Plasma Exchange in Neurological Disorders

Focus on Myasthenia Gravis and Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Sherry Shariatmadar, M.D.
Director, Transfusion Medicine and Apheresis Services
North Shore University Hospital at Northwell Health
Manhasset, NY

Northwell Health℠

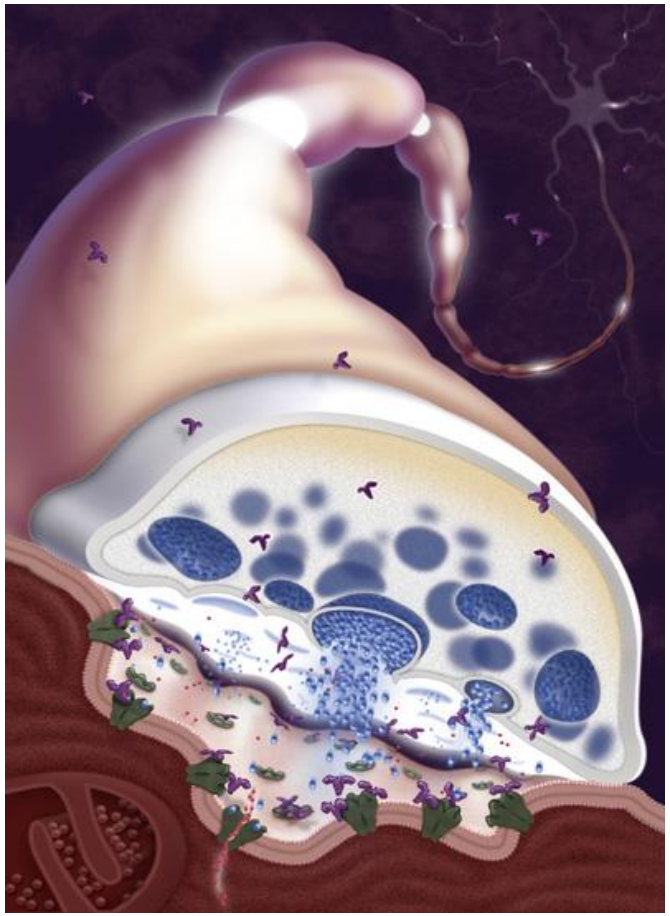
Objectives

- Myasthenia Gravis
    - Background
    - Plasma Exchange and other therapeutic options

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
    - Background
    - Plasma Exchange and other therapeutic options

Myasthenia Gravis

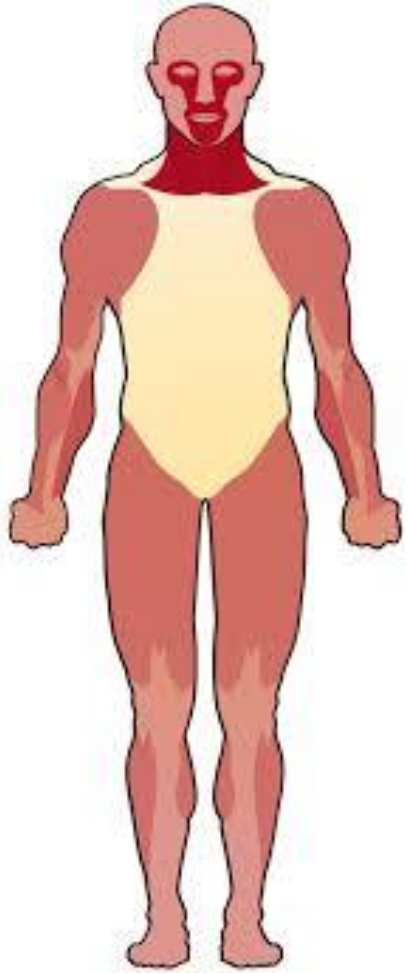
- Autoimmune disorder causing post synaptic neuromuscular junction dysfunction, leading to fluctuating weakness of skeletal muscles
- Diagnosed through clinical findings, serum antibodies and electrodiagnostic tests
- Treated with a wide variety of therapies, most immunomodulatory



Myasthenia Gravis

Ocular vs Generalized

- Ptosis/Diplopia, proximal limb weakness, jaw fatigue, Dysphagia, Dysarthria, Dyspnea



Generalized Myasthenia Gravis - serostatus

- Acetylcholine receptor (AChR) antibodies – 85%
- Muscle specific kinase (MuSK) antibodies – 5%
- Lipoprotein receptors-related protein (LRP4) Antibodies – 3%
- Seronegative- 7%

Thymomatous vs non-thymomatous

- 10% of those with AChR antibodies have thymoma

Generalized Myasthenia Gravis – Current Treatment Options

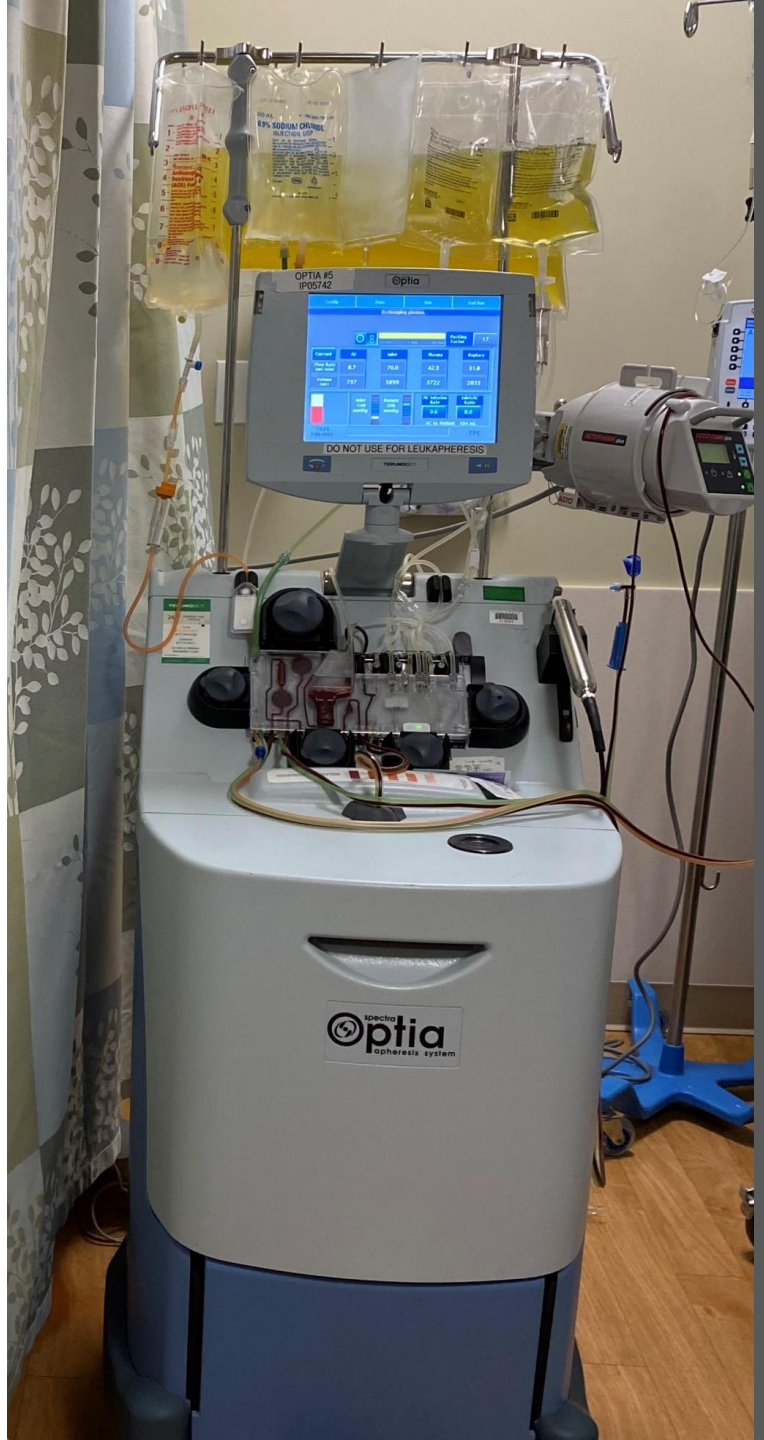
Symptomatic	"Cornerstone"	Rapid Acting/ Rescue Therapies	Steroid Sparing Therapies	Other Maintenance Therapies	
Pyridostigmine	Corticosteroids	Plasma Exchange	Azathioprine	Rituximab	Thymectomy
		IVIG	Mycophenolate	Eculizumab Ravulizumab	
			Cyclosporin Tacrolimus Methotrexate Cytoxan	Efgartigimod	

Northwell Health℠

Treatment Goal: Remission or minimal manifestations with minimal medication side effects

Plasma Exchange (PLEX) in Myasthenia Gravis

- Lack of placebo-controlled studies
- Proven efficacy based on large body of evidence (observational studies, case series) in acute disease and prior to thymectomy (supported by MGFA, EFNS, ASFA)
  - Removes autoantibodies
  - Immunomodulatory changes



Northwell Health℠

American Society for Apheresis (ASFA) Categories

ASFA Category	Definition
I	Primary treatment, either stand-alone or in conjunction with other therapies
II	Secondary treatment, either stand-alone or in conjunction with other therapies
III	Role of apheresis is uncertain, and decision-making should be individualized
IV	Evidence demonstrates apheresis to be ineffective or harmful

Northwell Health

Padmanabhan A. J Clin Apher 2019

TABLE 3 Grading Recommendations, Strength and Quality of Evidence

Recommendation	Description	Methodological Quality of Supporting Evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low- quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT = Randomized controlled trial

Adopted from Guyatt, 2006; 2008.

ASFA Recommendations for PLEX in Myasthenia Gravis

Acute-short term treatment for moderate to severe disease

Category I (recommendation grade 1B)

- Myasthenic Crisis
- Acute exacerbations, esp. with bulbar or severe generalized symptoms
- Prior to thymectomy with unstable disease

  -Shorter ICU stay, less time on ventilator in patients who underwent PLEX prior to thymectomy surgery (Kamel, 2019)

Long-term treatment: Category II (recommendation grade 2B)

- Maintenance therapy in refractory MG

Northwell Health

Padmanabhan A. J Clin Apher 2019

PLEX in Myasthenia Gravis

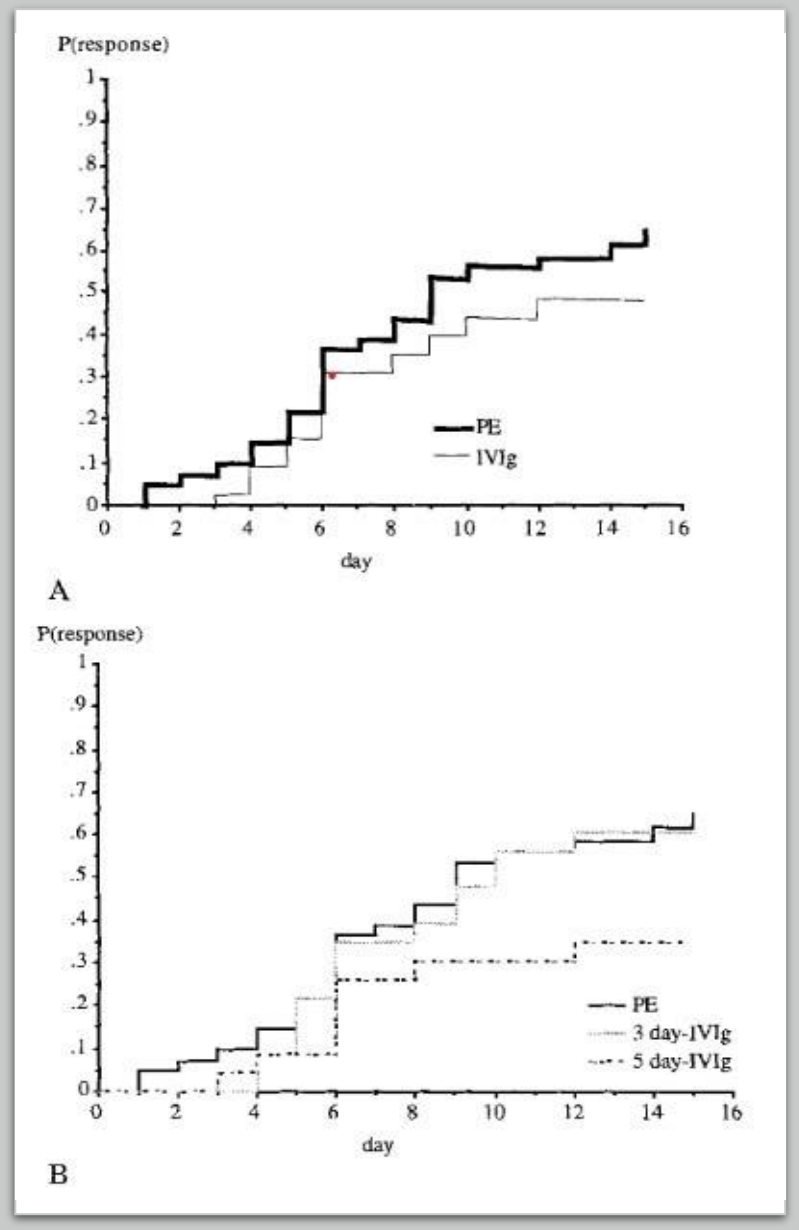
- Volume treated: 1-1.5 plasma volume
- Replacement Fluid: 5% albumin
- Frequency:
  - Acute attack/exacerbations
    - i- 3-6 PLEX over 10-14 days
    - ii- Clinical effect with in 24 hours to 1 week
    - iii- Response usually lasts a few weeks, needs concurrent IS therapy
- Maintenance therapy: Individually adjusted
    - i- Weekly to biweekly
    - ii- 3 procedures in a week every month

PLEX vs IVIG in Myasthenia Gravis

Gajdos P, Ann Neurol 1997

- Prospective randomized trial
- Comparison in MG exacerbation in 87 patients
- PLEX x 3 or IVIG 1 gm/kg over 3-5 days

- No difference in functional outcomes on day 15
- Onset of improvement faster with PLEX in MG crisis



Northwell Health

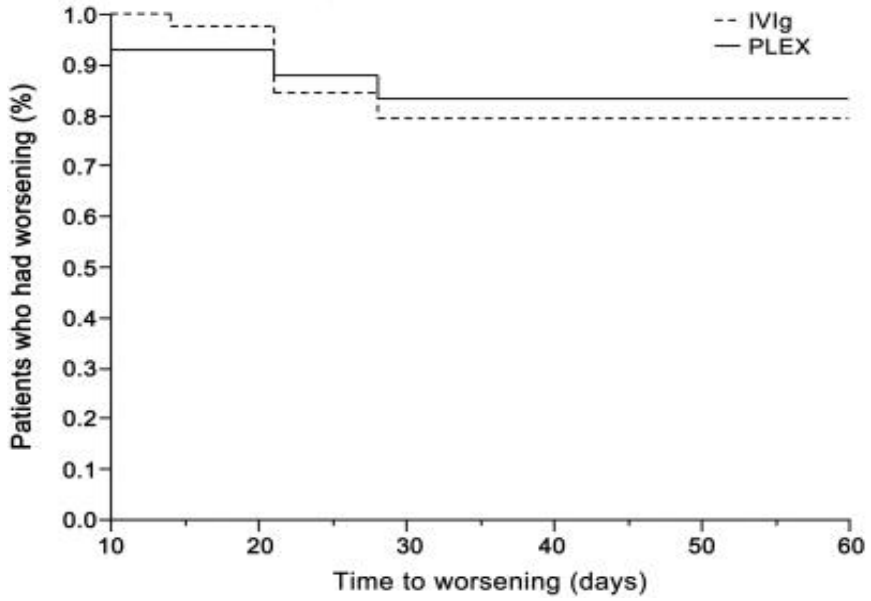
PLEX vs IVIG in Myasthenia Gravis

Barth D, Neurology 2011

- 84 patients with moderate-severe MG randomized to IVIG 2 gm/kg over 2 days vs PLEX (1 plasma volume exchange) x 5.
- Evaluated for efficacy (QMG score) at 14 days and followed for 60 days after treatment
- Similar proportion and duration of improvement noted in both groups (69% of IVIG and 65% of PLEX patients improved)

Table 2 Mean ± SD change in QMGS for disease severity from baseline to days 14, 21, and 28[a]

	IVIg (n = 41)	PLEX (n = 43)	p Value[b]
Baseline QMGS	14.2 ± 4	14.4 ± 3.8	0.83
Δ QMGS			
Day 0-14[c]	3.2 ± 4.1	4.7 ± 4.9	0.13
Day 0-21	3.3 ± 3.6	5.3 ± 5.5	0.07
Day 0-28	2.6 ± 4.0	4.7 ± 5.7	0.08



Northwell Health

PLEX vs IVIG in Myasthenia Gravis

- PLEX and IVIG are considered equally effective for patients with acute MG and prior to thymectomy
- Choice of PLEX or IVIG is often dictated by presence of comorbidities, and practical factors such as availability/convenience
  - PLEX preferred treatment in MG crisis (respiratory impairment, ventilator dependent or unable to swallow without risk of aspiration) due to more rapid onset of action
  - PLEX also preferred in patients with MuSK antibodies (IgG4)
- Limited comparative data in maintenance therapy- Considered equally effective

Alipour- Faz A. Acta Neurol Belg 2017
Quereshi AI. Neurology 1999
Guptill JTT. Muscle Nerve 2011
Ronager J. Artif Organs 2001

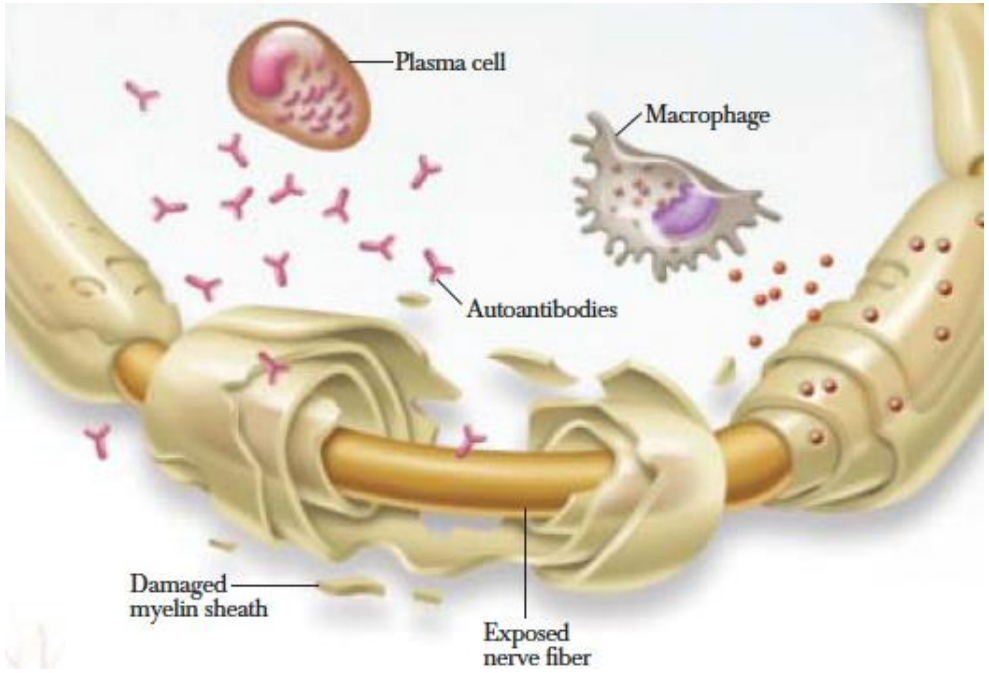
Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

- Acquired immune-mediated peripheral neuropathy, typically characterized by proximal and distal symmetrical weakness, areflexia and disease progression that continues beyond 8 weeks.
- CIDP variants (distal, focal, multifocal, sensory, motor)
- Diagnosed through clinical findings, supported by electrodiagnostic and ancillary studies
- Treatment with immunomodulatory therapy

Northwell Health™

CIDP

- Exact immune targets not known
  - Cellular and Humoral immune responses
  - Autoantibodies (IgG4) to Proteins near or at the node of Ranvier (10% of the patients)
    - Neurofascin-155 and 186
    - Contactin-1 and Contactin-associated protein 1 (CASPR1)



Northwell Health

CIDP – Induction Therapy

First Line Therapy

(Proven Efficacy)

- IV immunoglobulin (IVIG)
- Corticosteroids
- PLEX

Second-line Therapies

Used when failure of first line therapy

(If still likely CIDP)

- Rituximab
- Cyclophosphamide
- Cyclosporin

Northwell Health℠

Van den Bergh PYK. J Peripher Nerv Syst 2021

PLEX in CIDP

Prospective double blind, sham controlled trial of PLEX vs sham PLEX 2x/week for 3 weeks, showed significant improvement with PLEX, improvement waned in 2 weeks (Dyck, 1986)

Crossover, sham-controlled, prospective trial demonstrated the benefits of PLEX (80% with substantial improvement in neurological function after 10 exchanges) although 66% relapsed within 1-2 weeks (Hahn 1996)

Prospective, crossover trial of PLEX vs IVIG for 6 weeks resulted in significant neurological improvement with no significant difference between the two therapies (Dyck, 1994)

CIDP Treatment- Induction

Induction Therapy (proven efficacy)

- Corticosteroids
- IV Immunoglobulin (IVIG)
- Plasma Exchange (PLEX)

- Should be started early to prevent permanent disability (60-80% response)
- Response based on improvement and stabilization of symptoms
- Maintenance therapy required in 40-60%

CIDP Treatment- Induction

- Initial choice based on presence of comorbidities, adverse effects, availability and convenience
- IVIG generally favored if available and no contraindications
  - IVIG treatment of choice for motor CIDP- deterioration with corticosteroids
- Consider PLEX in those with suboptimal response or intolerance to IVIG and/or corticosteroids or **in a rapidly worsening patients**
  - Removal of antibodies, cytokines, complement
  - ASFA recommendations: Category I (recommendation grade 1B)
  - 1-1.5 plasma volume with 5% albumin
  - 2-3/week until improvement, then tapered e.g., weekly or monthly

CIDP – Maintenance Treatment

Maintenance Treatment

- Corticosteroids
- IVIG or SC immunoglobulin (SCIG)
- Plasma Exchange (PLEX)

Once plateau is achieved

Periodically reduce dose/frequency

- Try to stop treatment in remission
- Restart if deterioration (active disease)

Consider one of the following as a corticosteroid sparing, IVIG dose/frequency reducing or to wean off PLEX

- Mycophenolate
- Azathioprine
- Cyclosporin

Summary

- Plasma exchange plays an important role in the treatment of myasthenia gravis and chronic inflammatory demyelinating polyradiculoneuropathy
- Other therapeutic options may provide similar efficacy
- The choice of therapy is often dictated by presence of comorbidities, availability and convenience
- Therapy should be based on evidence-based review of the literature

- Thank you

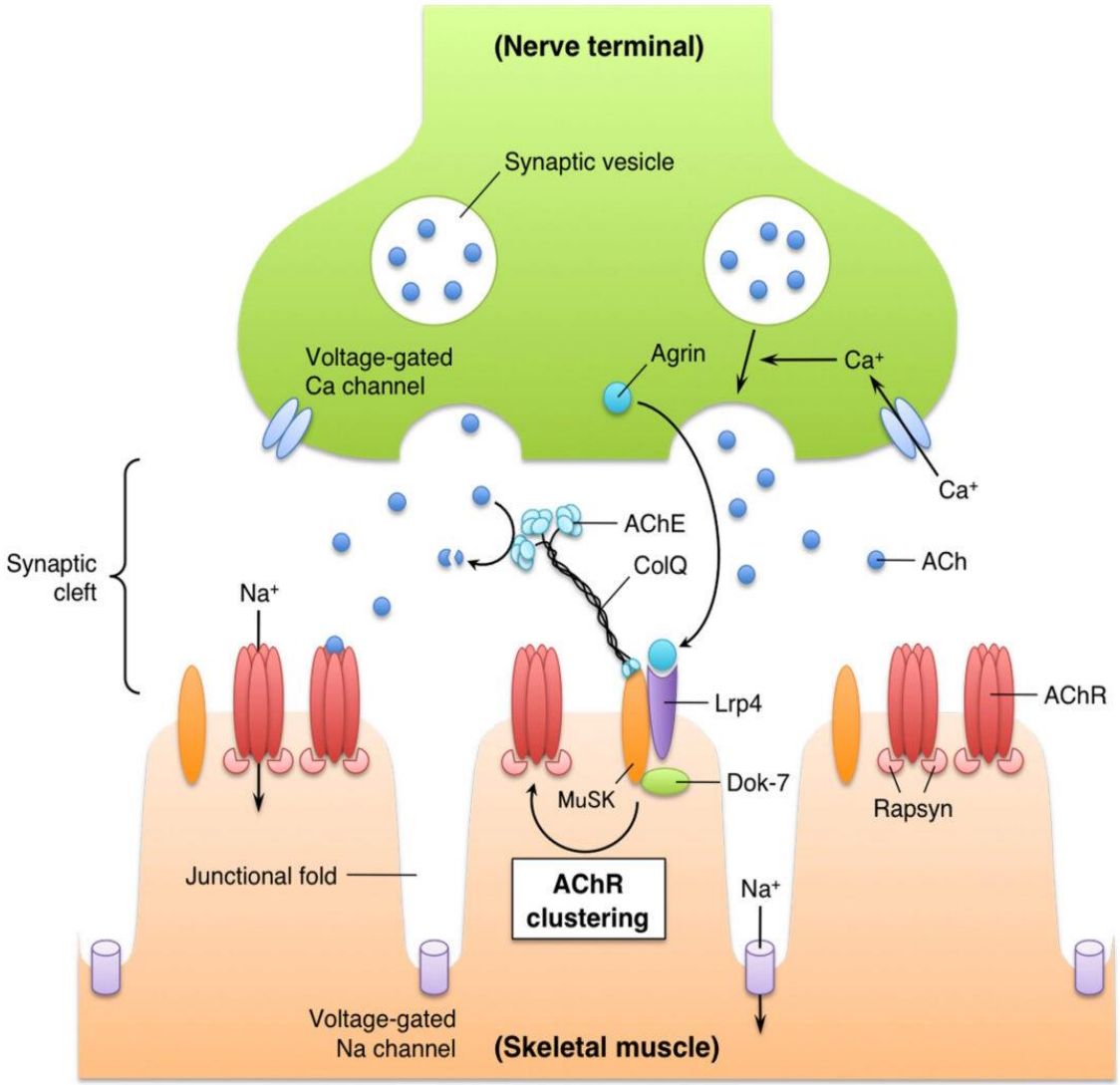
Northwell Health℠

MG Treatment Goal

- To Achieve :
  - Remission (no clinical symptoms or physical findings) or minimal manifestations
  - Minimal side effects with medication

- Choice of therapy is based on severity of the disease, co-morbid diagnosis, and antibody status

Myasthenia Gravis



AChR Antibodies:

- Functional blockade of AChR
- Crosslinking/Internalization of AChR
- Complement activation, loss of integrity of neuromuscular junction

MuSK and LRP4 Antibodies:

- Decrease clustering of AChR at Neuromuscular junction

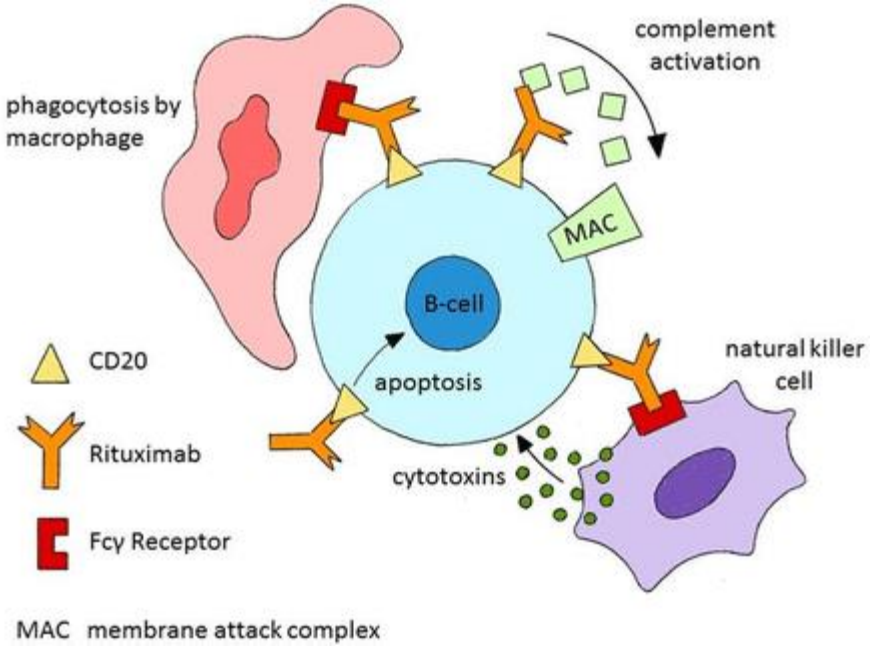
PLEX vs IVIG in Myasthenia Gravis

Ipe TS et al. A systematic literature review and meta-analysis of comparative evidence. Front Neurol 2021

- Medline and Cochrane library data bases 1997-2017
- 165 articles reviewed, 64 included for systematic literature and 11 for meta-analysis
- Higher response rate with PLEX than IVIG in acute MG and those undergoing thymectomy
- No difference in mortality between the 2 groups

Targeted Therapies: Rituximab

- Anti-CD20 agent- Monoclonal antibodies that bind to cell surface receptors on activated B cells, reducing pathogenic antibodies that attack NM junction
- BEAT MG study did not how benefit over 12 months in generalized AChR ab+ MG
- Blinded prospective review suggests benefit in MuSK+ MG
- International consensus guidelines (2020):
  - Consider early in MuSK antibody+ MG
  - May be used for refractory AChR antibody+ MG
- Time to therapeutic effect is ~3-6 months.

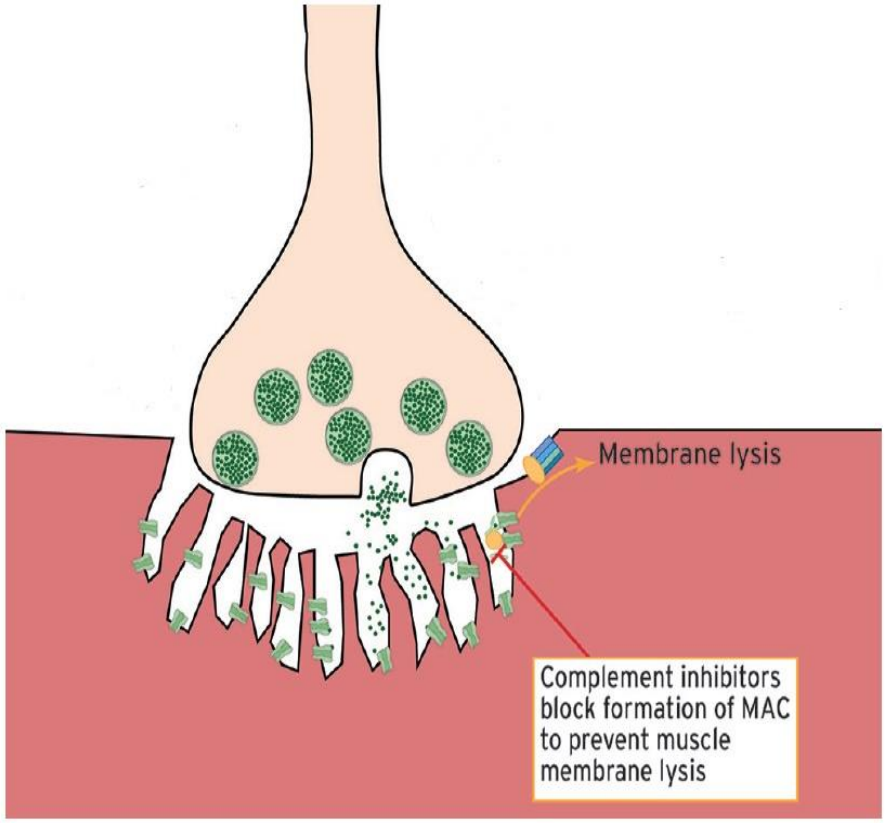


Northwell Health™

Nowak RJ et al Neurology 2022

Targeted Therapies: Complement inhibition: Eculizumab and Ravulizumab

- Monoclonal antibodies prevent cleavage of C5 into C5a and C5b
- REGAIN and CHAMPION Studies:
  - Effective in treating AChR+ generalized MG (IgG1/IgG3)
  - Not effective for MuSK MG (IgG4)
    - PLEX more effective in MuSK MG, also early rituximab
- Risks: Meningococcal infections, requirement for vaccination
- Expensive therapy: Used in refractory AChR+ MG unresponsive to multiple other therapies.



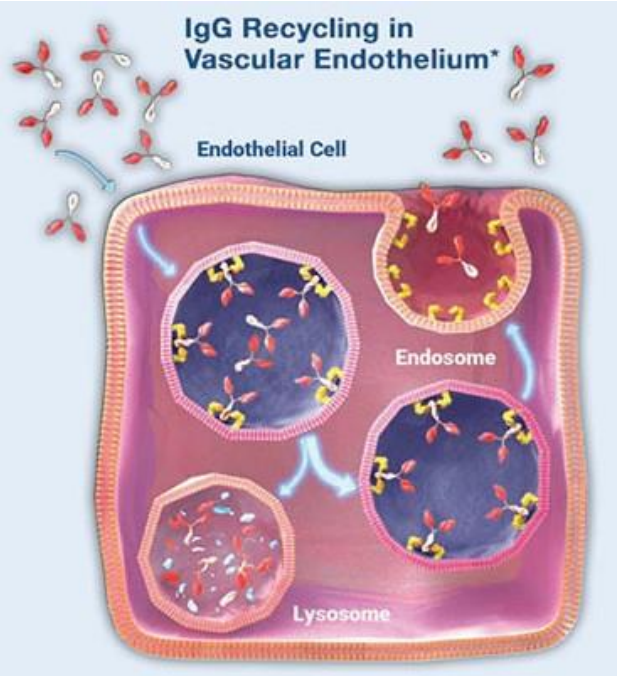
Howard JF Lancet Neurol 2017
Vu T Neurology 2022

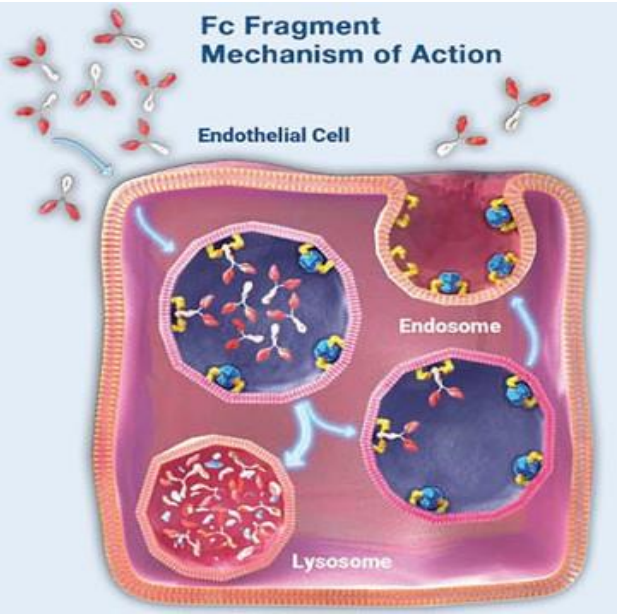
Northwell Health

Targeted Therapies: FcRn inhibition - Efgartigimod

- FcRn receptors known to extend the half life and availability of pathogenic antibodies
- FcRN inhibitors bind with high affinity to FcRn receptors, lead to degradation of unbound IgG including pathogenic IgG

- ADAPT trial: Efgartigimod shown to be effective in treating AChR+, LPR4 antibody+, and seronegative MG
  - 84% response within 2 weeks/ 4 weekly infusions
  - FDA Approved December 2021
  - Expensive: Used in refractory MG unresponsive to pyridostigmine, corticosteroids and IS medications





Howard et al. Lancet Neurol 2021