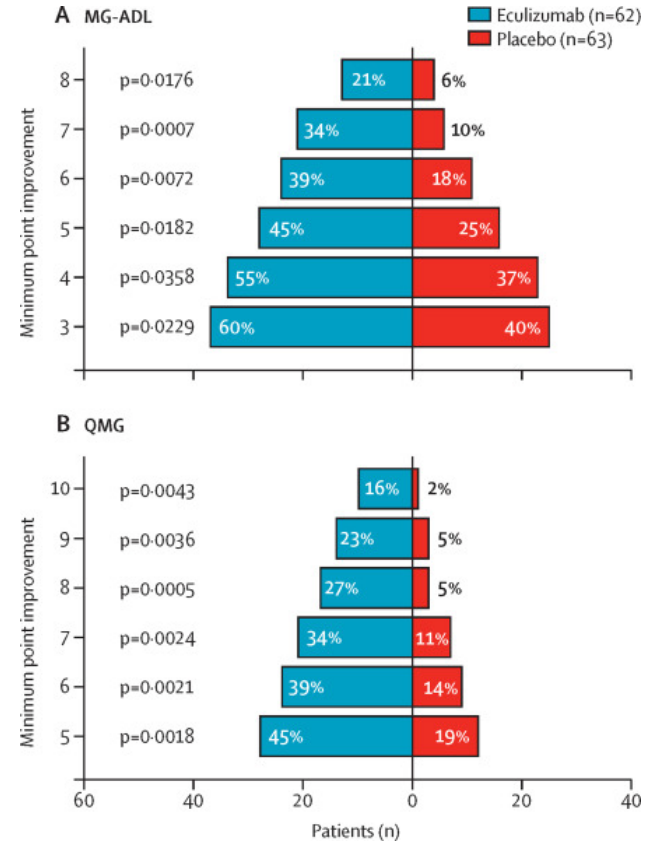
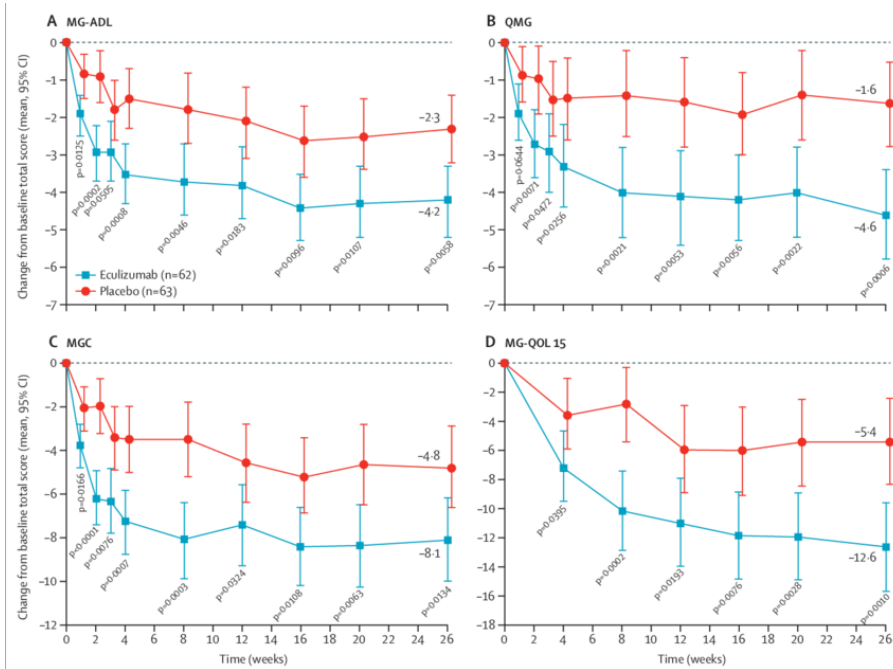
**Complement inhibitors
FcRn blockers**

**FcRn blockers
Complement inhibitors**

New immunotherapies in myasthenia gravis



Eculizumab in MG



Moab inhibiting C5 cleavage

- Phase 3 study positive (but not for primary end-point)
- Fast action
- Safe
- Cost-benefit ???

A Nordic initiative on MG treatment?

- International
- Experts in all countries
- Similar treatment traditions and health systems
- User involvement
- Acta Neurol Scand?

- Guideline
- Systematic review
- Review
- Guidance article

- New treatments
- Costs
- Refunding policies
- Access and limitations

Generalized myasthenia gravis with acetylcholine receptor antibodies; a Nordic guidance for treatment


- Symptomatic drug treatment
- Standard immunosuppressive drug treatment
- New immunosuppressive drug treatment
- Thymectomy
- Experimental treatment
- Physical activity
- Supportive therapy
- Treatment for crisis and exacerbations

Living with myasthenia gravis

Updates on psychosocial issues and training

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