

State of Art Immunotherapies

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Disclosure:

- No disclosure
- No conflict of interest

Short term immunosuppression:

- **IVIg** (0.4g/kg/day) x 5 days or **Plasmapheresis** (5-6 exchanges over 1-2 wks)
- Appear equally effective when given in the first 2 wks after onset
- AAN practice parameters, For GBS
 - PE is recommended for non-ambulant adult patients with GBS who seek treatment within 4 weeks and should be considered for ambulant patients within 2 weeks of the onset of symptoms
 - IVIg for non-ambulant adult patients with GBS within 2 or possible 4 weeks of the onset
 - Corticosteroids are not recommended
 - Sequential treatment with PE followed by IVIg is not recommended
 - PE and IVIg are treatment options for children with severe GBS
- Reduce the duration of the disease and improve the neurological outcome



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Evidence for Immunotherapy in GBS management

	Plasma Exchange (PE)	IV Immunoglobulin (IVIg)	Combined Treatments	Corticosteroids
Strong evidence supports	PE recommended in nonambulant patients within 4 weeks of onset of neuropathic symptoms. (Level A*, Class II**)	IVIg recommended in nonambulant patients within 2 weeks of onset of neuropathic symptoms. (Level A, Class II)	Sequential treatment with PE followed by IVIg does not have a greater effect than either treatment given alone. (Level A, Class I)	Steroids not recommended in the treatment of GBS. (Level A, Class I)

	Plasma Exchange (PE)	IV Immunoglobulin (IVIg)
Good evidence supports	<p>PE recommended for ambulant patients within 2 weeks of onset of neuropathic symptoms. (Level B, limited Class II)</p> <p>If PE started within 2 weeks of onset, there are equivalent effects of PE and IVIg in patients requiring walking aids. (Level B, Class I)</p> <p>PE is a treatment option for children with severe GBS. (Level B, derived from Class II evidence in adults)</p>	<p>IVIg recommended in nonambulant patients started within 4 weeks from the onset of neuropathic symptoms. (Level B, Class II)</p> <p>If started within 2 weeks of onset, IVIg has comparable efficacy to PE in patients requiring walking aids if started within 2 weeks of onset. (Level B, Class I)</p> <p>IVIg is a treatment option for children with severe GBS. (Level B, derived from Class II evidence in adults)</p>



Articles

Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome

Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group 

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Summary

Background

The relative efficacy of plasma exchange (PE) and intravenous immunoglobulin (IVIg) for the treatment of Guillain-Barré syndrome has not been established. We compared PE with IVIg, and with a combined regimen of PE followed by IVIg, in an international, multicentre, randomised trial of 383 adult patients with Guillain-Barré syndrome.

Conclusion:

In treatment of severe GBS during the first 2 weeks after onset of neuropathic symptoms, PE and IVIG had equivalent efficacy.

The combination of PE with IVIG did not confer a significant advantage.

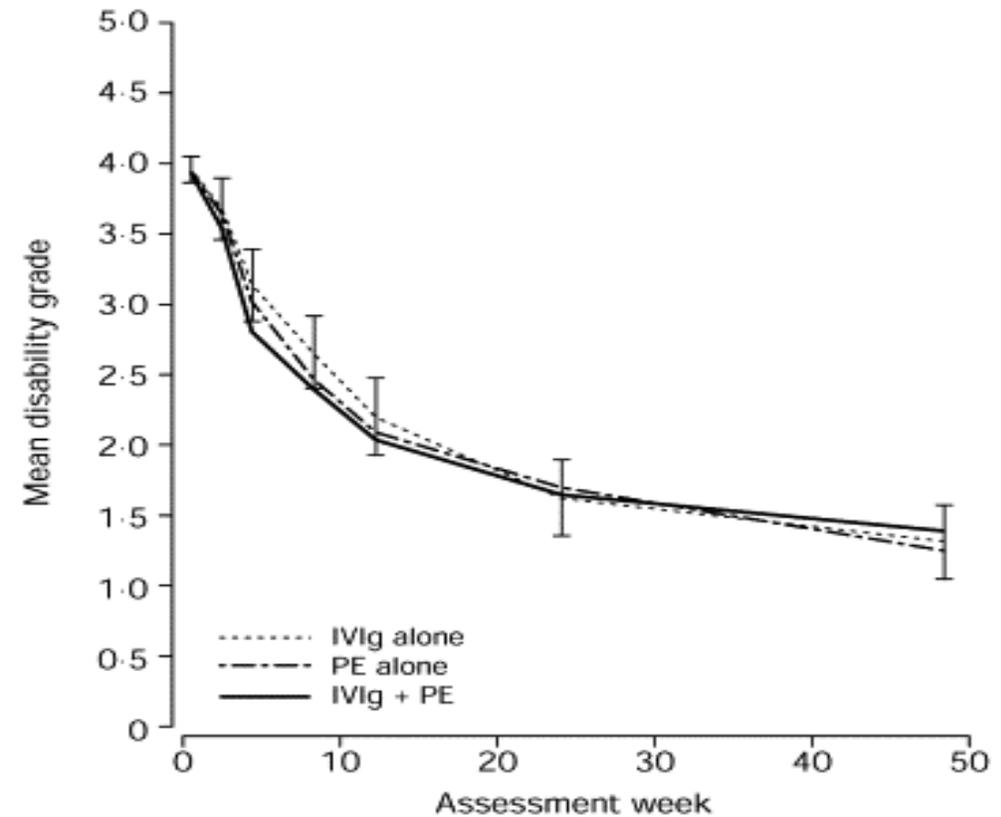
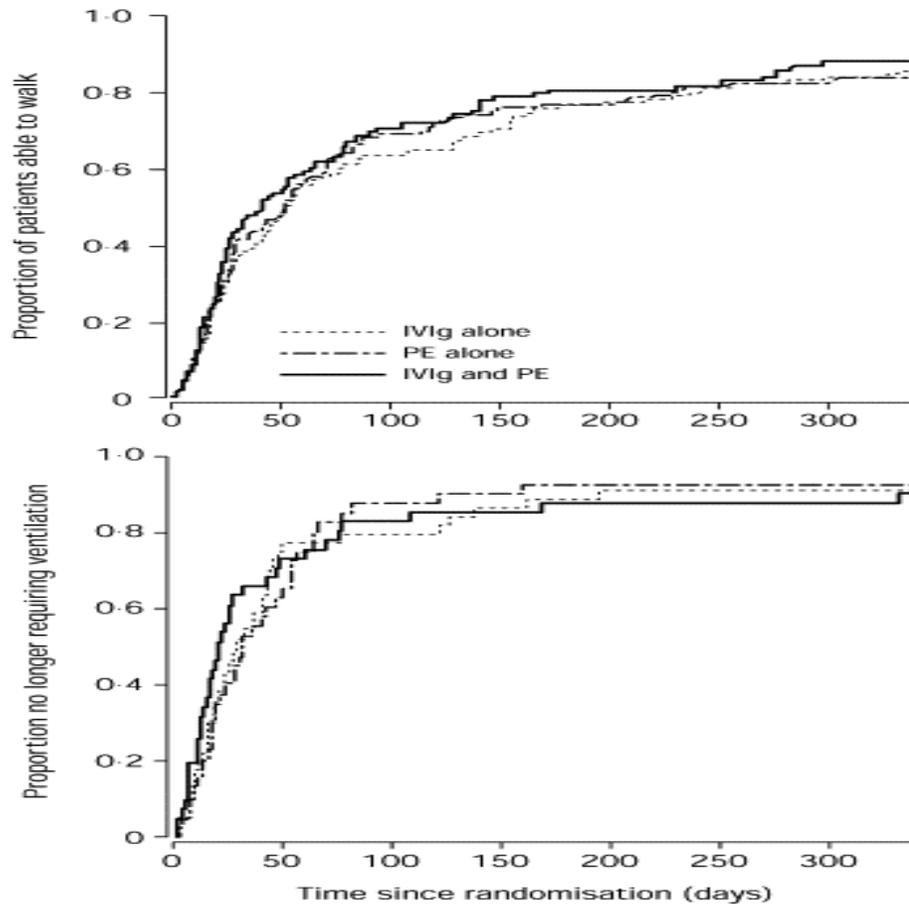


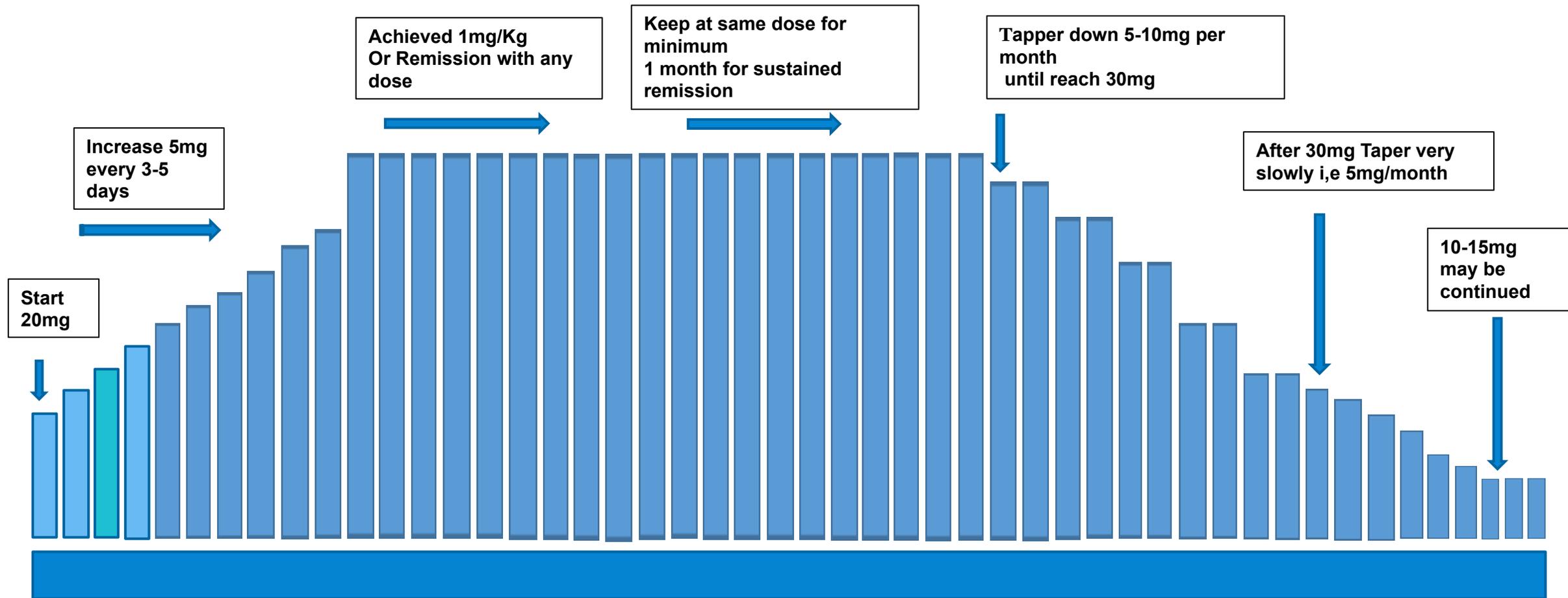
TABLE 8-6

Comparison of Intravenous Immunoglobulin and Plasma Exchange

Treatment	Side Effects	Advantages	Disadvantages
IV Immunoglobulin (IVIg)	Reversible encephalopathy; chest pain at initiation; infusion-related side effects (up to 24 hours) including fatigue, fever, nausea; thromboembolism; aseptic meningitis; acute kidney injury; migraine; allergic reactions (IgA deficiency)	Convenience, could be infused in peripheral veins, patient comfort, easy to initiate	Expensive, contraindicated in patients with congestive heart failure or renal insufficiency
Plasma exchange	Paresthesia (hypocalcemia secondary to citrate in exchange solution), transfusion reaction, hypotension, central access complications, infection, pneumothorax, hematoma	Allows for IVIg use as second course of treatment in patients who are refractory to treatment	Requires central line access; may not be available in facilities with poor resources; contraindicated in patients with septic shock, myocardial infarction within 6 months; marked dysautonomia; active bleeding

Glucocorticoids:

- Due to their rapid onset of effect, glucocorticoids are the most commonly used initial immunosuppressive therapy
- The administration of moderate or high glucocorticoids produces remission in approximately 30 percent of patients and marked improvement in another 50 percent.
- Up to 50 percent of patients of MG develop a transient deterioration that can be serious and up to 10 percent have respiratory failure requiring mechanical ventilation. The transient worsening usually occurs 5 to 10 days after the initiation of glucocorticoids and lasts approximately 5-6 days.
- For this reason, glucocorticoids are most often started in high doses only in hospitalized patients



Azathioprine:

- purine antimetabolite that interferes with T-cell and B-cell proliferation.
- Retrospective studies indicate that AZA is effective in 70% to 90% of patients with MG, but the onset of benefit may be delayed for as long as 12 months

DOSAGE AND TITRATION:

To initiated at 50 mg per day.
In the absence of systemic side effects the dose is then gradually titrated upward by 50 mg per week until a dose of 2-3 mg/kg/d is reached.

Pregnancy: Pregnant patients: ≤ 2 mg/kg/day (Category C)

ADVERSE REACTION:

- usually well tolerated, but 10% to 15% of patients develop an **idiosyncratic reaction characterized by fever, nausea, vomiting, and abdominal pain or a skin rash**, which are reasons to permanently discontinue AZA as these symptoms resolve quickly with stopping the drug but recur upon re-challenge.
- Hepatotoxicity and leukopenia
- May increase the risk of developing certain **malignancies**. This risk is likely dose and duration dependent.

MONITORING:

White blood cell counts and **liver enzymes** should be monitored at least monthly.

INDICATIONS:

- Myasthenia
- CIDP
- Inflammatory myopathies
- Immune Neuropathies

Mycophenolate Mofetil:

- Mycophenolate mofetil (MMF) selectively blocks purine synthesis, thereby suppressing both T-cell and B-cell proliferation.
- Commonly used for allograft rejection, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and some systemic vasculitides.

DOSAGE AND TITRATION:

- Initial: 500 mg twice daily; increase based on response and tolerability to a maintenance dose of 1 g to 1.5 g twice daily.
- May be started as monotherapy or in conjunction with glucocorticoids
- Should be avoided in Pregnancy and lactation.

ADVERSE REACTION:

- Myelosuppression
- diarrhea, nausea, and abdominal pain
- Increased risk of , infection, like pharyngitis,/ RTI, UTI, sepsis
- Long-term use may be associated with an increased risk for certain malignancies.
- Use during pregnancy contains risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available.

MONITORING:

Complete blood count (weekly for first month, twice monthly during months 2 and 3, then monthly thereafter through the first year);
renal and liver function

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Cyclosporine :

- Cyclosporine inhibits T-cell proliferation via disruption of calcineurin signaling, which blocks the synthesis of interleukin (IL)-2 and other proteins essential to the function of CD4⁺ T cells.

DOSAGE AND TITRATION:

- The recommended initial dose of cyclosporine is 4 -6 mg/kg/d in two divided doses.
- Maintenance dosing of 3- 4 mg/kg/d or less is often adequate to maintain the effect.
- onset of response may be expected 1 to 2 months

ADVERSE REACTION:

- Hirsutism, tremor, gum hyperplasia, and anemia, but hypertension and nephrotoxicity are the main treatment-limiting adverse reactions.
- The risk of certain malignancies (melanoma, lymphoma) may be increased with long-term use.
- Pregnancy: cyclosporine crosses the placenta; maternal concentrations do not correlate with those found in the umbilical cord. premature births and low birth weight were consistently observed in pregnant ladies. So use should be very careful if highly required
- Lactation: discontinue cyclosporine or to discontinue breastfeeding

MONITORING:

Blood pressure, Renal function, and serum cyclosporine trough levels should be monitored monthly.

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Cyclophosphamide:

- Cyclophosphamide is reserved for patients with severe generalized MG refractory to conventional therapies.
- Its used only in Refractory disease.

DOSAGE AND TITRATION:

- 500mg/ m² area of body X monthly.
- After initial dose, titrate to achieve target trough concentrations.

ADVERSE REACTION:

- Myelosuppression, hemorrhagic cystitis, and an increased risk of malignancy.
- Women of childbearing potential should avoid pregnancy while receiving cyclophosphamide and for up to 1 year after completion of treatment. Males partners using it should use a contraception during and at least 4 months after treatment.
- For potential for serious S/E in the breastfed infant, a decision should be made to discontinue cyclophosphamide or to discontinue breastfeeding

MONITORING:

CBC with differential and platelets, BUN, UA, serum electrolytes, serum creatinine; Liver functions and Echocardiography monitor for signs/symptoms of hemorrhagic cystitis

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Tacrolimus:

- Tacrolimus inhibits calcium-dependent events, such as interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis.
- T cell proliferation in response to ligation of the T cell receptor is inhibited by tacrolimus.
- Large-scale controlled studies of tacrolimus in MG are underway in Japan and may better clarify the role of this agent in MG therapy.

DOSAGE AND TITRATION:

- 3 -5 mg/d have been used in various studies, and a favorable side effect profile has been observed.

ADVERSE REACTION:

- Acute cardiorespiratory failure, angina , cardiac arrhythmia, cardiac failure
- agitation, amnesia, anxiety, ataxia
- Anemia
- Hepatotoxicity
- Not recommended in pregnancy because of Miscarriage, preterm delivery, low birth weight, birth defects (including cardiac, craniofacial, neurologic)

MONITORING:

Renal function, hepatic function, serum electrolytes (magnesium, phosphate), glucose and blood pressure, measure 3 times/week for first few weeks, then gradually decrease frequency as patient stabilizes

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Commonly used therapies for myasthenia gravis

	Time to onset of effect*	Time to maximal effect*
Symptomatic therapy		
Pyridostigmine	10 to 15 minutes	2 hours
Chronic immunotherapies		
Prednisone	2 to 3 weeks	5 to 6 months
Azathioprine	~12 months	1 to 2 years
Mycophenolate mofetil	6 to 12 months	1 to 2 years
Cyclosporine and tacrolimus	~6 months	~12 months
Rapid immunotherapies		
Plasmapheresis	1 to 7 days	1 to 3 weeks
Intravenous immune globulin	1 to 2 weeks	1 to 3 weeks
Surgery		
Thymectomy	1 to 10 years	1 to 10 years

* Estimated times are rough guidelines based upon clinical experience in myasthenia gravis.

Targeting B-cells: Rituximab:

- Rituximab is a monoclonal B-cell-depleting anti-CD20 antibody. CD20 is expressed from the early pre-B-cell stage and remains present in mature B cells.
- Direct apoptosis of B cells induced by RTX binding.
- Check Hep B and C, CMV, HZV, HIV , TB before starting
- Vaccination

DOSAGE AND TITRATION:

- Dosage regimen is 375 mg/m² once weekly for 4 doses and repeat cycle after 6 months.
- 1g on days 1 and 15 , subsequent courses may be administered every 24 weeks

ADVERSE REACTION:

- Peripheral edema, hypertension/ hypotension
- Renal failure, Cardiac arrhythmia, chest pain, skin rash
- Nausea , diarrhea , abdominal pain, weight gain
- Arthritis
- PML (few cases)

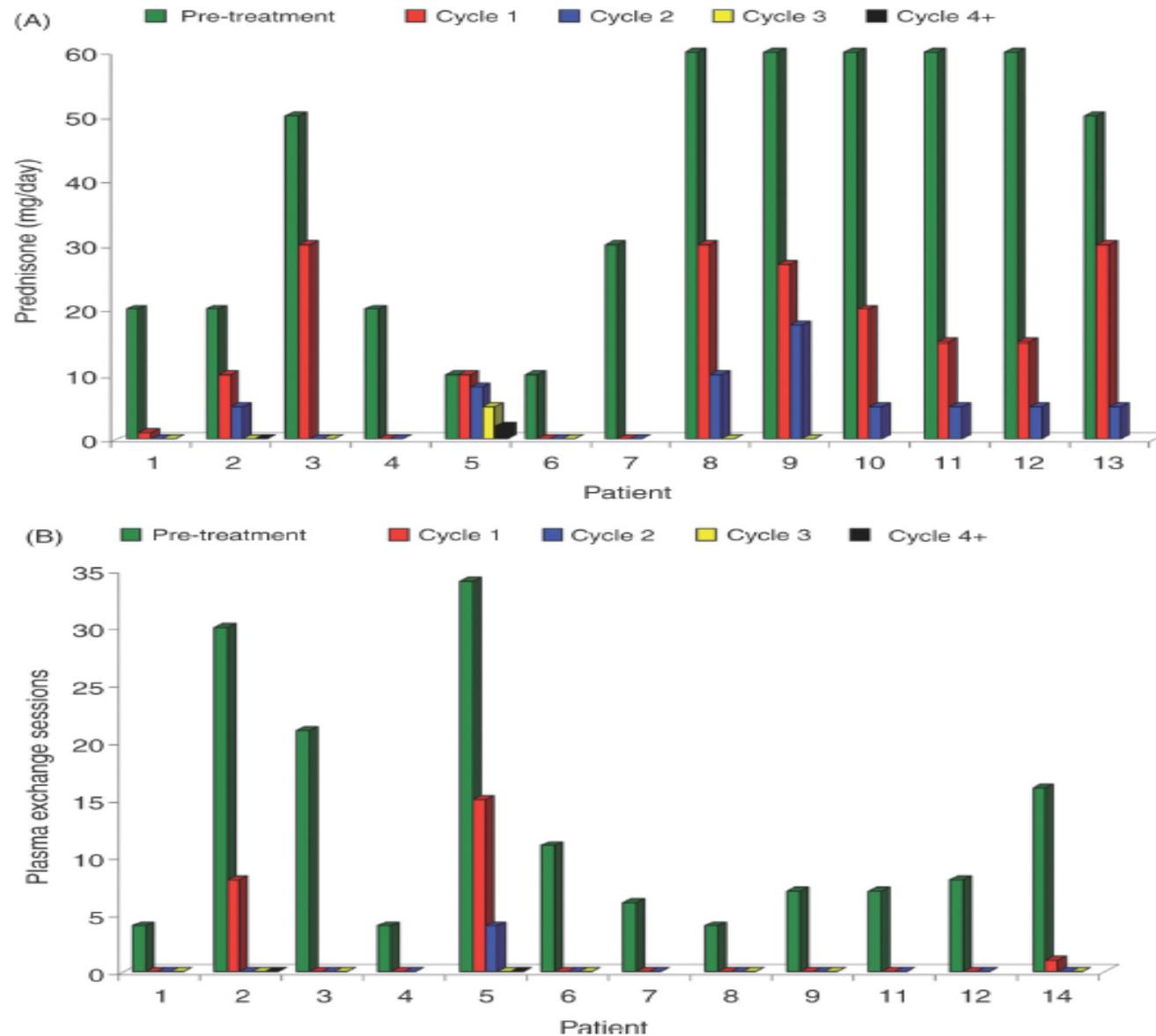
MONITORING:

CBC, Renal functions monthly, and cardiac functions quarterly, CD 19, CD20 count before doses.

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Case series of refractory MG treated with RTX and showed significant improvement. 2011

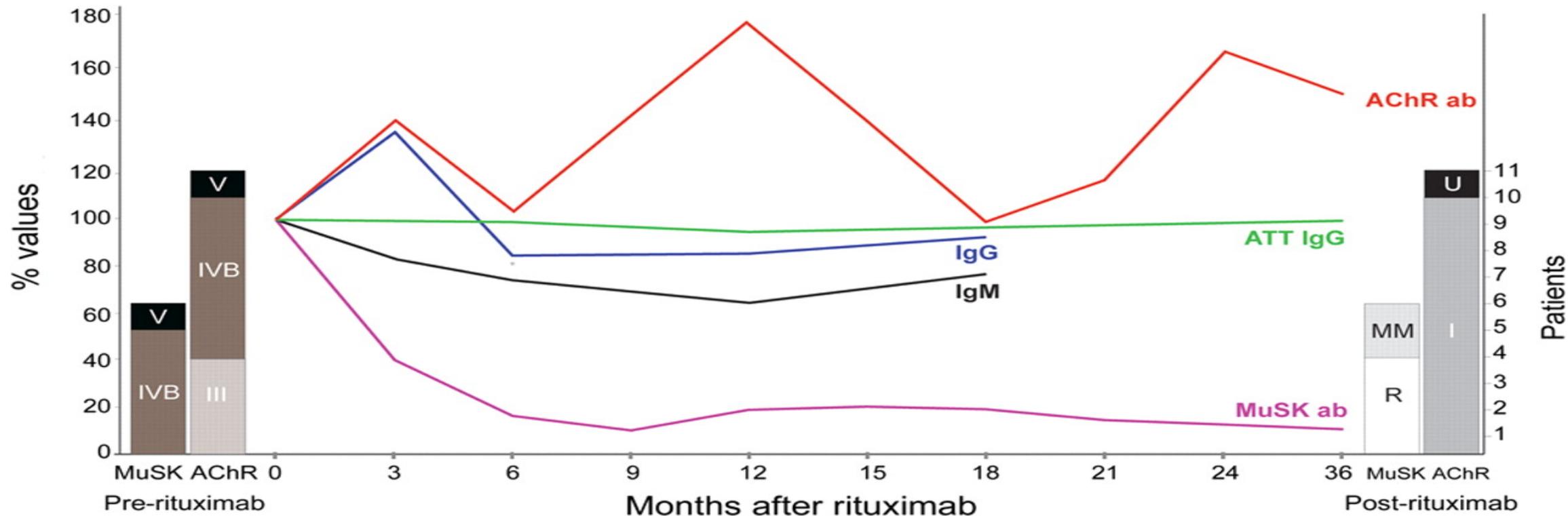


Rituximab is beneficial and well tolerated in managing refractory myasthenia.

We propose that B-cell-directed therapies may become an attractive option and suggest pursuit of a prospective trials.

January 17, 2012; 78 (3) ARTICLES

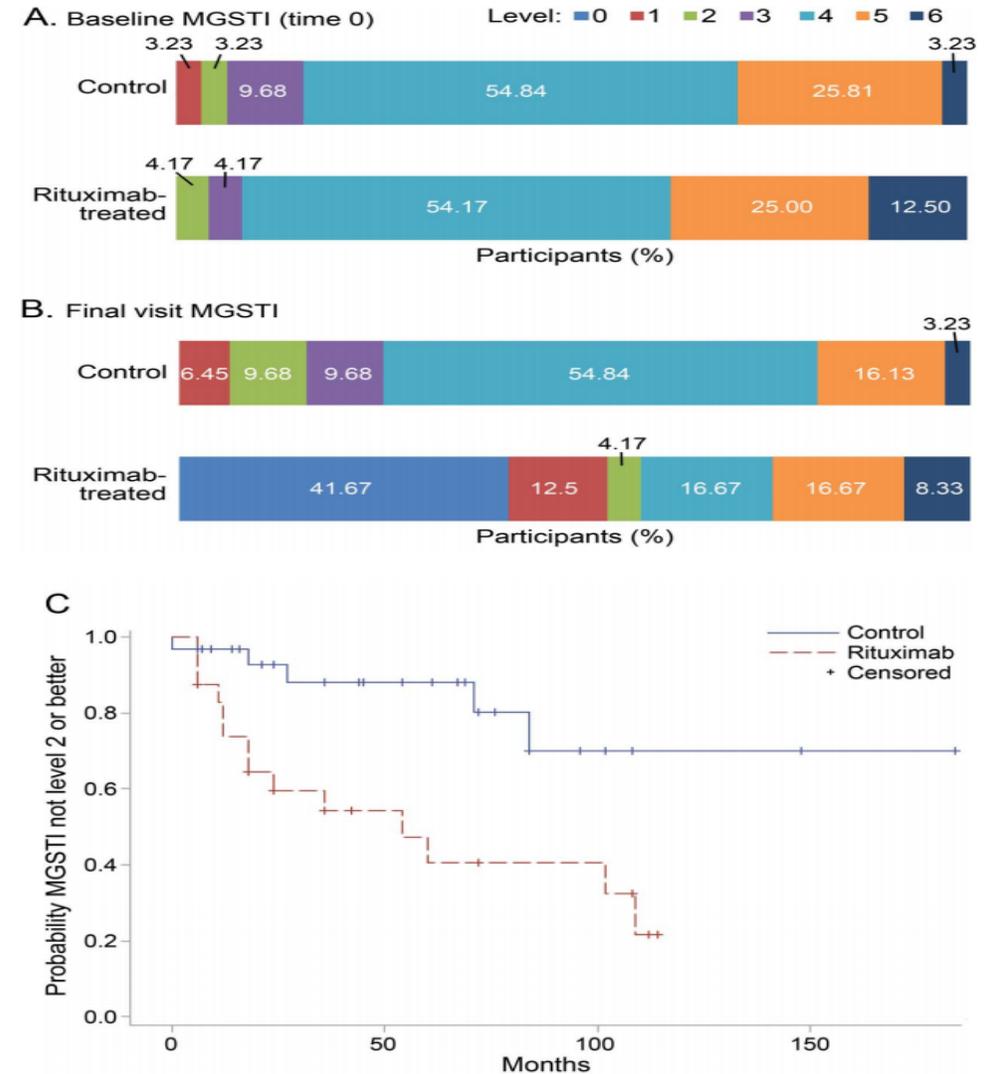
Long-lasting treatment effect of rituximab in MuSK myasthenia

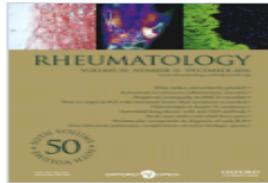


Diaz-Manera, J., Martínez-Hernández, E., Querol, L., Klooster, R., Rojas-García, R., Suarez-Calvet, X., ... & Juárez, C. (2012). Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology*, 78(3), 189-193.

Rituximab in MuSK + MG

- This was a multicenter, blinded, prospective review, comparing anti-MuSK-positive patients with MG treated with rituximab to those not treated with rituximab. 2017
- Myasthenia Gravis Status and Treatment Intensity (MGSTI) score was used to define a favorable outcome.





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December 2011

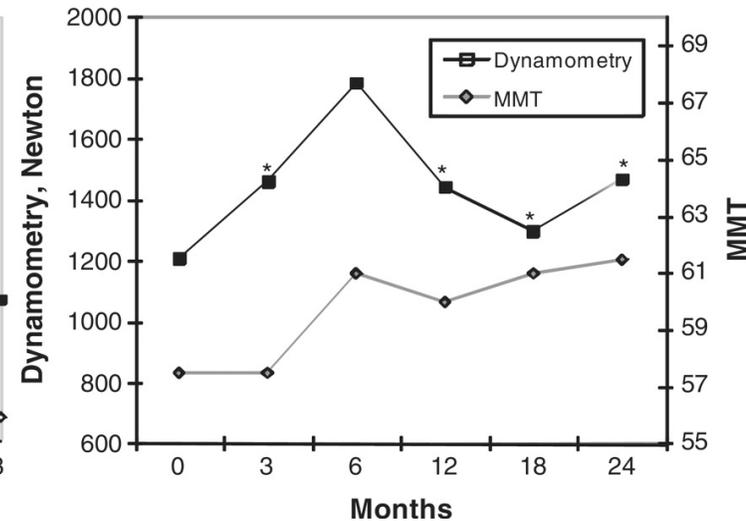
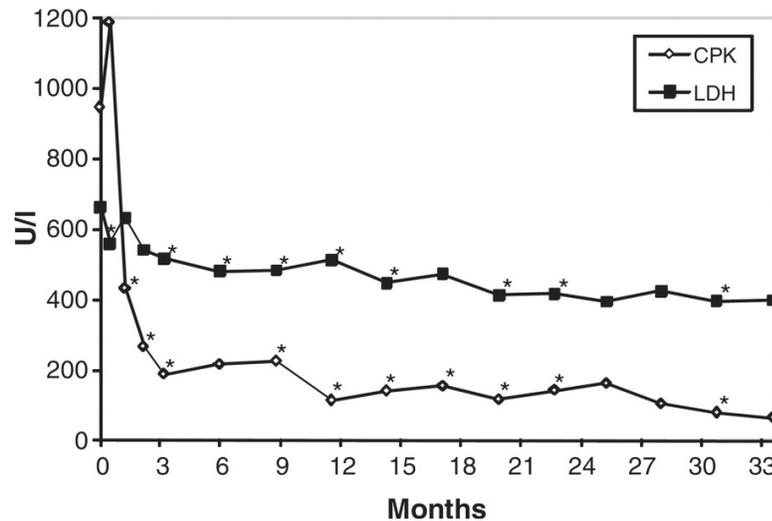
Rituximab treatment in patients with refractory inflammatory myopathies ^{FREE}

Elien A. M. Mahler, Marlies Blom, Nicol C. Voermans, Baziel G. M. van Engelen, Piet L. C. M. van Riel, Madelon C. Vonk

Rheumatology, Volume 50, Issue 12, December 2011, Pages 2206–2213,

<https://doi.org/10.1093/rheumatology/ker088>

Published: 13 May 2011 [Article history ▾](#)



Rituximab is an effective treatment in refractory inflammatory myopathies, showing a decrease in CPK and LDH, an increase in muscle strength and improvement in scores of disease activity, general health, functional ability and health related quality of life with sustained effect during a median of 27.1 months of follow-up.

Therapy that targets complement:

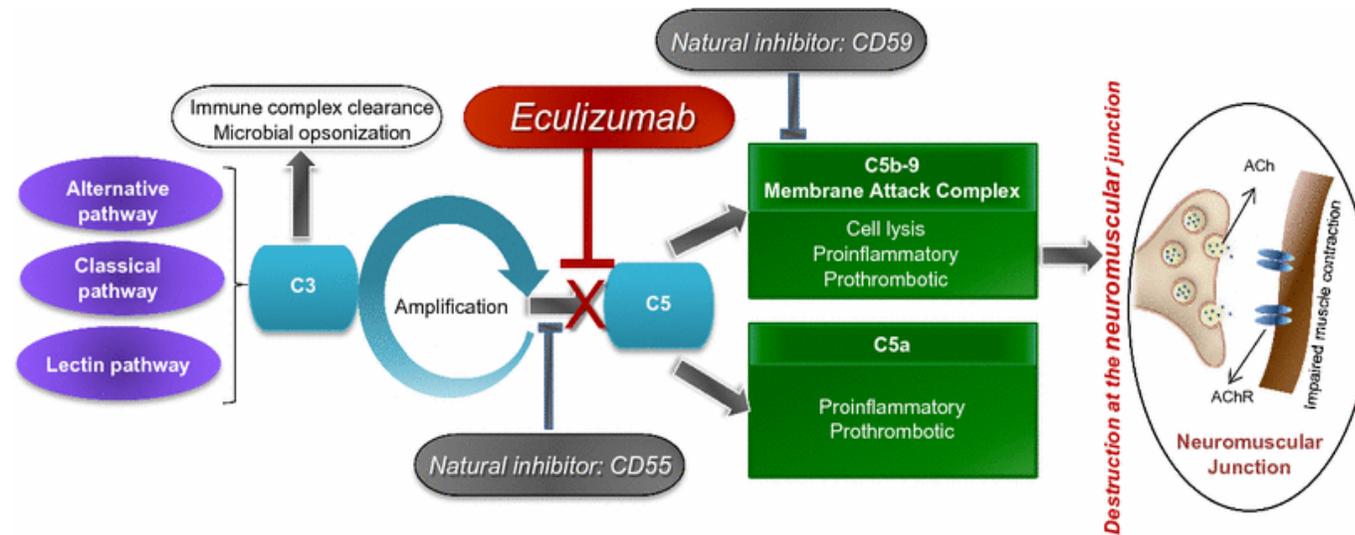
- Eculizumab

Dosage and titration:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

Monitoring:

- C5b-9 complex, every 3 months for the first year and then annually thereafter
- Renal function
- Full blood count
- Lactate dehydrogenase

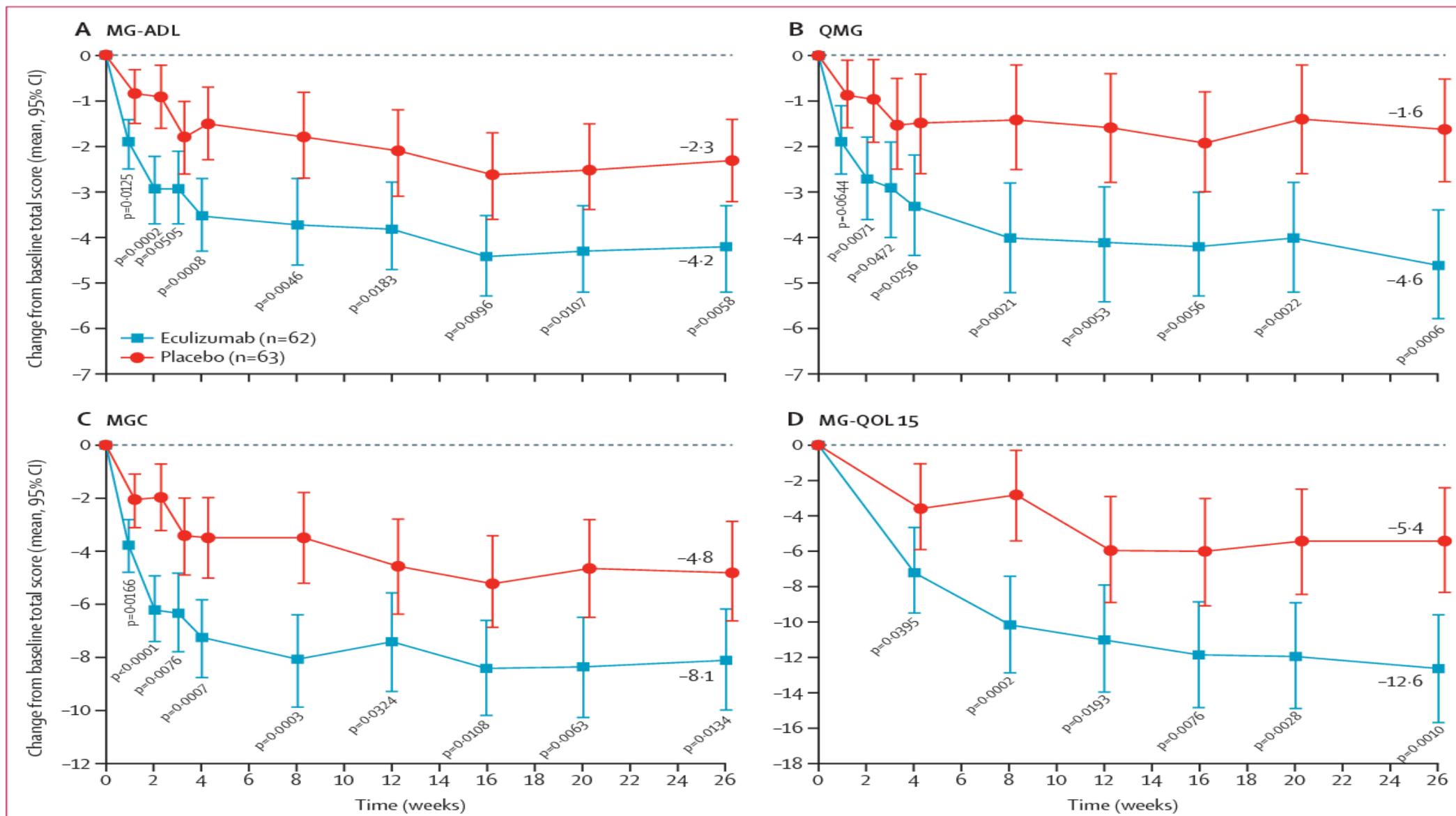


Side Effects:

- Hypertension
- Headache
- Leukopenia
- Anemia
- Hemolysis
- GI upset
- Nasopharyngitis
- Prone to Infections

- Haptoglobin
- Urinalysis
- Urine Protein/Creatinine ratio
- Meningococcal vaccine to be given before it

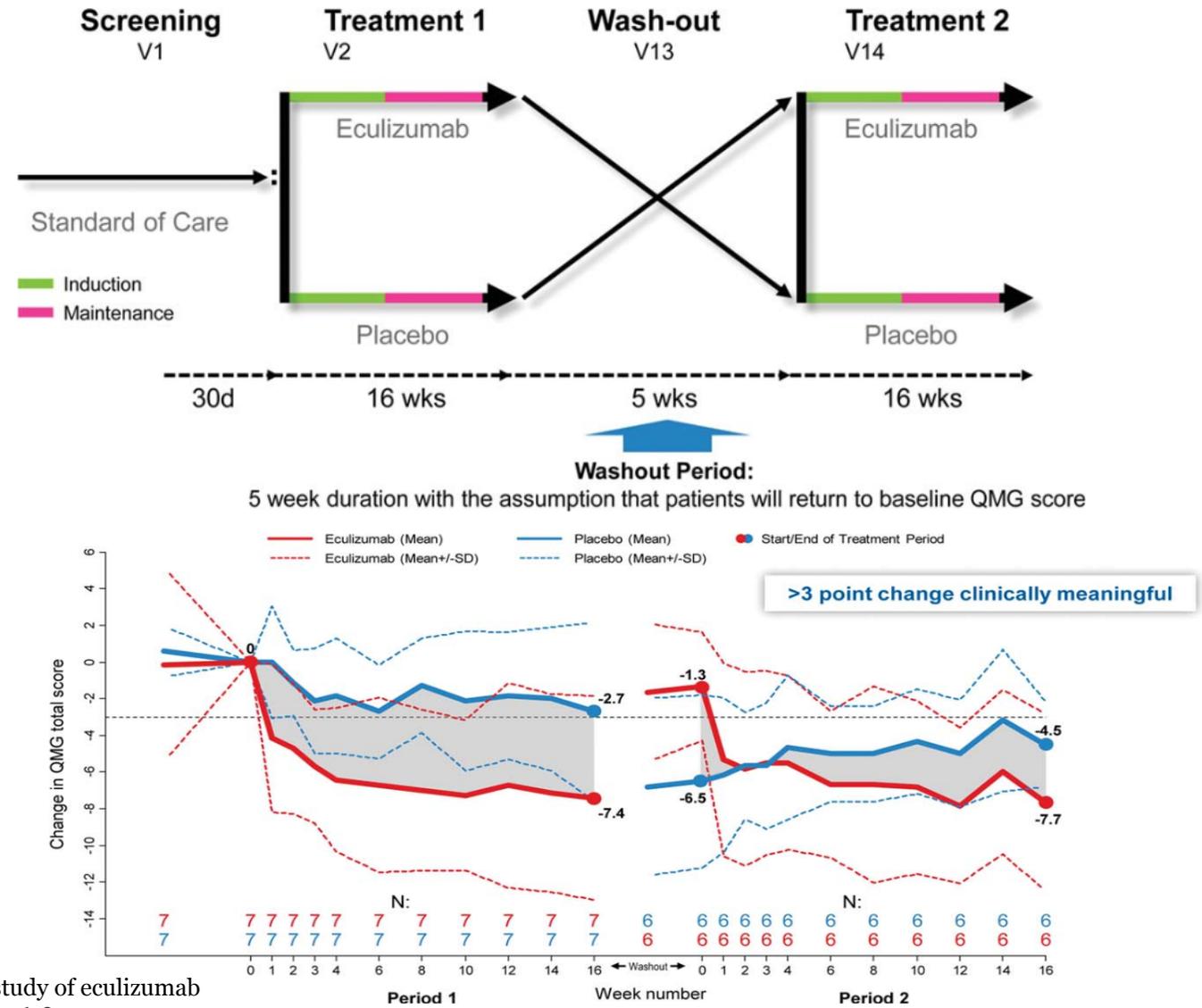
Eculizumab:



Howard, James F et al. "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." *The Lancet Neurology* 16 (2017): 976-986.

Eculizumab in MG

- This study was a randomized, double-blind, placebo controlled, crossover trial involving 14 patients with severe, refractory generalized MG (gMG).
- Examining both treatment periods, the overall change in mean QMG total score was significantly different between eculizumab and placebo ($P < 0.0001$)



Howard Jr, James F., et al. "A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis." *Muscle & nerve* 48.1 (2013): 76-84.

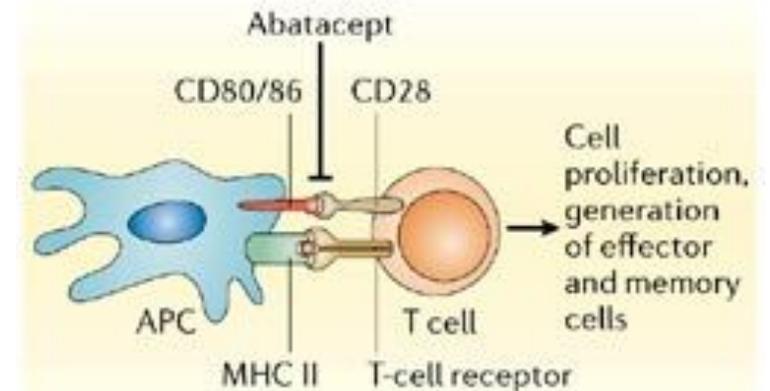
FIGURE 2. Breakdown of total QMG score reduction by treatment.

NMDs and Pregnancy:

- The risk of generalized MG is highest in the first 2 to 3 years after onset. During these years, it is advisable for a patient to delay pregnancy, thereby reducing potential worsening.
- Corticosteroids, plasma exchange, and IV immunoglobulin (IVIg) have been used safely during pregnancy and are agents often chosen for treatment of exacerbation of weakness.
- Prednisolone, and IVIG are pregnancy category C. All have been used frequently during pregnancy in many other autoimmune diseases.
- Increase in cleft palate with use of prednisone in the first trimester and premature rupture of membrane with high doses is also noticed.
- Azathioprine and Cyclosporin can be used in highly difficult situation with low risk.

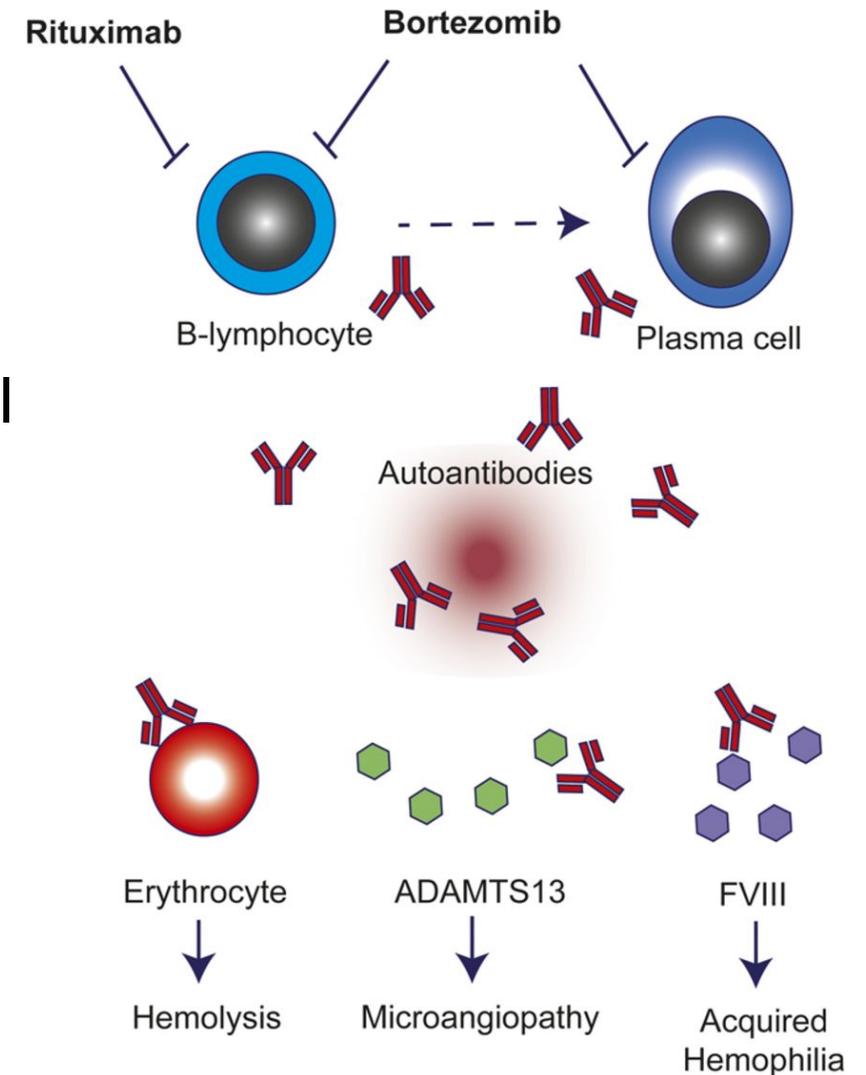
Abatacept

- Abatacept (Co-stimulation Modulator CTLA4) is a new agent which targets T-cell activation.
- cytotoxic T-lymphocyte protein 4 (CTLA-4) is a co-inhibitory molecule expressed on CD4+ T cells upon activation, which also binds CD80 and CD86, and plays a critical role in the down regulation of antigen-activated immune responses.
- This pathway can be blocked using abatacept, which binds to CD80/CD86 and blocks both activating (CD28) and inhibitory signals (CTLA-4).
- Abatacept has been tested and is found to be effective and safe, and is currently used for treatment of rheumatoid arthritis (RA) ; however, importantly, it failed to show efficacy in early-phase trials in multiple sclerosis (MS) and ulcerative colitis
- pilot research study is being done to determine its role in NMD especially MG
- 2017- 2020 in USA



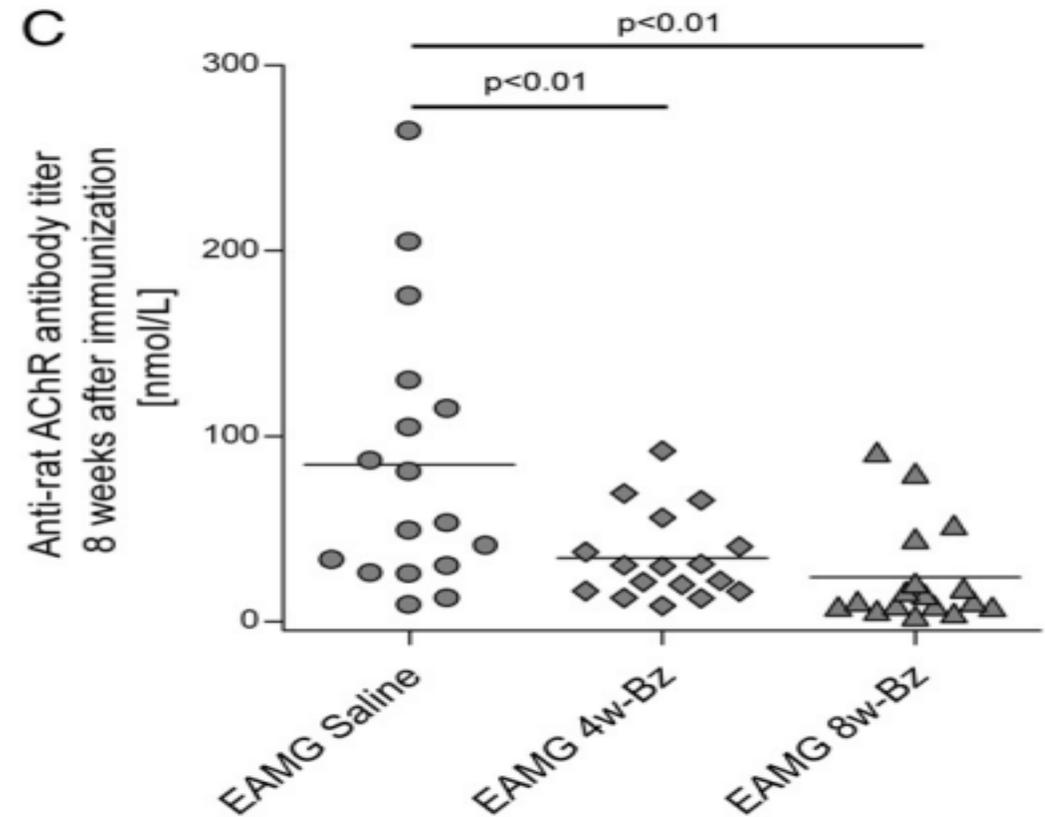
Bortezomib

- Bortezomib is a small-molecule proteasome inhibitor. By this activity in plasma cells, it disrupts proteolytic pathways leading to protein accumulation within plasma cells and ultimately cell death.
- Indicated for the treatment of patients with multiple myeloma and mantle cell lymphoma.



Bortezomib

- In an experimental model of MG, Bortezomib given twice a week s.c. injections (0.2 mg/kg in saline)
- Apoptosis in bone marrow cells ensued and reduced the amount of plasma cells in the bone marrow by up to 81% was found.
- It efficiently reduced the rise of anti-AChR autoantibody titers, prevented ultrastructural damage of the postsynaptic membrane and decreased myasthenic symptoms.



Therapy targeting B-cell activating factor (BAFF) in myasthenia gravis

- B-cell activating factor (BAFF) is important in the differentiation and maturation of B cells and plasma cells. Although the mechanism(s) by which BAFF and its receptors help regulate B-cell function and tolerance is not known, it may play a significant role in the immune process involved in myasthenia gravis.
- **Belimumab** is a monoclonal antibody that inhibits BAFF and has been approved for the treatment of SLE.
- BAFF levels are increased in patients with autoimmune MG. Current data suggest that BAFF is likely to play a role in the pathogenesis of MG by promoting the survival and maturation of autoreactive B cells.

Belimumab

- Belimumab binds to soluble BAFF and reduces B-cell activation and differentiation into antibody-producing plasma cells.
- B cell numbers are also reduced but not nearly to the extent observed with anti-CD20 monoclonal antibodies, such as rituximab.
- An international, phase II study of belimumab to assess its efficacy in patients with AChR and MuSK MG with generalized disease is ongoing.

