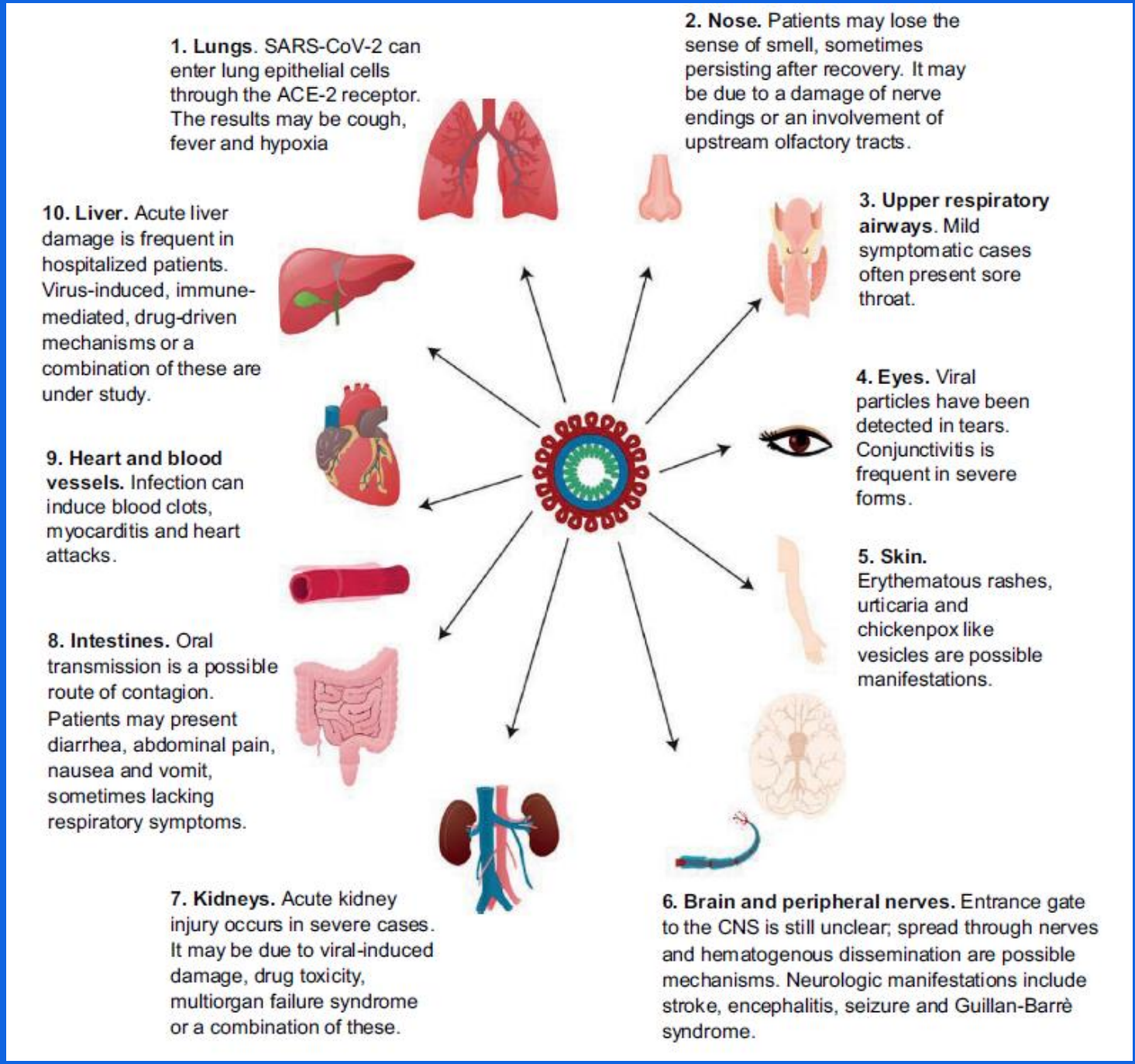
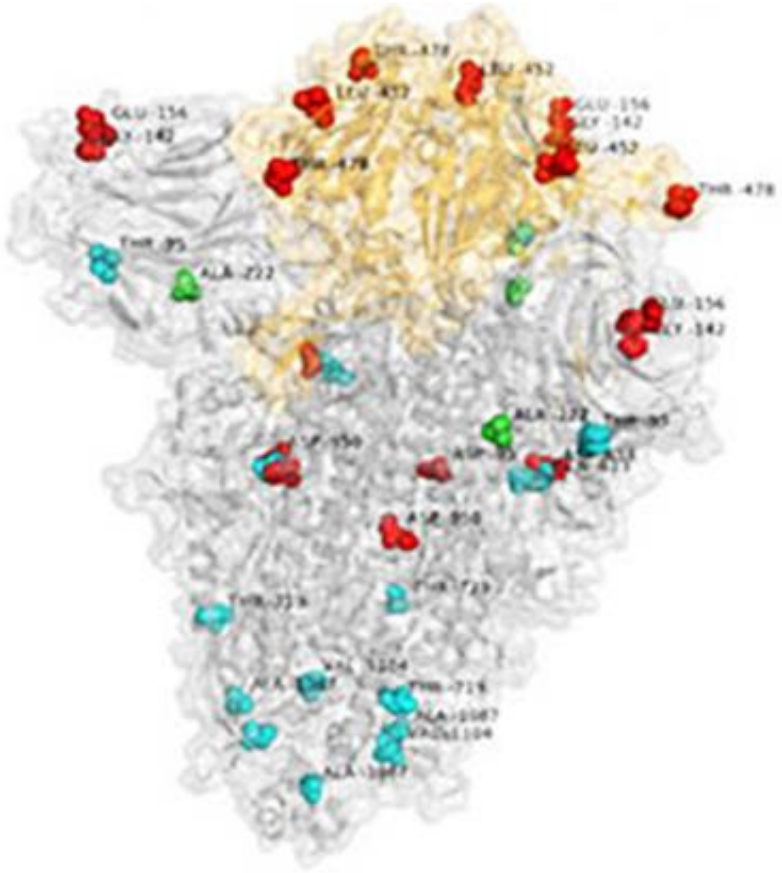
Myasthenia Gravis, COVID19 and New MG Treatment

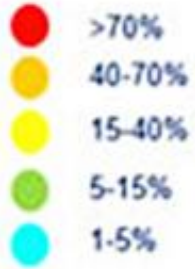
COVID virus affects more than one body part, not just lungs.



Delta

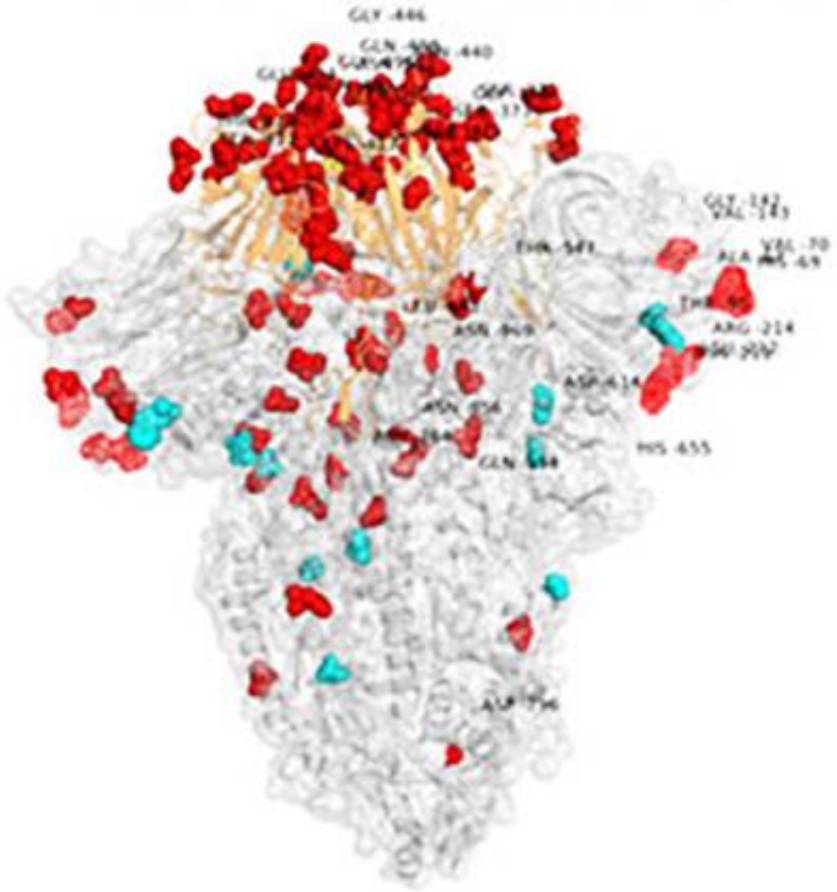
18 aa mutated residues in the Spike protein



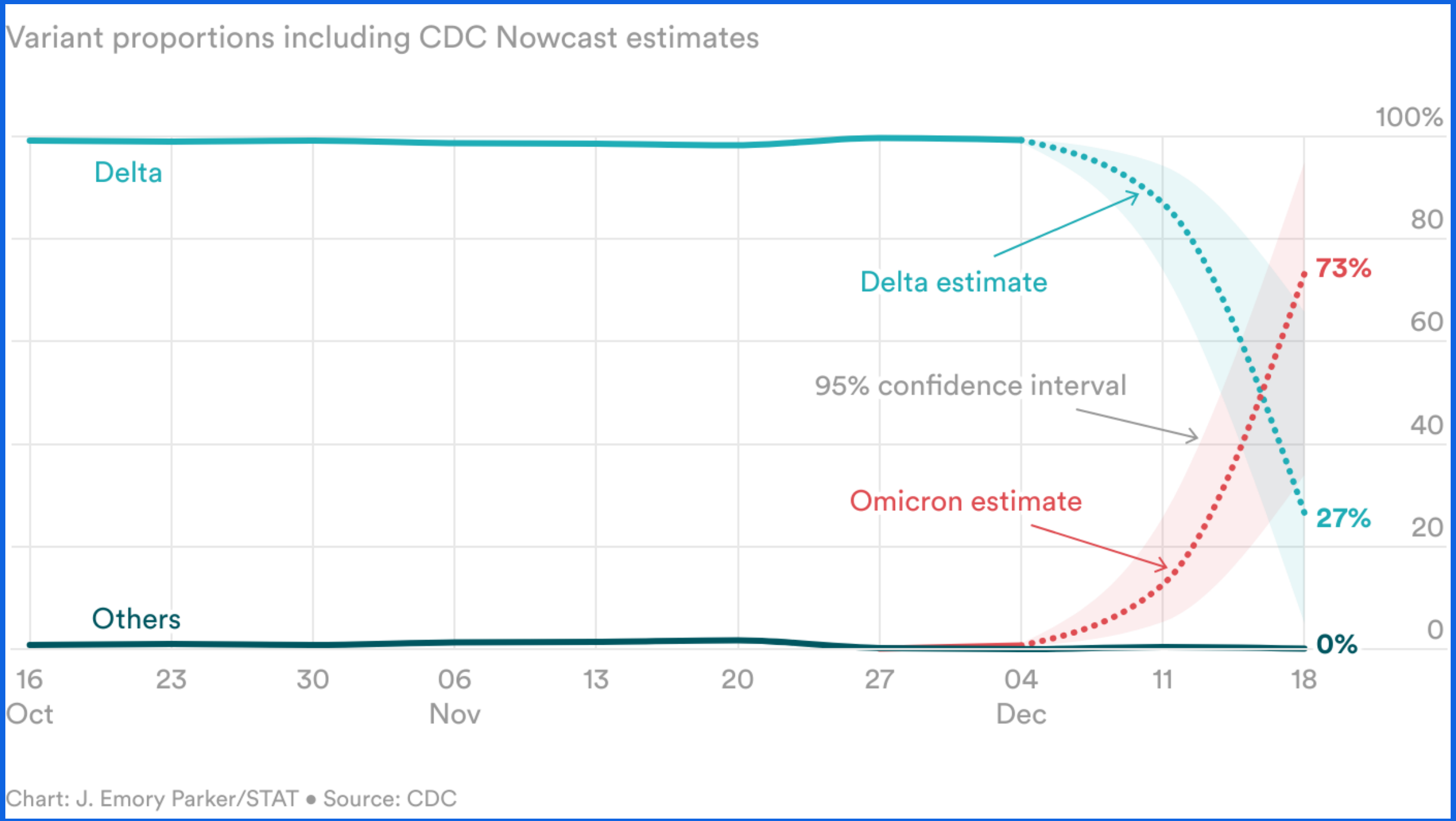


Omicron

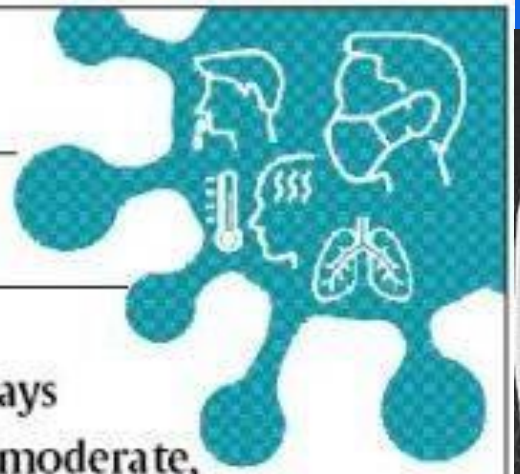
43 aa mutated residues in the Spike protein



The structure of SARS-CoV-2 spike protein showing the active site in orange and the residues coloured against different mutational rate


Variant proportions including CDC Nowcast estimates
Delta
Others
Delta estimate
95% confidence interval
Omicron estimate
73%
27%
0%
100%
80
60
40
20
0
16
23
30
06
13
20
27
04
11
18
Oct
Nov
Dec
Chart: J. Emory Parker/STAT • Source: CDC

HOW THE VARIANTS DIFFER



DELTA

SYMPTOMS last about 10 days

HIGH FEVER, 101-103F

LOSS of smell (anosmia) and taste (ageusia)

LUNG ENTRY within couple of days of infection

HYPER IMMUNE response in the second week of infection in some

BREATHING is difficult, pain in the chest

OXYGEN saturation levels fall

LUNG DAMAGE visible in CT scan

MOST PATIENTS were unvaccinated, breakthrough infection occurred mostly in healthcare workers

OMICRON

SYMPTOMS last about 4-5 days

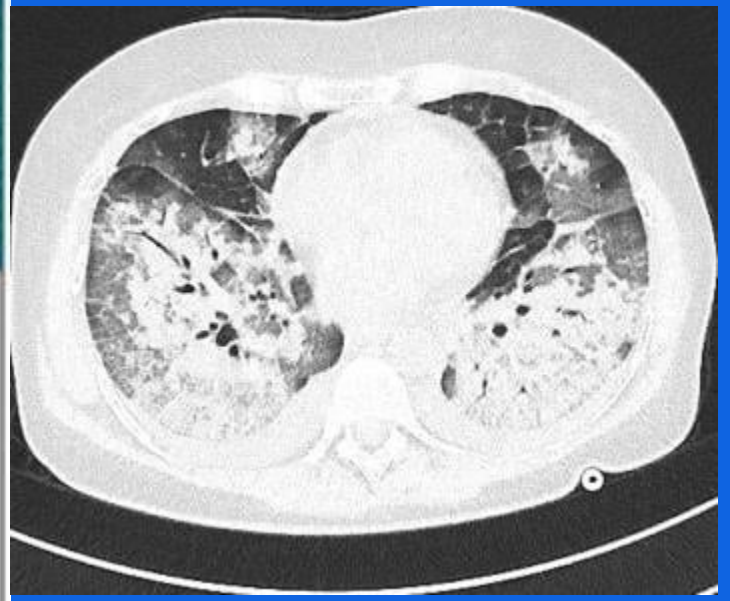
FEVER: Low to moderate, 99.5-100F EXTREME fatigue

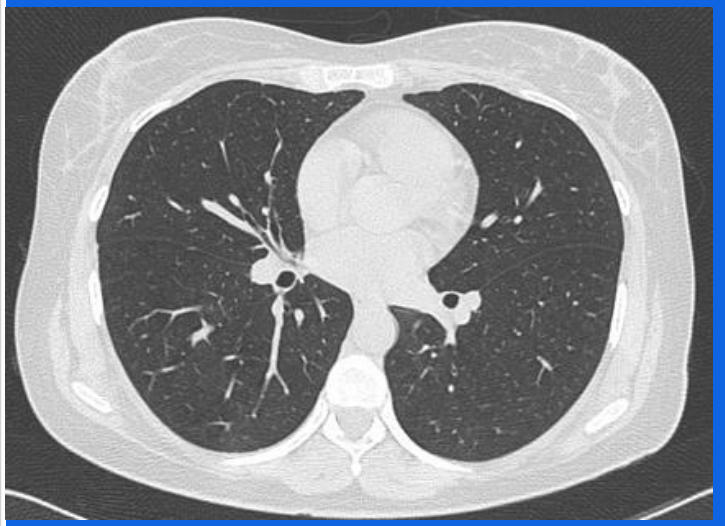
DIZZINESS and nausea

NO LUNG pneumonia or apparent damage reported so far

MOST patients were fully vaccinated, breakthrough infection rates very high

Based on broad clinical observations; specific cases will differ. Older or immunocompromised patients and those with comorbidities are impacted more, and are at greater risk of more severe disease in all cases.





How do COVID19 influence myasthenia gravis?

Businaro P, Vaghi G, Marchioni E, Diamanti L, Arceri S, Bini P, Colombo E, Cosentino G, Alfonsi E, Costa A, Ravaglia S, Mallucci G, Ballante E, Franciotta D, Gastaldi M. COVID-19 in patients with myasthenia gravis: Epidemiology and disease course. Muscle Nerve. 2021 Aug;64(2):206-211.

- 162 Italian MG patients (median age, 66 y; interquartile range 41-77; males 59.9%).
- Three patients had probable and eight had probable-COVID-19.
- Of 11 MG patients with probable/confirmed-COVID-19, 3 required ventilator support, and 2 elderly patients died of COVID-19 respiratory insufficiency. Only 1 of11 patients experienced worsening MG symptoms, which improved after increasing steroid dose.

- Conclusion: The risk of COVID-19 in MG patients seems to be no higher than that of the general population, regardless of immunosuppressive therapies. In this cohort, COVID-19 barely affected MG course.

How do COVID19 influence myasthenia gravis?

Solé G, Mathis S, Friedman D, Salort-Campana E, Tard C, Bouhour F, Magot A, Annane D, Clair B, Le Masson G, Soulages A, Duval F, Carla L, Violleau MH, Saulnier T, Segovia-Kueny S, Kern L, Antoine JC, Beaudonnet G, Audic F, Kremer L, Chanson JB, Nadaj-Pakleza A, Stojkovic T, Cintas P, Spinazzi M, Foubert-Samier A, Attarian S. Impact of Coronavirus Disease 2019 in a French Cohort of Myasthenia Gravis. Neurology. 2021 Apr 20;96(16):e2109-e2120.

- Among 3,558 French MG patients, 34 (0.96%) had COVID-19.
- By the end of the study, 28 patients recovered from COVID-19, 1 remained affected, and 5 died.
- Only high Myasthenia Gravis Foundation of America (MGFA) class (≥IV) before COVID-19 was associated with severe COVID-19 ((odds ratio, 102.6, $p = 0.004$).
- Type of MG treatment had no independent effect on COVID-19 severity.

- Conclusion: COVID-19 had a limited effect on most patients, and immunosuppressive medications and corticosteroids used for MG management are not risk factors for poorer outcomes. However, the risk of severe COVID-19 is elevated in patients with high MGFA classes (poorly controlled).

Table 1 Factors conferring a high or very high risk of developing severe COVID-19 complications

Muscular weakness of the chest and/or diaphragm, resulting in respiratory volumes less than 60% predicted
Use of non-invasive or invasive ventilation devices
Presence of tracheostomy
Presence of dysphagia and oropharyngeal weakness (reduced airway clearance)
Primary cardiac involvement
Risk of deterioration with fever, fasting or infection
Risk of rhabdomyolysis with fever, fasting or infection
Concomitant diabetes, obesity, neoplastic diseases, severe cerebrovascular diseases or severe heart diseases (heart failure, ischemic heart disease)

Costamagna G, Abati E, Bresolin N, Comi GP, Corti S. Management of patients with neuromuscular disorders at the time of the SARS-CoV-2 pandemic. J Neurol. 2021 May;268(5):1580-1591. Risk factors of developing more severe COVID symptoms in patients with neuromuscular disorders including MG.

Table 2 Additional risk factors increasing the risk of developing severe COVID-19 disease

Kyphoscoliosis
Highly-active immune-mediated neuromuscular disease
Mild respiratory muscle weakness
Other medical comorbidities: • Pulmonary diseases • Liver diseases • Neutropenia/lymphopenia • Renal diseases/impairment
Older age
Pregnancy (possible)
Concomitant additional neurologic diseases
Dependence from caregivers in hygiene, mobilization and feeding

Would COVID19 itself trigger new-onset MG?

- To date, at least 10 patients of new-onset MG following COVID-19 with the following features:
  - time interval between COVID-19 and MG (5-56 days)
  - mean age 51 years
  - male gender (6)
  - generalized MG (7)
  - Anti-AChR antibodies (9) and anti-MUSK (2)

- Truth: Hard to tell whether COVID has anything to do with the development of MG in these patients, or it is just a coincidence.

Prevention of COVID: What can you do?

- Virtual visit (telemedicine): has many limitations but appropriate for stable MG patients.
- Home infusion option if you are on infusion.
- COVID check of visitors to your house
- COVID vaccination remains effective even in the ear of new omicron variants.
  - Taking California state as an example. Nearly 40 million people.
  - At the end of 2021, vaccination rate of 80.2%, 563,000 patients infected, 76,000 patients died.

Odds	Not vaccinated versus vaccinated	Protection efficacy
Odds of being infected	3.9 higher	79.5%
Odds of being hospitalized	10.1 higher	91%
Odds of dying	16.6 higher	94.3%

Would any vaccination TRIGGER or WORSE myasthenia gravis?

- The overall rate of autoimmune reactions after vaccination is less than 0.01% (1 in 10,000) of all vaccinations worldwide.

- Prior studies revealed that flu and tetanus vaccines are safe for MG patients.
  - No clinical exacerbation
  - No elevation AChR antibody titers.

- A prior Korean study demonstrate that benefits of influenza vaccination outweigh risks
  - The risk of MG exacerbation following influenza vaccination was very low (2 of 258, 1.5%)
  - The risk of MG exacerbation following influenza was higher (10 of 258, 4%).

- Most studies were conducted in the stable MG patients. So patients with unstable MG may not apply.
- Persons with prior-vaccination autoimmune phenomena should be cautious.

Would COVID vaccines TRIGGER or WORSE myasthenia gravis?

- Rare case reports of new onset MG or worsening MG following COVID vaccination.
  - Two new onset MG cases were identified after the second dose of BNT162b2 (Pfizer) vaccine, one being severe. Both occurred within one week of vaccination.
  - A case of MG crisis occurred one week after the second dose of Moderna COVID-19 vaccine. At basaline, the patient's MG is inadequately controlled.
  - These are likely under-reported but the overall incidence of COVID vaccination induced MG is truly small.

- The World Health Organization (WHO) has formulated four basic principles for assessing the adverse events (AEs) of vaccines
  - Consistency
  - Strength
  - Specificity
  - Temporal relation

- The rare case reports preclude a definite association.

Will immunosuppression in MG reduce vaccination efficacy?

- Theoretically, protection rate of vaccination can be lower in immunocompromised than in immunocompetent patients in the following aspects:
  - Magnitude of protection: amount of immune response at any time point
  - Breadth of protection: How many variants can be protected?
  - Persistence of protection: How long can protection last?

- Factors influencing protection rate of immunocompromised patients
  - Older age
  - Type of immunosuppressive medications
  - Vaccine doses and administrative schedules: Immunocompromised patients often require larger doses or frequent administration
  - Timing: better vaccine-mediated protection can be obtained before the initiation of immunosuppressive treatment.

Will immunosuppression in MG reduce vaccination efficacy?

- Study #1: found no significant differences in antibody responses and immune protection from diphtheria and tetanus vaccination in patients with and MG, relative to healthy subjects.
- Study #2: Tetanus revaccination in MG patients showed that immunotherapy slightly reduced pre- and post-tetanus antibody titers, but antibody titers still increased by an average of 6-fold in MG patients.
- Study #3: A post-vaccination seroprotective titer for three strains of seasonal influenza vaccine was 40.4% in MG and 51% in healthy controls, respectively
- Study #4: A 10-year longitudinal study found a significant 48% reduction in mortality and a 27% reduction in hospital admissions after influenza vaccination in patients with autoimmune disorders.
- Bottom line: Somewhat reduced efficacy but vaccinations still have significant protective value against infection.

Will immunosuppression affect COVID vaccination efficacy?

- Di Fusco, Manuela, et al. "Evaluation of COVID-19 vaccine breakthrough infections among immunocompromised patients fully vaccinated with BNT162b2." Journal of medical economics 24.1 (2021): 1248-1260.
  - 1,277,747 individuals received 2 BNT162b2 doses
  - 225,796 (17.7%) were identified as IC (median age: 58 years). The most prevalent IC conditions were solid malignancy (32.0%), kidney disease (19.5%), and rheumatologic/inflammatory conditions (16.7%).
  - A total of 978 breakthrough infections were observed; 124 (12.7%) resulted in hospitalization.
  - IC individuals accounted for 38.2% (N = 374) of all breakthrough infections and 59.7% (N = 74) of all hospitalizations.
  - The proportion with breakthrough infections was 3 times higher in the IC cohort (N = 374 [0.18%]) compared to the non-IC cohort (N = 604 [0.06%]).
  - Organ transplant recipients had the highest incidence rate
  - Incidence rates in older (≥65 years old) IC individuals were generally higher versus younger individuals (<65).

Will immunosuppression in MG affect vaccination efficacy?

- Rituximab is significantly associated with severe immune inhibition. Thus, most guidelines suggest patients on Rituximab should be vaccinated either one month before initiation or 6-8 months after the Rituximab infusion.
  - Some patients on rituximab therapy still developed adequate titers of antibodies against SARS-CoV-2 despite having undetectable B cells.

- Patients on mycophenolate mofetil exhibited significantly lower SARS-CoV-2 antibody titers. However, it is unclear whether this renders patients prone to COVID19 infection or not.

- Prednisone elicited slightly reduced immune response.

- Dosage of medications may matter.

COVID19 specific treatment

- Emergency use authorization (EUA)
- Who need treatment?
  - Patients with mild to moderate COVID-19 and risk factors for progression to severe disease.
  - Not for individuals who have asymptomatic SARS-CoV-2 infection.
- Nirmatrelvir-ritonavir (Paxlovid) is the recommended treatment.
- Monoclonal antibodies and remdesivir (Veklury) are administered intravenously.
- If nirmatrelvir-ritonavir, monoclonal antibody therapy, or are not feasible options, molnupiravir (Molnulup) is an alternative. However, it may not be as effective as the other interventions and there are other safety considerations.

COVID19 specific treatment

- Nirmatrelvir-ritonavir (Paxlovid):
  - The dose is 300 mg nirmatrelvir (two 150 mg tablets) with one 100 mg ritonavir tablet taken together orally twice daily for 5 days.
  - It should be initiated as soon as possible following COVID-19 diagnosis and within five days of symptom onset.
  - Adjustment needed for patient with liver and kidney problems.

- Side effects: loss of taste, diarrhea, high blood pressure, muscle ache

- Nirmatrelvir-ritonavir is contraindicated with many drugs:
  piroxicam, amiodarone, colchicine, clozapine, lurasidone, lovastatin, simvastatin, triazolam, carbamaz epine, phenobarbital, phenytoin, rifampin, St. John's Wort

Peters BJ, Rabinstein AA, DuBrock HM. Use of Remdesivir in Myasthenia gravis and COVID-19. Pharmacotherapy. 2021 Jun;41(6):546-550.
Bhagavan SM, Ramaswamy SB, Govindarajan R. A case report of COVID-19 in refractory myasthenia: Outcome with remdesivir and dexamethasone. Medicine (Baltimore). 2021 May 7;100(18):e25701:

- Four MG patients:
  - A 71-year-old male on mycophenolic acid monotherapy.
  - A 41-year-old female had been diagnosed with MG in 1995. She had undergone thymectomy and was treated with mycophenolate mofetil, prednisone, and pyridostigmine.
  - A 59-year-old male had a recent diagnosis of MG Comorbidities include type 2 diabetes mellitus, sleep apnea, obesity, and asthma. MG therapy included azathioprine, pyridostigmine, monthly infusions of intravenous immune globulin (IVIG), and prednisone.
  - A 77-year-old male with tracheostomy, percutaneous gastrostomy tube, on pyridostigmine, prednisone 40mg daily, mycophenolate 1000mg BID and maintenance plasmapheresis (3 exchanges every 4 weeks).
- All were treated with remdesivir and dexamethasone. No crisis. Patient three were intubated due to COVID and extubated successfully.
- Conclusion: The use of the antiviral remdesivir in combination with dexamethasone did not precipitate a MG exacerbation or crisis.

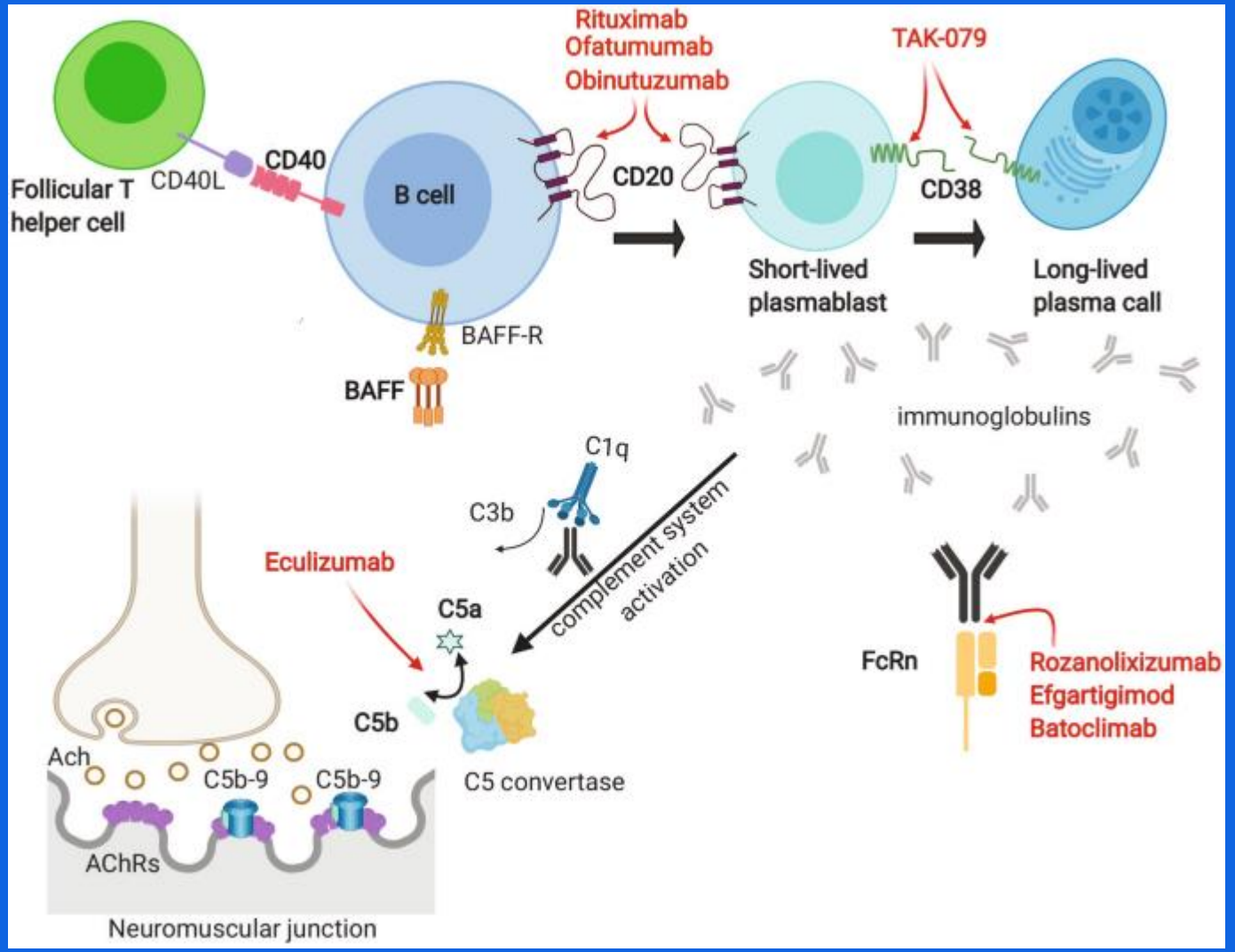
Monoclonal antibody treatment for COVID

- Monoclonal antibodies targeting the spike protein of SARS-CoV-2 can be options for symptomatic outpatients with risk factors for developing severe disease.
-
- Have limited availability, require parenteral administration. However, high-quality data in vaccinated populations are lacking.

- Mutations in the spike protein of SARS-CoV-2 variants may impact the clinical efficacy of monoclonal antibody therapies. The omicron variant only responds to sotrovimab (Xevudy), but not casirivimab-imdevimab (REGEN-COV) or bamlanivimab-etesevimab (from Eli Lily).

- Sotrovimab is available for:
  - Non-hospitalized patients with mild to moderate COVID-19 (eg, not requiring supplemental oxygen)
  - Who have certain risk factors for severe disease
  - Administered as a single 500 mg intravenous (IV) dose
  - Must be given early in the course of illness (<10 days)

New Treatment in Myasthenia Gravis



Eculizumab (Solirius)

- A recombinant humanized monoclonal antibody directed against the human C5 complement.
- Approved for atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH) and AChR+ generalized MG.
- It creates susceptibility to infection from encapsulated bacteria.
- Other common side effects: >10% of patients are headache, myalgia, and arthralgia. Effectively removed by plasmapheresis.

Eculizumab: phase III results

- Howard JF et al. Safety and efficacy of eculizumab in antiacetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol*. 2017;16:976-986.
- 125 patients with refractory AChR antibody + GMG.
  - Have received treatment with two or more immunosuppressive therapies.
  - Or at least one immunosuppressive therapy with IVIG or PLEX given at least 4 times per year
- Randomized to either eculizumab or placebo over an initial blinded period of 26 weeks.
- Primary outcome: change from baseline to week 26 in MG-ADL total score.

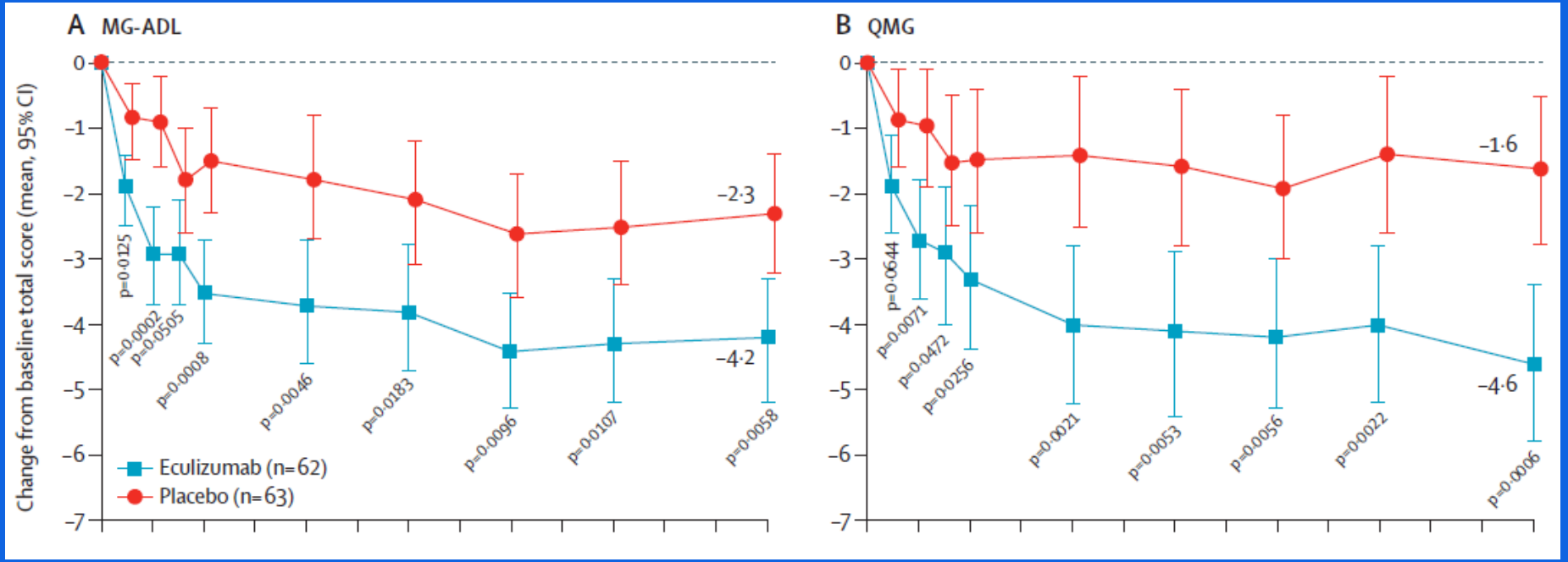
MG-ADL (Activity of Daily Living) Score

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score _____

Eculizumab: phase III results

- All outcome (MG-ADL, MGC and QMG) scores showed significant improvement in the treated group compared with placebo.
- A rapid response within the first 4 weeks in most responders, and all responders demonstrated change by 12 weeks.
- Clinically meaningful improvement is seen in 60% patients.
- In October 2017, approval by FDA for AChR antibody positive generalized myasthenia gravis.
- Expensive

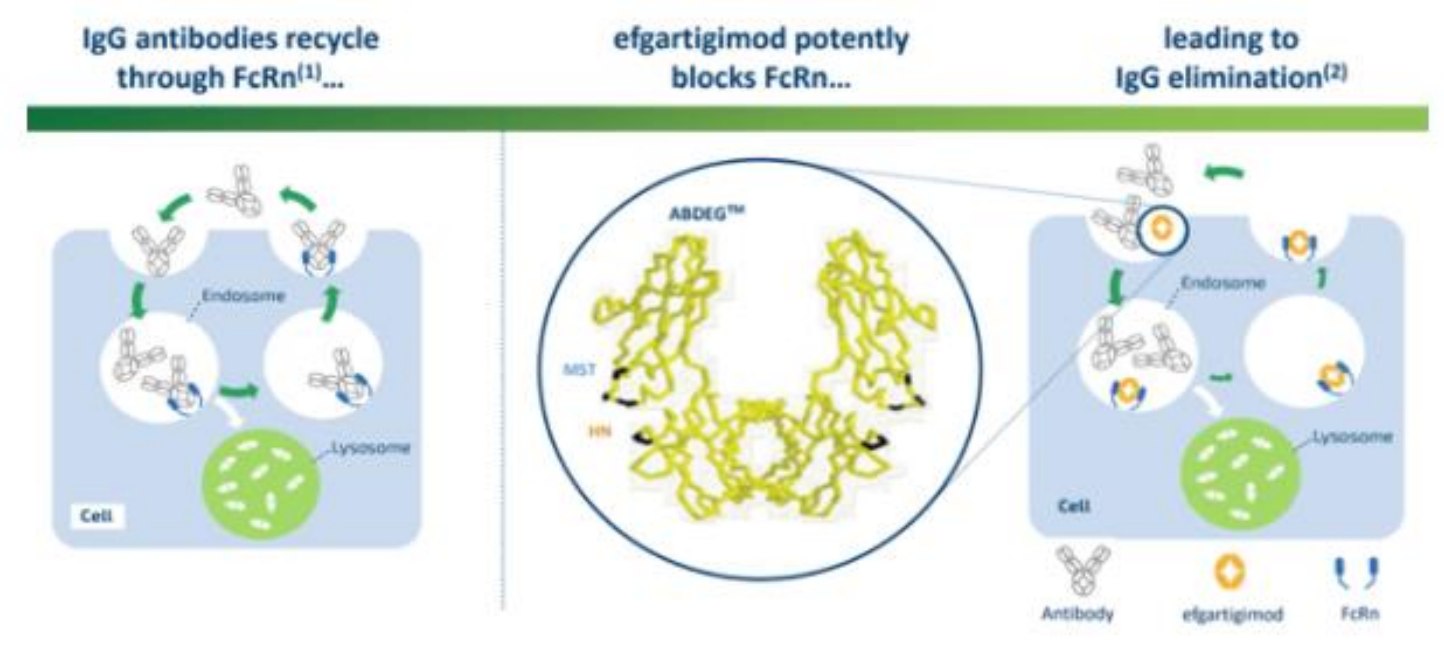


Eculizumab and Meningiococcal Infection Risk

- Associated with a 1000 to 2000-fold increased incidence.
- In trials, 2 of 196 PNH patients and 3 of 130 HUS patients developed serious meningococcal diseases.
- Post approval experience indicated a risk of 0.33 per 100 patient-years.
- MG patients: One had meningococcal infection (not meningitis).
- Instructions on vaccination:
  - MenACWY: 2 doses of MenACu794686WY-DT (Menactra) or MenACWY-CRM (Menveo), interchangeable) at least 8 weeks apart followed by 1 dose every 5 years thereafter if eculizumab is continued. AND
  - MenB: 2 doses of Bexsero (MenB-4C) at least 1 month apart or 3 doses of Trumenda (MenB-Fhbp) at 0, 1-2 months, 6 months. Non-interchangeable. Repeat a dose in one year then every 2-3 years after if eculizumab is continued.

FcRN Therapy

- Neonatal Fc receptor (FcRn) is an IgG transporter protein expressed in spleen, lymph node, liver, lung muscle, skin, and vascular endothelium through all ages.
- FcRn binds to the Fc segment of IgG on the apical surface of the cell, trancytoses and releases it back into the extracellular space (recycling).
  - Unbound IgG will be degraded in the lysosome.
- Efgartigimod is a human IgG1–derived Fc fragment that has been mutated at 5 residues (so-called ABDEG mutations), to increase its affinity for FcRn.
- It binds to FcRn, so FcRn can not recycle IgG through endosome.

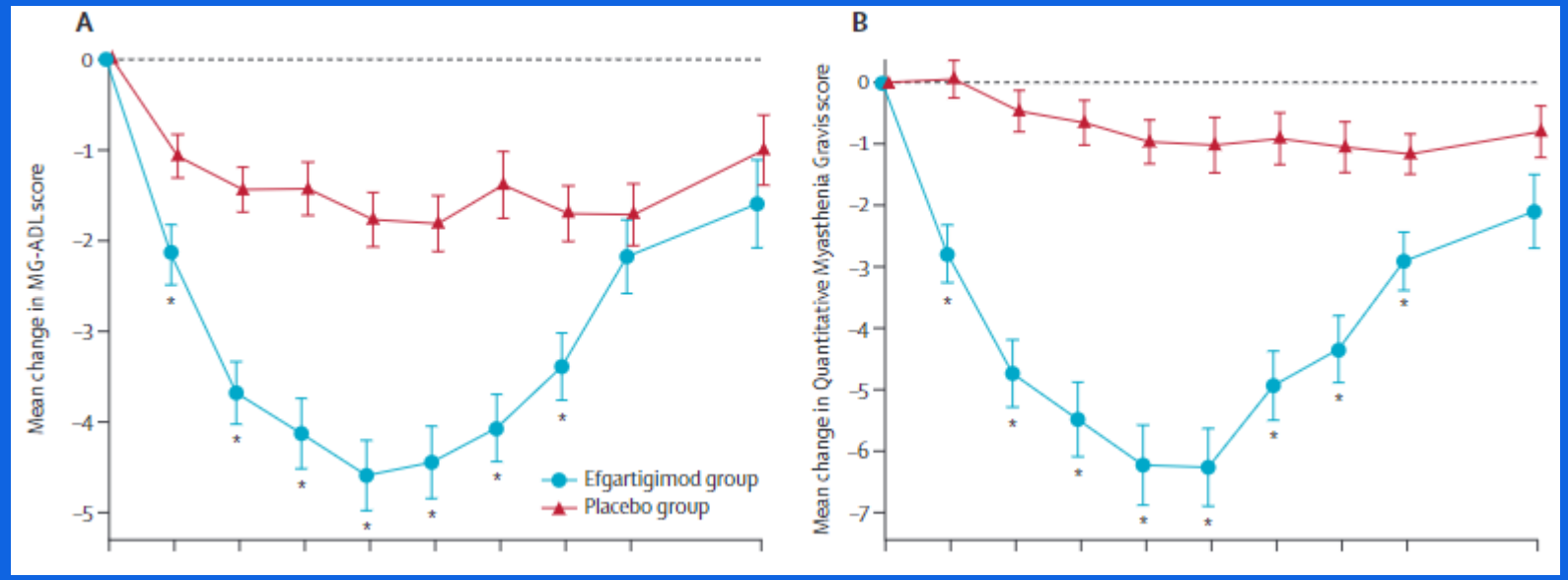


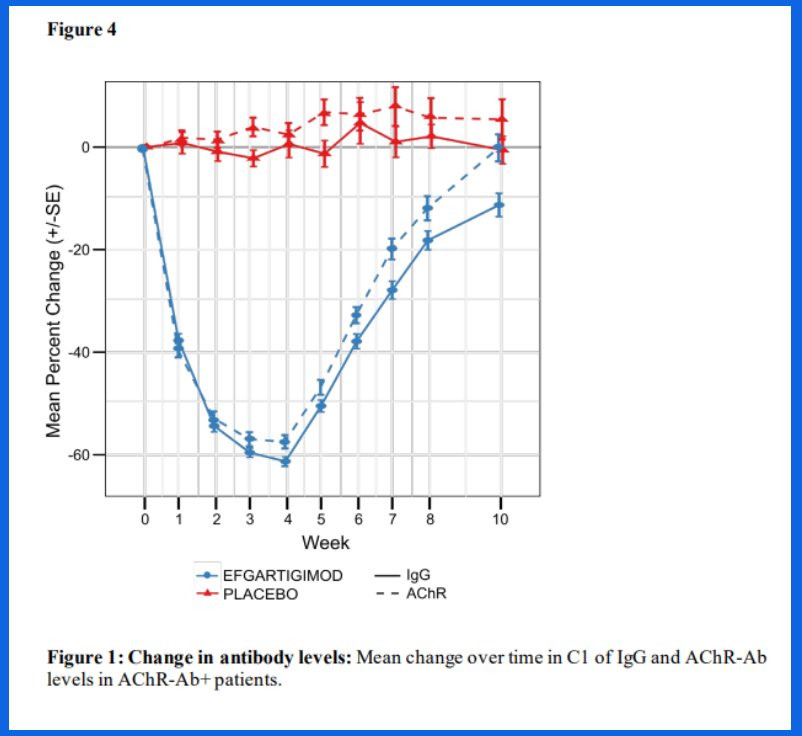
Efgartigimod Phase III trial

- Howard et al. ADAPT Investigator Study Group. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021 Jul;20(7):526-536.
- 167 patients: AChR Ab (+) 129 (77%), seronegative 32, MuSK-Ab (+) 6 patients.
- Randomized 1:1 to receive an initial 4 weekly 10 mg/kg infusions of efgartigimod or placebo for 26 weeks. Infusion repeat if MG-ADL within 2 points of the original ADL score. Same treatment given without crossover.
- Primary endpoint: percentage of AChR-Ab (+) patients who were MG-ADL responders (≥2 points improvement sustained for ≥ 4 weeks) after first treatment cycle.

Efgartigimod Phase III trial

- 68% AChR-Ab+ treated patients compared to 30% placebo-treated patients achieved the primary end point.





Efgartigimod Phase III trial: side effects

	Efgartigimod group (n=84)	Placebo group (n=83)
Any adverse event	65 (77%)	70 (84%)
Any serious adverse event	4 (5%)	7 (8%)
Any adverse event leading to discontinuation of study drug	3 (4%)	3 (4%)
Any infection	39 (46%)	31 (37%)
Infusion-related reaction event	3 (4%)	8 (10%)
Most common adverse events		
Headache	24 (29%)	23 (28%)
Nasopharyngitis	10 (12%)	15 (18%)
Nausea	7 (8%)	9 (11%)
Diarrhoea	6 (7%)	9 (11%)
Upper respiratory tract infection	9 (11%)	4 (5%)
Urinary tract infection	8 (10%)	4 (5%)

Data are n (%).

***Table 3*: Summary of adverse events in all patients**

Efgartigimod Phase III trial: AChR-Ab negative patients

- A similar number of MG-ADL responders in each treatment group in cycle 1:
  - 13 (68%) of 19 patients in the efgartigimod group versus 12 (63%) of 19 in the placebo group.

- Six MUSK-Ab positive, three in the treatment and three in the placebo group. All six patients were MG-ADL responders in cycle 1.

Vyvgart (Efgartigimod alpha fcab)

- VYVGART is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
- Dosage:10 mg/kg administered once weekly for 4 weeks, and 1200mg per infusion for patients weighing 120 kg or more.
- Administer subsequent treatment cycles based on clinical evaluation; the safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.
- Administer as an intravenous infusion over one hour. Monitor for another hour for hypersensitivity reactions. No premedication is required.
- Dosage form: 400 mg in 20 mL (20 mg/mL) single-dose vial. Must be diluted with 0.9% Sodium Chloride to make a total volume of 125 mL for intravenous infusion.

Vyvgart (Efgartigimod alpha fcab)

- Infections:
  - Delay administration of VYVGART to patients with an active infection.
  - Monitor for signs and symptoms of infection.
  - If serious infection occurs, administer appropriate treatment and consider withholding VYVGART until the infection has resolved.

- Hypersensitivity reactions: Angioedema, dyspnea, and rash have occurred. If occurs, discontinue the infusion and institute appropriate therapy.

- Immunization with vaccines during VYVGART treatment has not been studied.
  - Vaccination with live-attenuated or live vaccines is not recommended during treatment with VYVGART.

Vyvgart (Efgartigimod alpha fcab): Price

- The cost of per vial is $5950 per vial (400mg).
- The annual net price of Vyvgart for a typical patient will be $225,000.
- The actual price will vary depending on several factors, including a patient’s weight and the number of treatment cycles required, as well as insurance coverage, rebates, and discounts.

Upcoming

- Upcoming MG treatment
  - Rozanolixizumab (UCB), FcRN therapy, phase III result positive
  - Ravulizumab (Alexion), complement inhibitor, phase III result positive
  - Alexion: possible new oral drug for MG
  - Zilucoplan (Ra Pharma-UCB): complement inhibitor, phase III result pending
  - Nipocalimab (Momenta), FcRN, Phase III ongoing
  - Batoclimab (Immunovant), FcRN, Phase III being planned
  - Pozelimab and Cemdisiran combination. Complement inhibitor Regeneron. Phase III trial planned.
  - Inebilizumab (Uplizna), CD19 directed monoclonal antibody, FDA approved for neuromyelitis optica. Similar to Rituximab. Sponsored by Viela Bio. MINT trial started.

- Efgartigimod
  - Subcutaneous dosage form
  - Study of chronic maintenance therapy with different intervals