PLACE DES ANTI-COMPLÉMENTS DANS LA MYASTHÉNIE ET LE SYNDROME DE GUILLAIN-BARRÉ

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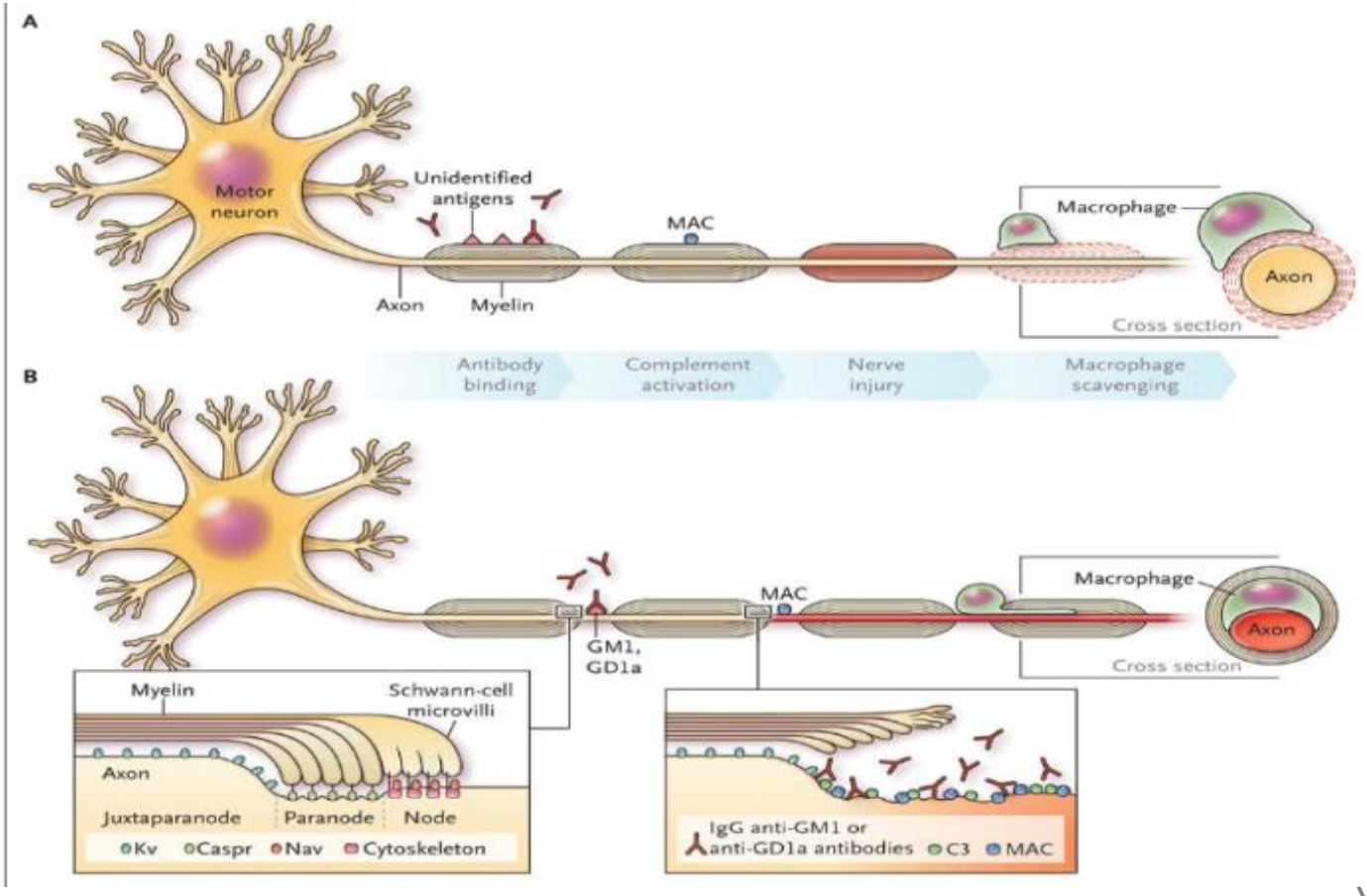
IHU PROMETHEUS

GUILLAIN BARRÉ SYNDROME

- Principale cause de paralysie aiguë
- Incidence = 0,8 – 1,9/ 100 000 par an *(Europe & USA)*
- Homme > femme
- Prévalence augmente avec age
- Mortalité: 3.5 % - 12%
- Variation saisonnière parallèle variations des maladies infectieuses (*Cytomegalovirus*, *Campylobacter jejuni*, *Epstein Bar Virus*, *Mycoplasme pneumoniae* ,*H. influenzae H1N1)*

Sejvar, Neuroepidemiology, 2011
Yuki, The Lancet infect dis, 2001
Dos Santos , NEJM 2016

PHYSIOPATHOLOGIE



Type démyélinisant

Type axonal

Yuki, NEJM, 2012

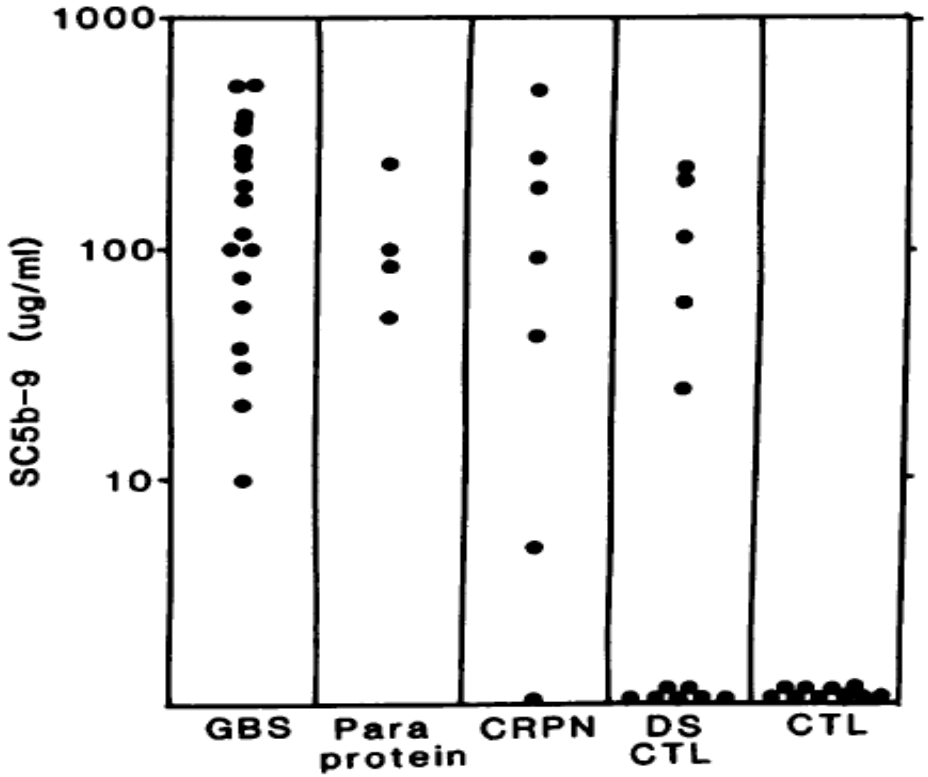


Figure 1. SC5b-9 in the serum of patients with demyelinating neuropathies. SC5b-9, detected in serum by a quantitative micro ELISA, is expressed in micrograms per milliliter on a log scale. Serum concentrations of SC5b-9 from 19 GBS patients, 4 patients with paraproteinemia and peripheral neuropathy, and 7 patients with CRPN are given, respectively, in columns from left to right. 12

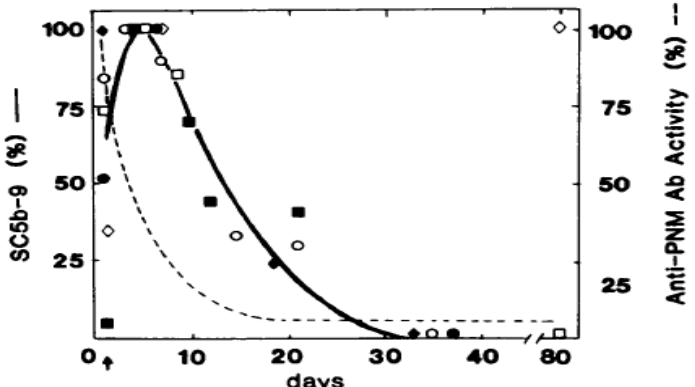
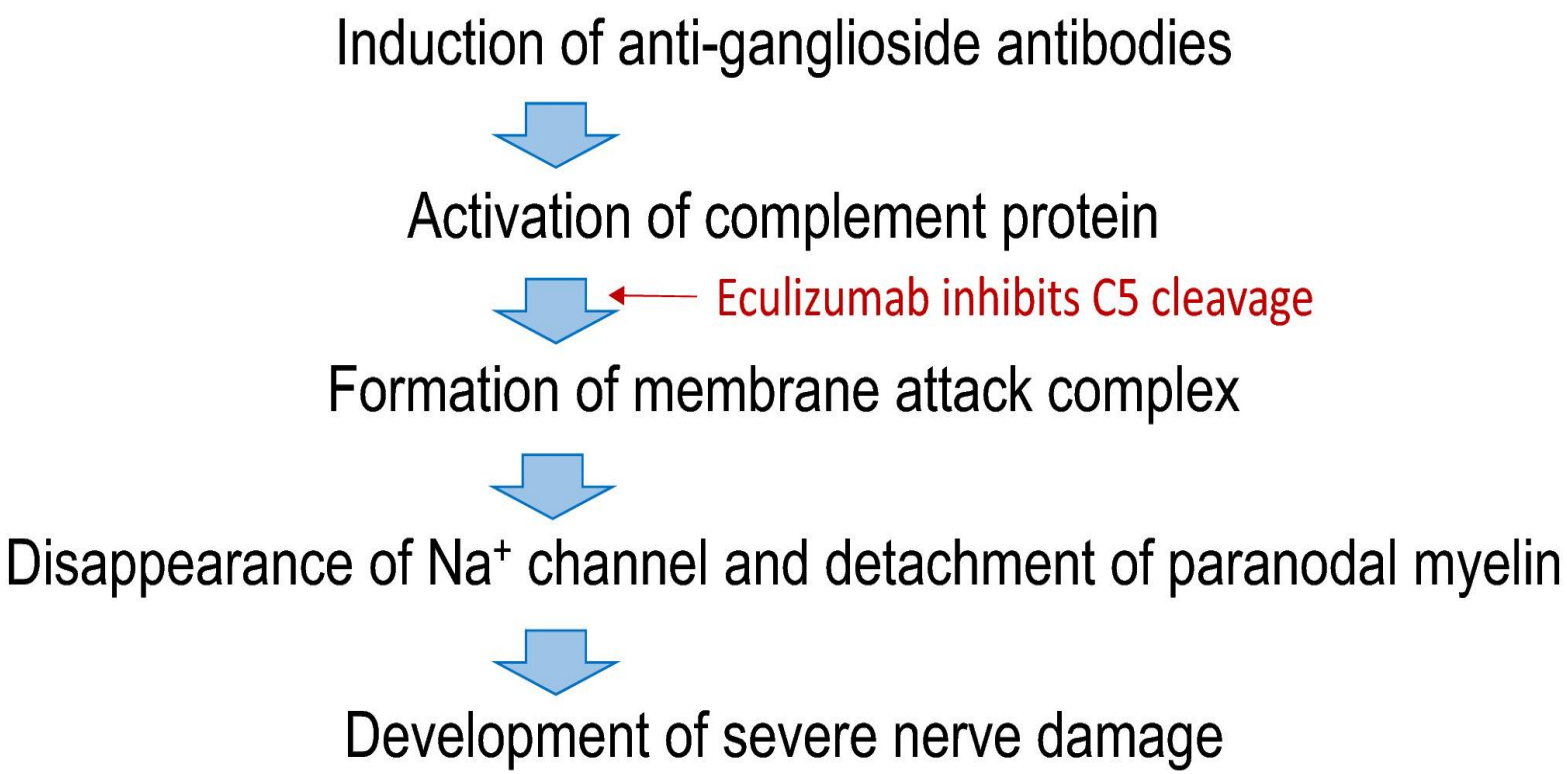
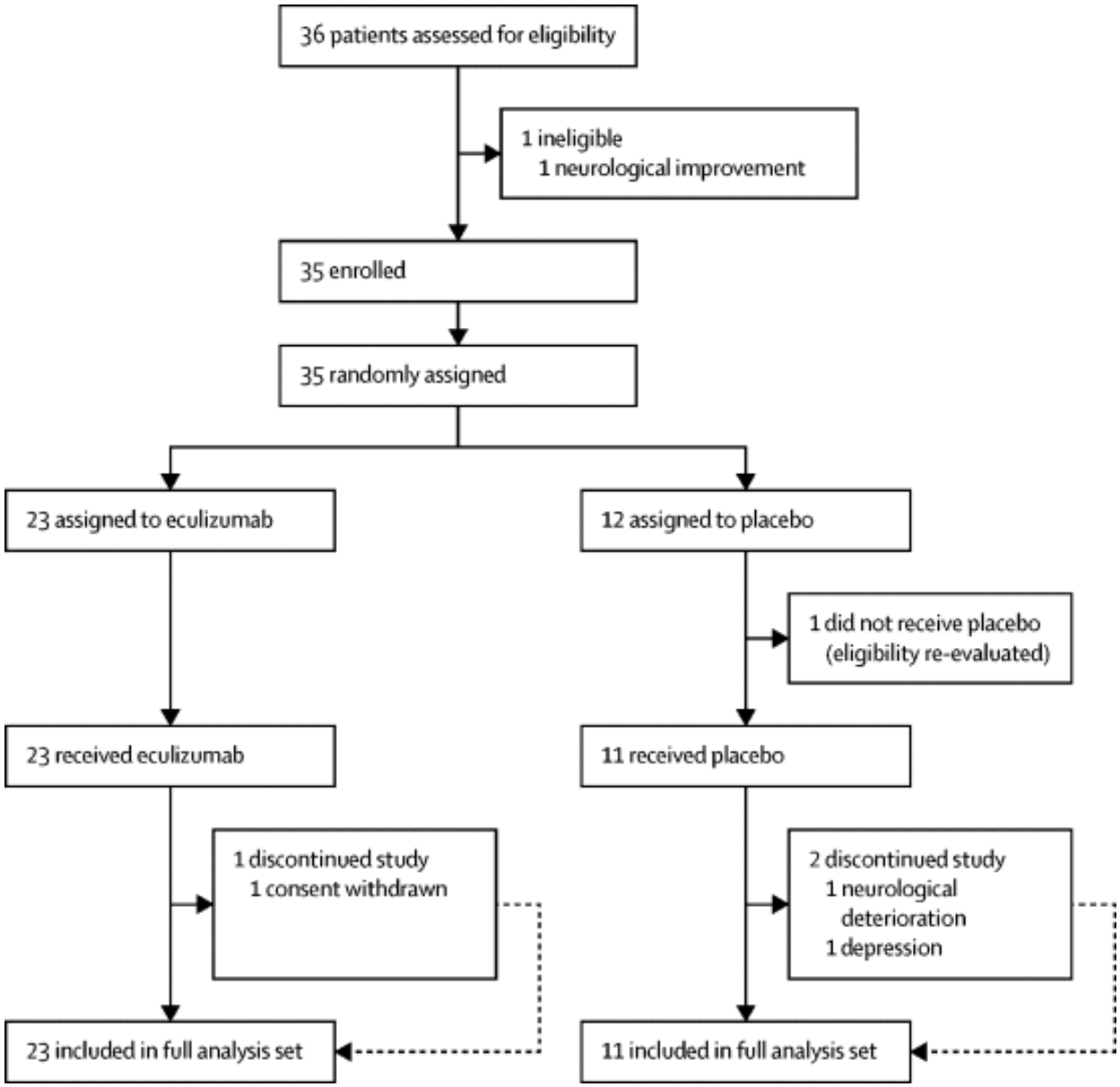


Figure 3. Kinetics of SC5b-9 in five GBS patients. SC5b-9 concentrations were determined on three or more serial samples obtained from each GBS patient. Symbols and samples in Fig. 3 are the same as those in Fig. 2. SC5b-9

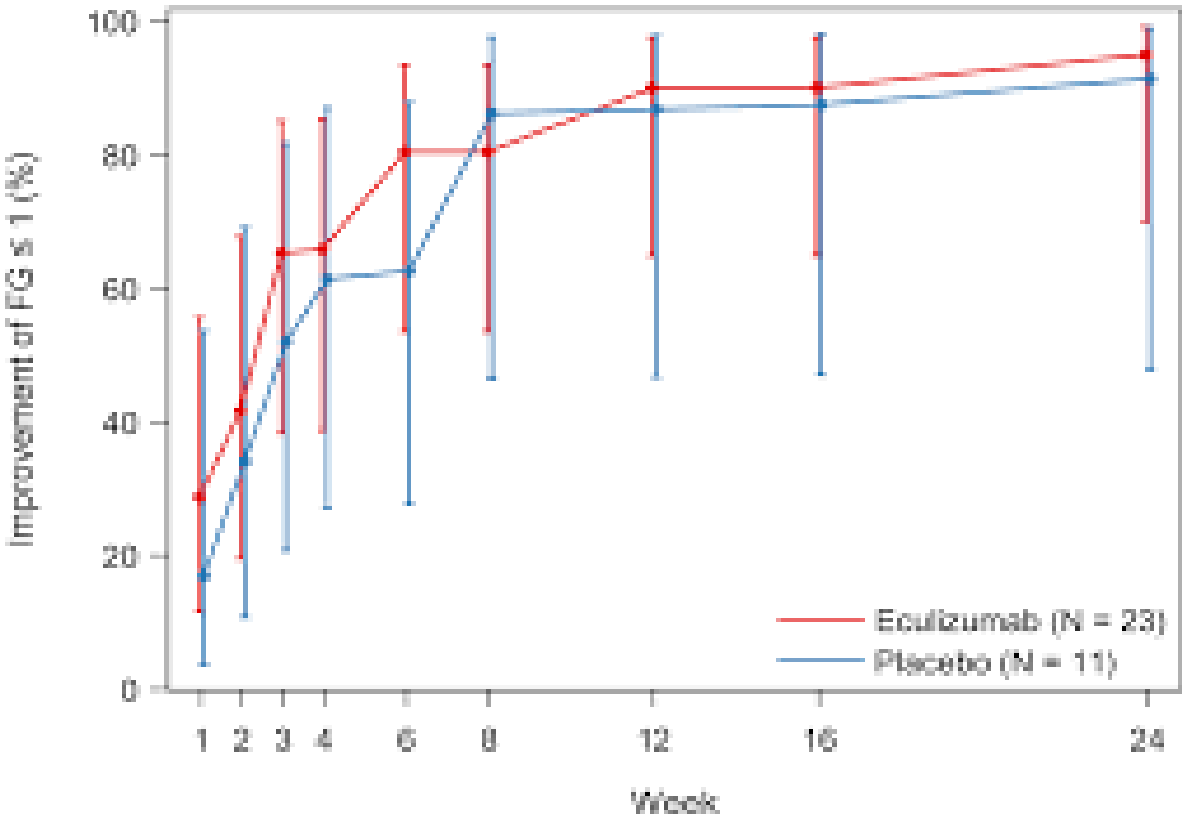
Koski JCI 1987



Misawa C & E Neuroimmunol 2020



Misawa, Lancet Neuro 2018



Misawa, Lancet Neuro 2018

ClinicalTrials.gov BETA

National Library of Medicine
National Center for Biotechnology Information

COMPLETED

ClinicalTrials.gov Identifier: NCT04752566

A Study to Evaluate the Efficacy and Safety of Eculizumab in Guillain-Barré Syndrome

Information provided by Alexion (Responsible Party)

Last Update Posted: 2022-08-29

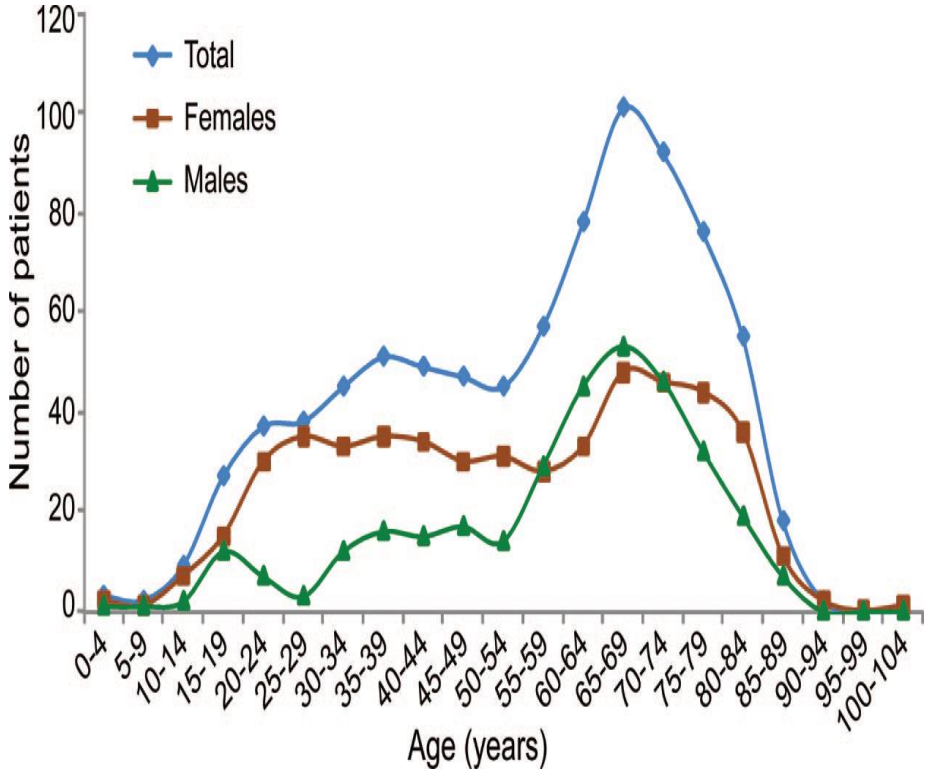
Study Completion Date (Actual)	ICMJE
2022-08-03	

Completed

Enrollment (Actual) **(Submitted: 2021-02-09)**	ICMJE
57	

MYASTHÉNIE AUTO-IMMUNE

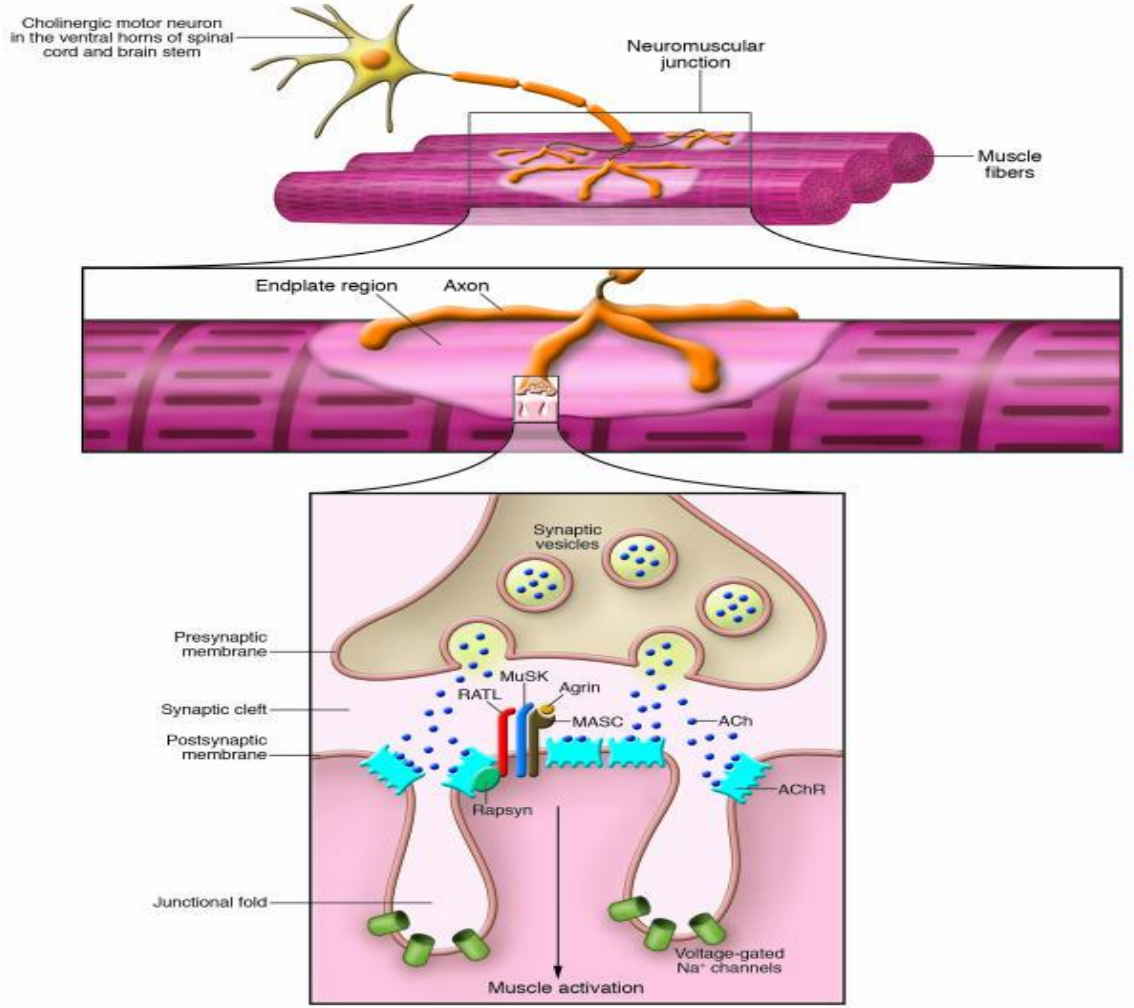
- Prévalence: 5 cas pour 100 000 personnes
- Incidence (nouveaux cas): 2 à 5 cas/an/1 000 000 hab
- 3 à 4 000 patients en France ?
- Homme et Femme
- Quel que soit l'âge



(Heldal, Neurology, 2009)

PHYSIOPATHOLOGIE

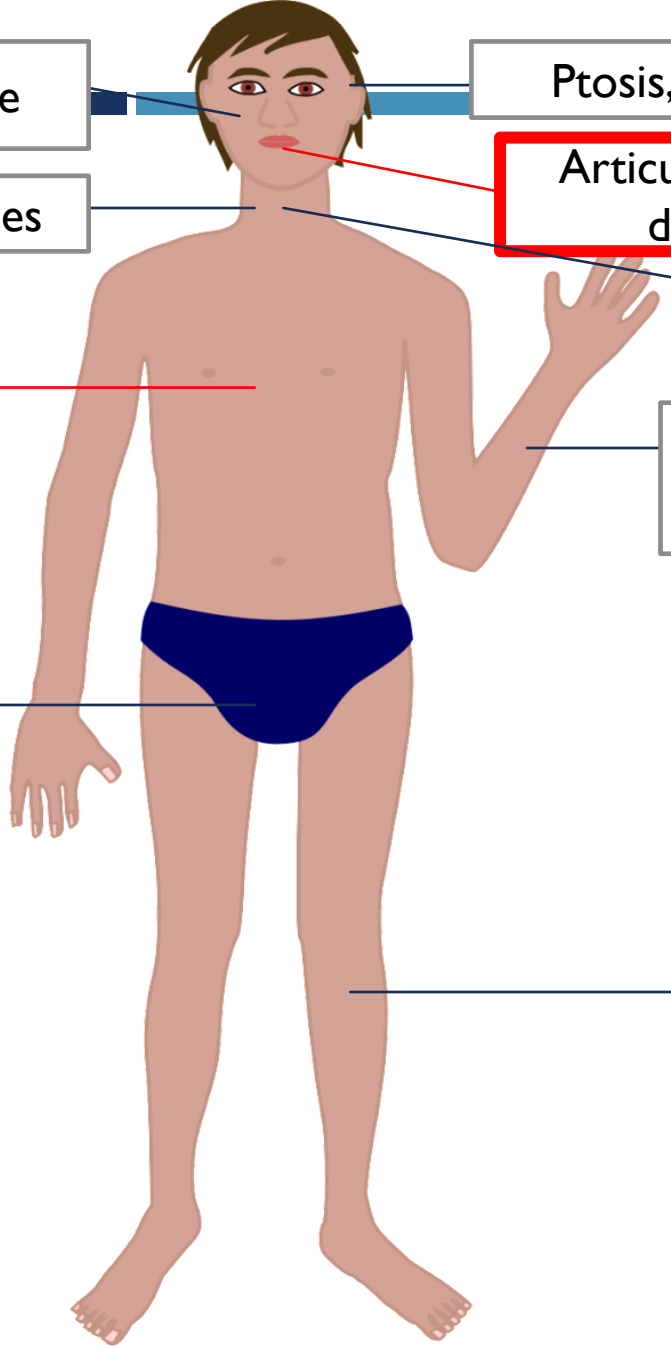
- Ac anti Récepteur Acétylcholine
- Blocage du site de fixation de l'Ach
- Dégradation accélérée du récepteur à Ach
- Destruction de la membrane post synaptique



SYMPTÔMES INITIAUX

805 patients (Ooster Luis – 1987)

- Atteinte oculaire (diplopie, ptôsis) 59 %
- Atteinte faciale ou bulbaire (mastication, déglutition, phonation) 30 %
- Déficit des membres 16 %
- Déficit cervical 9 %
- Atteinte respiratoire 1 %



« paralysie »visage

Ptosis, diplopie

Articulation, mastication, langu
déglutition: blocage, FR

Chute de tête, cervicalgies

dysphonie

Dyspnée, orthopnée, toux faible, tachypnée, oppression, angoisse

Difficultés: se laver, s'habiller, porter, bras en l'air

Fuites urinaires

Difficultés: station debout, marcher, escaliers

Fatigue

FHU SEPSIS
Personalized Interventions

SYMPTÔMES

- URGENCE:

  - déglutition

  - respiration

Consultation dans les 24h

Tel SAMU (15)

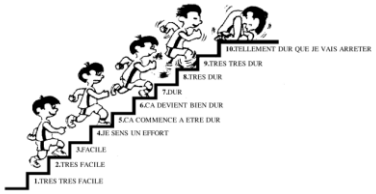
Réa

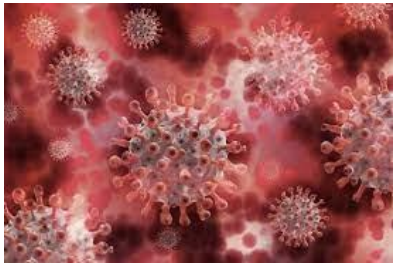
- Peut attendre:

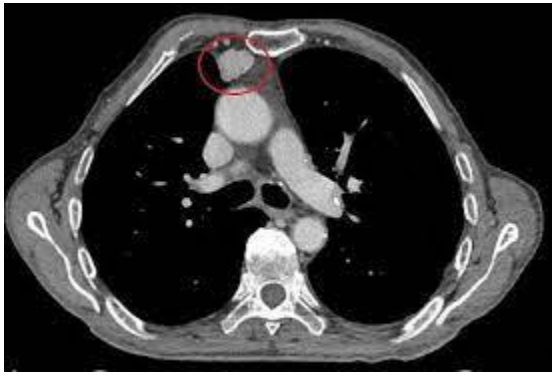
le reste…

Repos puis consultation

FACTEURS DÉCLENCHANTS







Infection: 30-40% (Thomas, Neurology 1997)

Grossesse : 19% (Batocchi, Neurology 1999)/Accouchement (myasthénie néo-natale: 10%)

Membres supérieurs étendus à l'horizontale en antéroposition :	
▪ pendant 150 secondes	15
Membres inférieurs, malade en décubitus dorsal, cuisses fléchies à 90° sur le bassin, jambes à 90° sur les cuisses :	
▪ pendant 75 secondes	15
Flexion de la tête, le malade en décubitus dorsal :	
▪ contre résistance	10
▪ sans résistance	5
▪ impossible	0
Passage de la position couchée à la position assise :	
▪ sans l'aide des mains	10
▪ impossible	0
Oculomotricité extrinsèque :	
▪ normale	10
▪ ptosis isolé	5
▪ diplopie	0
Occlusion palpébrale :	
▪ complète	10
▪ Incomplète	7
▪ Avec recouvrement cornéen	5
▪ Sans recouvrement cornéen	0
Mastication :	
▪ normale	10
▪ diminuée	5
▪ nulle	0
Déglutition :	
▪ normale	10
▪ difficile	5
▪ Fausse route	0
Phonation :	
▪ voix normale	10
▪ voix nasonnée	5
▪ aphonie	0

SCORE MYASTHÉNIQUE GAJDOS, GARCHES

FHU SEPSIS
Personalized Interventions

TRAITEMENT

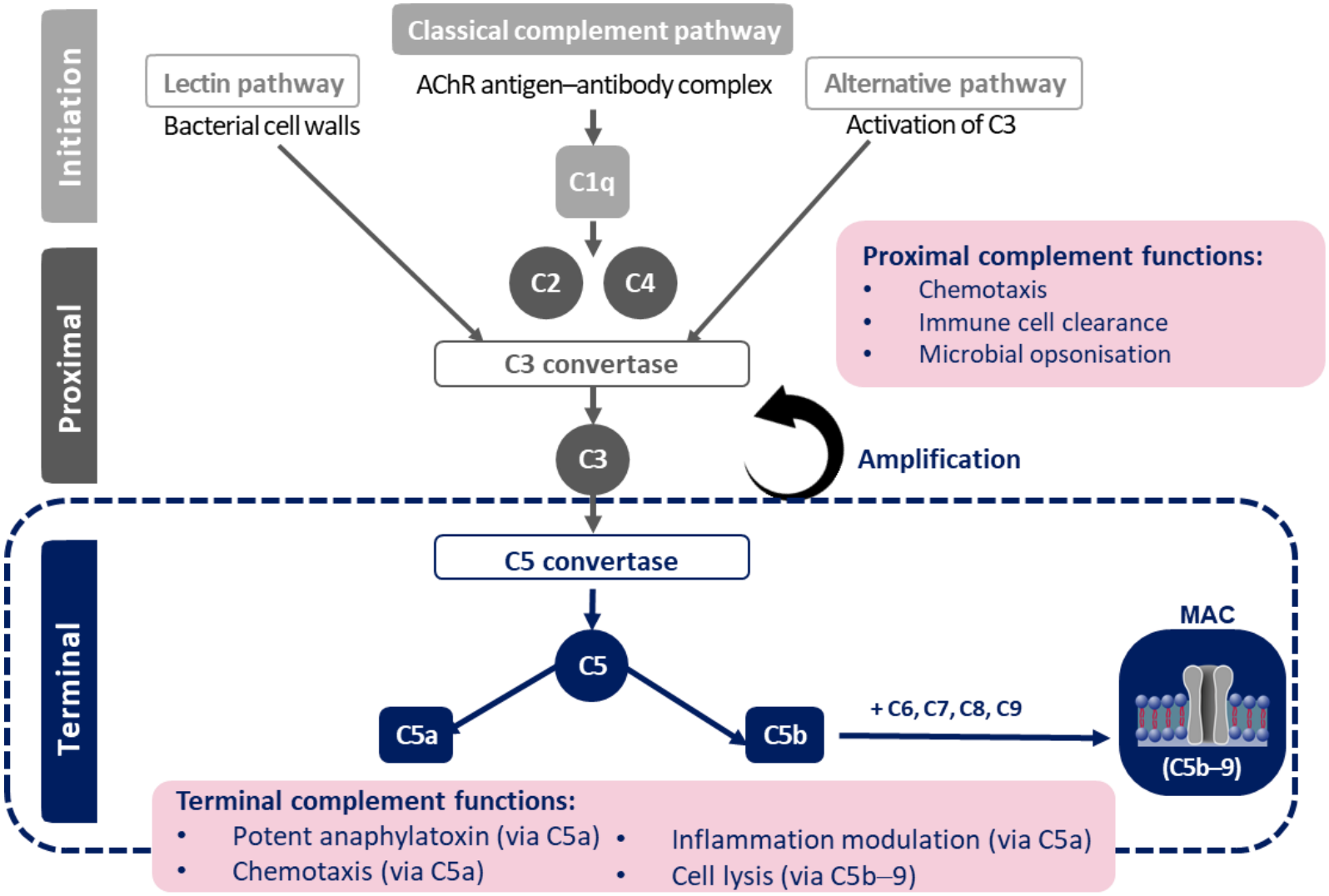
- Anticholinestérasiques: Mytélase/Mestinon, Mestinon Retard (+/- atropine)
- Traitement de fond (atteinte respi, bulbaire, ou déficit majeur):

- Cortisone

- Immunosuppresseurs : Azathioprine(Imurel), mycophenolate mofetil (Cellcept), ciclosporine (Neoral), cyclophosphamide (Endoxan), rituximab (Mabtera), eculizumab (Soliris), ravulizumab (Ultomiris)

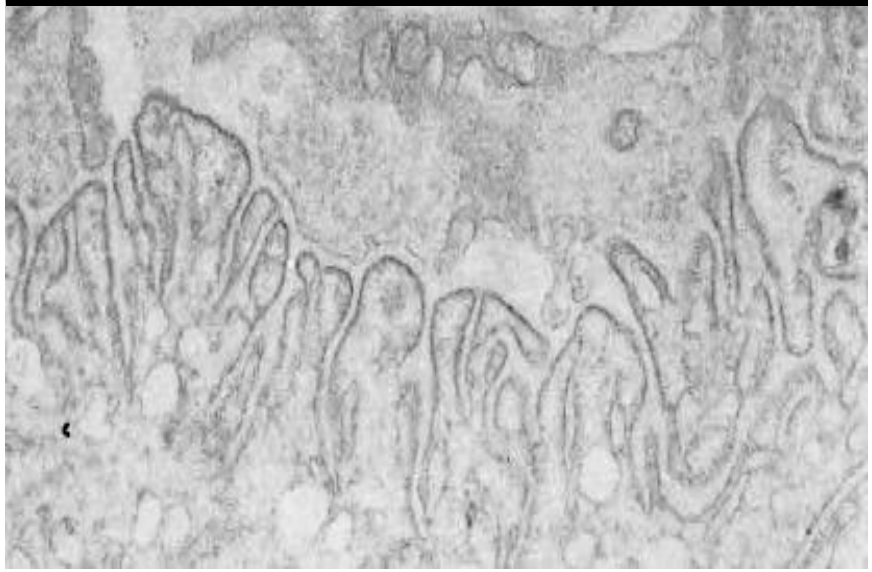
- Immunoglobulines, Plasmaphérèses
- Chirurgie thymus (thymome, âge jeune) +/- radiothérapie, chimiothérapie (RCP Rythmic)
- SNG
- Ventilation invasive (Sevrage progressif si CV>15ml/kg). Pas VNI. Mode VAC.

Voies du complément

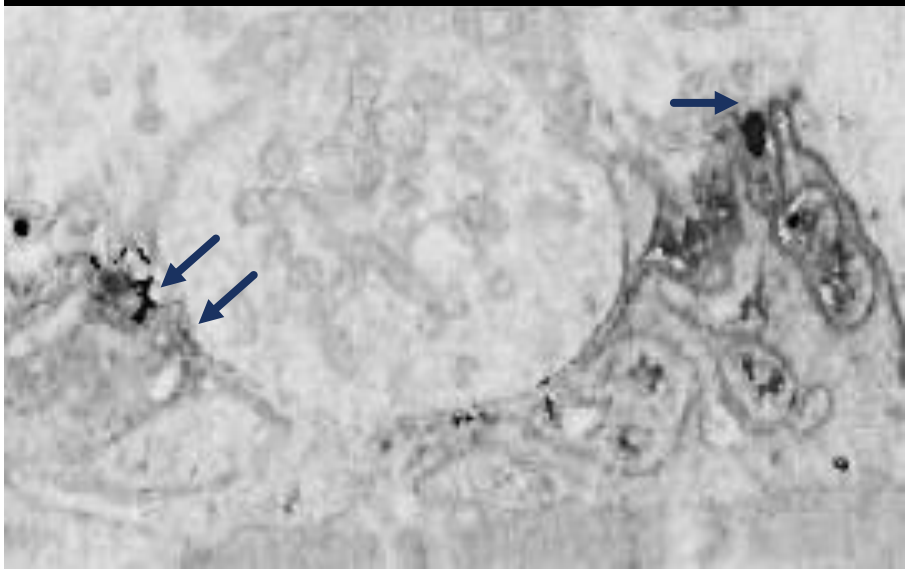


FHU SEPSIS
Personalized Interventions

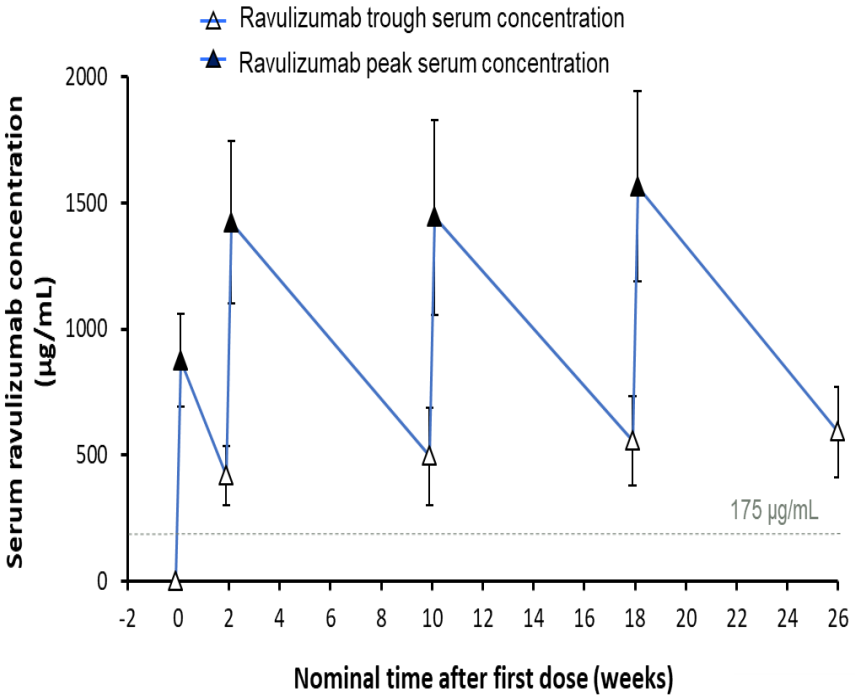
Undamaged NMJ in a healthy individual[a,2]

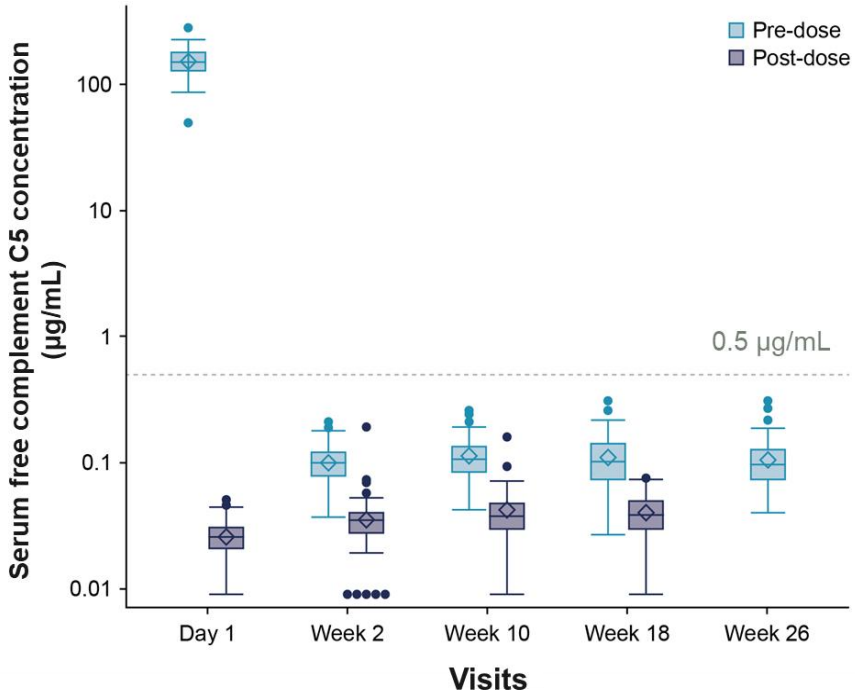


Complement-mediated damage of the NMJ in a patient with MG[b,5]



Howard JF, Jr. Ann N Y Acad Sci 2018


Ravulizumab trough serum concentration
Ravulizumab peak serum concentration
Serum ravulizumab concentration (µg/mL)
2000
1500
1000
500
0
175 µg/mL
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Nominal time after first dose (weeks)


Pre-dose
Post-dose
Serum free complement C5 concentration (µg/mL)
100
10
1
0.1
0.01
0.5 µg/mL
Day 1
Week 2
Week 10
Week 18
Week 26
Visits

Posted February 26, 2022

NEJM Evidence

DOI: 10.1056/EVIDoa2100066

ORIGINAL ARTICLE

Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis

Tuan Vu, M.D.,[1] Andreas Meisel, M.D.,[2] Renato Mantegazza, M.D.,[3] Djillali Annane, M.D.,[4] Masahisa Katsuno, M.D.,[5] Rasha Aguzzi, M.S.,[6] Ahmed Enayetallah, M.D., Ph.D.,[6] Kathleen N. Beasley, Pharm.D.,[6] Nishi Rampal, M.D.,[6] James F. Howard Jr., M.D.,[7] and the CHAMPION MG Study Group*

Aim: To evaluate the efficacy and safety of the long-acting terminal complement C5 inhibitor ravulizuma
adults with anti-AChR antibody-positive gMG

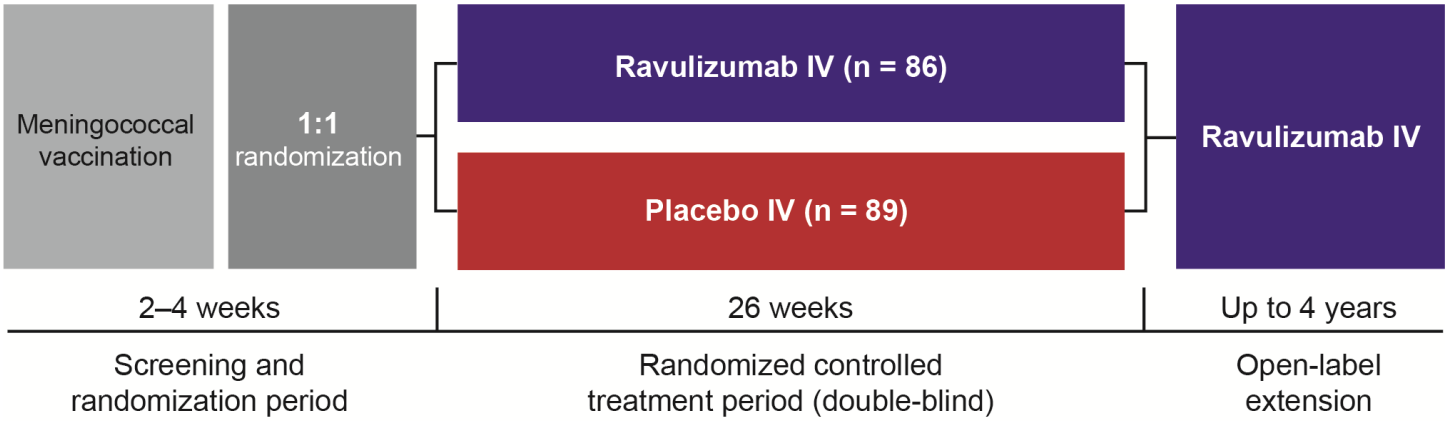
FHU SEPSIS
Personalized Interventions

Study design

- Phase 3, randomized, double-blind, placebo-controlled, multinational study with 26-week treatment duration
- Stable-dose pyridostigmine and ISTs were permitted throughout the study
- Patients completing the randomized phase were permitted to enter the open-label extension

Intravenous dosing

- Ravulizumab loading dose (2400/2700/3000 mg) on Day 1, maintenance dose (3000/3300/3600 mg) on Day 15, and then every 8 weeks
- Loading and maintenance dosing for ravulizumab and placebo were based on the patient's weight[1,2]



BASELINE CHARACTERISTICS

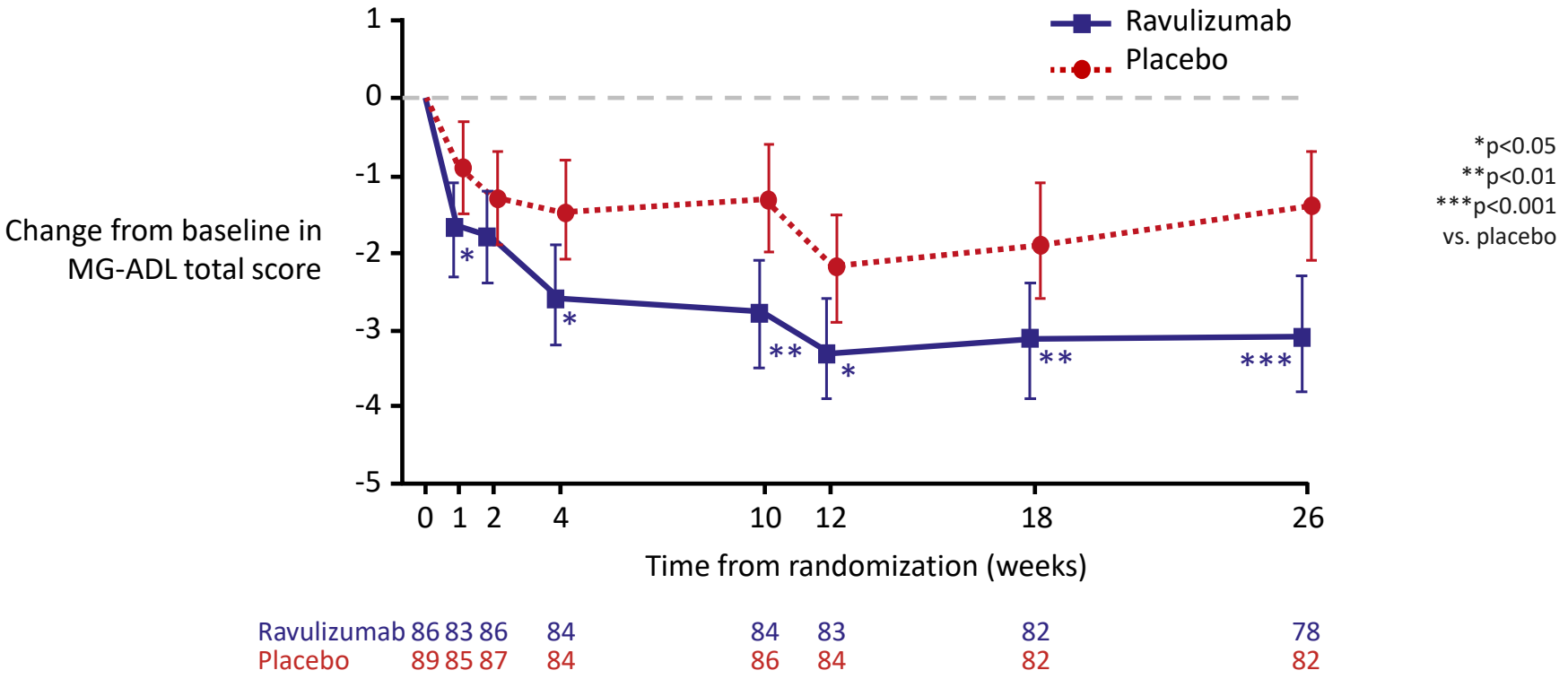
Characteristic	Ravulizumab (n=86)	Placebo (n=89)	All patients (N=175)
Female, n (%)	44 (51)	45 (51)	89 (51)
Age at first study dose, mean (SD) years	58.0 (13.8)	53.3 (16.1)	55.6 (15.1)
Race, n (%)			
White	67 (78)	61 (69)	128 (73)
Asian	15 (17)	16 (18)	31 (18)
Black or African American	2 (2)	4 (5)	6 (3)
Other	0 (0)	3 (3)	3 (2)
Not reported	2 (2)	5 (6)	7 (4)
Time since MG diagnosis, mean (SD) years [range]	9.8 (9.7) [0.5–39.5]	10.0 (8.9) [0.5–36.1]	9.9 (9.3) [0.5–39.5]
MG-ADL score at baseline, mean (SD) [range]	9.1 (2.6) [6.0–24.0]	8.9 (2.3) [6.0–15.0]	9.0 (2.5) [6.0–24.0]
QMG score at baseline, mean (SD) [range]	14.8 (5.2) [6.0–39.0]	14.5 (5.3) [2.0–27.0]	14.7 (5.2) [2.0–39.0]
Baseline MGFA classification, n (%)			
Class II (mild weakness)	39 (45)	39 (44)	78 (45)
Class III (moderate weakness)	41 (48)	45 (51)	86 (49)
Class IV (severe weakness)	6 (7)	5 (6)	11 (6)
Use of any IST[a] at baseline, n (%)	76 (88)	81 (91)	157 (90)

[a]Corticosteroids, azathioprine, ciclosporin, cyclophosphamide, methotrexate, mycophenolate mofetil, or tacrolimus

IST, immunosuppressant therapy; MG-ADL, Myasthenia Gravis–Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; QMG, Quantitative Myasthenia Gravis; SD, standard deviation

CHANGE FROM BASELINE IN MG-ADL TOTAL SCORE (PRIMARY ENDPO

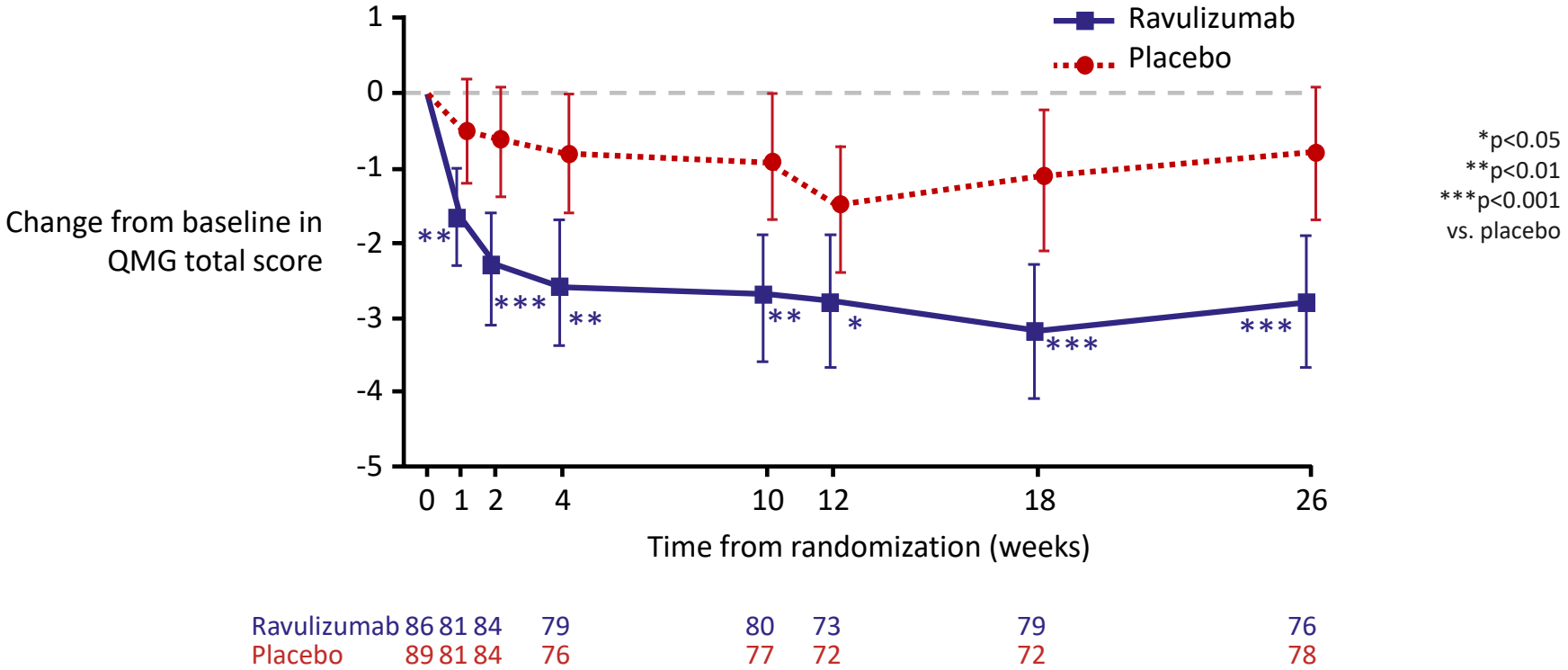
- Mean MG-ADL total score change from baseline at week 26: ravulizumab -3.1 (SEM: 0.38) vs. placebo -1.4 (SEM: 0.37)
  - Treatment difference: -1.6 (95% CI: -2.6, -0.7); p=0.0009
- Improvements in MG-ADL scores were observed within 1 week of ravulizumab treatment and sustained through 26 weeks



Data plotted are least-squares means and 95% CIs, using a mixed model for repeated measures. Data are offset for clarity
CI, confidence interval; MG-ADL, Myasthenia Gravis–Activities of Daily Living; SEM, standard error of the mean

CHANGE FROM BASELINE IN QMG TOTAL SCORE (FIRST SECONDARY ENDPOINT)

- Mean QMG total score change from baseline at week 26: ravulizumab -2.8 (SEM: 0.46) vs. placebo -0.8 (SEM: 0.45)
  - Treatment difference: -2.0 (95% CI: -3.2, -0.8); p=0.0009
- Improvements in QMG scores were observed within 1 week of ravulizumab treatment and sustained through 26 weeks



Data plotted are least-squares means and 95% CIs, using a mixed model for repeated measures. Data are offset for clarity
CI, confidence interval; QMG, Quantitative Myasthenia Gravis; SEM, standard error of the mean

TRAITEMENT

- Éducation patient et entourage. Aide+++
- Suivi spécialisé/ centre de référence
- Assistante sociale (100%)
- Psychologue
- Carte myasthénique, livret information
- Médicaments contre-indiqués

Filnemus
Filière Neuromusculaire

maladies rares
CARTE D'URGENCE
Emergency card

MDPH maison départementale des personnes handicapées

CONCLUSION

- Inhibiteurs du complément :
  - NON pour SGB
  - OUI pour MG
  - NE SONT PAS des traitements de la phase aigue
  - Réservé aux centres de références de la filière FILENEMUS