Immunomodulerande behandling vid terapiresistent myastenia gravis (MG)

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Uppgivna förhållanden

FP har mottagit forskningsanslag för akademiskt initierade forskningsprojekt inom MS från Biogen, Genzyme and Novartis, samt personlig ersättning för uppdrag som ordförande för DMC för två fas III studier i NMO (Parexel).

FP har varit svensk huvudprövare för kliniska behandlingsstudier i MG sponsrade av Alexion samt Argenx.

FP är medlem i det Vetenskapliga rådet vid Läkemedelsverket. De slutsatser som framförs i denna presentation är författarens egna och representerar inte nödvändigtvis myndighetens syn.

- Allmän bakgrund
- Vad göra om behandlingen inte fungerar ?
  - -Nyheter kliniska studier
  - -Olika behandlingsalternativ
- Dags att tänka om gällande behandlingstrategi ?

84 år sedan den första effektiva behandlingen!

TREATMENT OF MYASTHENIA GRAVIS WITH PHYSOSTIGMINE

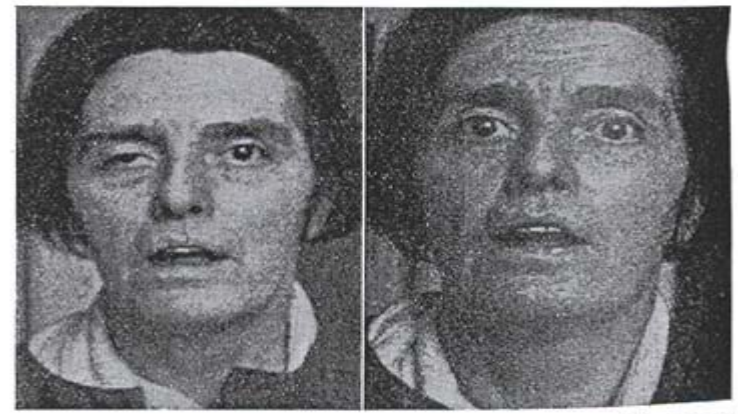
To the Editor of THE LANCET

SIR,—The abnormal fatiguability in myasthenia gravis has been thought to be due to curare-like poisoning of the motor nerve-endings or of the "myoneural junctions" in the affected muscles. It occurred to me recently that it would be worth while to try the effect of physostigmine, a partial antagonist to curare, on a case of myasthenia gravis at present in St. Alfege's Hospital, in the hope that it would counteract the effect of the unknown substance which might be exerting a curare-like effect on the myoneural junctions. I found that hypodermic injections of physostigmine salicylate did have a striking though temporary effect.

Mrs. M., aged 56, had had a previous attack of myasthenia gravis, lasting about six months, 14 years ago. Gastric ulcer four years ago. Non-specific infective arthritis seven months ago, now improved.

Towards the end of last February she found that she was unable to hold her shopping bag, and that her head used to fall forwards when she knelt to do the hearth. She had to remain in bed after March 18th, and had difficulty in sitting up. Her jaw then began to droop, she had to hold it up with her hand, and the left eyelid began to droop. Speech became indistinct when she was excited, swallowing was difficult, and fluid sometimes regurgitated through her nose. She was admitted to the hospital on March 28th, and a few days later weakness came on in the middle and ring fingers of both hands. The weakness is much increased by excitement, and is lessened by rest. It becomes worse as the day goes on. There is no wasting, and the tendon reflexes are all present. The masseters respond slightly or not at all to faradism; a myasthenic reaction has been obtained in the left deltoid. Radiograms show obsolete pulmonary tuberculosis. The thymus is not enlarged.

On April 11th treatment with hypodermic injections of physostigmine salicylate, gr. 1/60 once a day, was begun. In from half an hour to an hour after the injection the left eyelid "goes up" (see Figure), arm movements are much stronger, the jaw drops rather less, swallowing is improved, and the patient feels "less heavy." The effect wears off gradually in from 2–4 hours. With injections of gr. 1/50 the improvement is greater, and it lasts for 4–5 hours. Still greater improvement, lasting for 6–7 hours, followed an injection of gr. 1/45, but the patient felt rather faint and trembly, her "inside seemed all on the work," and she felt as if "something were going to happen." These feelings did not completely disappear till an hour after the injection. In all, 26 injections of physostigmine salicylate have been given. The effect is not quite uniform; on two occasions injections of gr. 1/45 and gr. 1/60 failed



Before injection the patient cannot raise her left eyelid. Thirty minutes after it the eye is fully open. (The photographs are reproduced from a cinematograph film and are reversed left for right.)

to produce any obvious effect. She feels better and more cheerful since the injections were begun.

Given by the mouth, physostigmine salicylate gr. 1/60 produced no obvious effect, but an hour after gr. 1/30 slight improvement occurred. No improvement followed control injections of water, pilocarpine gr. 1/20, strychnine gr. 1/30, adrenaline ℥ 5, ephedrine gr. ½, or acetylcholine 0·05 and 0·1 g.

I think that this effect of physostigmine on myasthenia gravis is important, though it is only temporary, for it improves swallowing and might tide a patient over a respiratory crisis. It supports the opinion that the fatiguability is due to a poisoning of the motor end-organs, or "myoneural junctions," rather than to an affection of the muscle itself. It may be significant that physostigmine inhibits the action of the esterase which destroys acetylcholine. I have not had the opportunity of treating another case to confirm the findings. The administration of other drugs whose action resembles that of physostigmine is under consideration. It is also possible that physostigmine might be of some service in botulism and in cobra poisoning, in both of which a curare-like poisoning of the "myoneural junctions" of the respiratory muscles has been stated to be the main cause of death.

I wish to thank Dr. Philip Hamill for his interest and advice, and Dr. W. D. Wiggins, medical superintendent of the hospital, for permission to publish the case.

I am, Sir, yours faithfully,

M. B. WALKER.

St. Alfege's Hospital, Greenwich, May 12th.

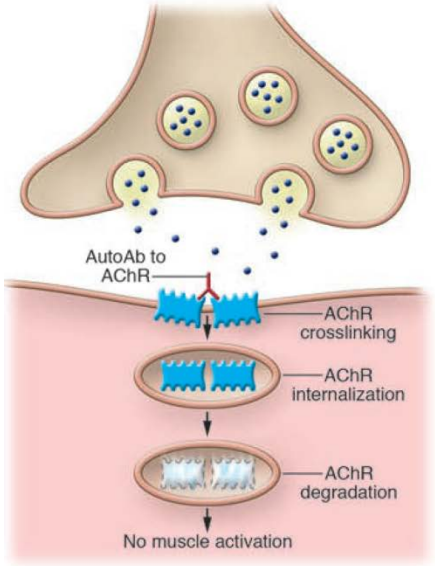
Inte en sjukdom; flera subtyper!

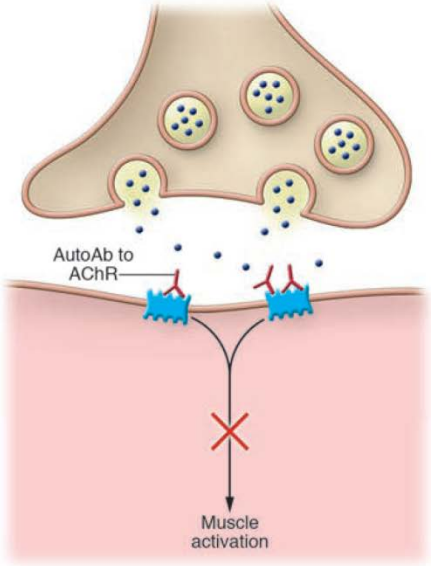
1. EOMG. Mest kvinnor. HLA B8-DR3. God effekt av tymektomi
2. LOMG. Mer män. HLA DRB1*1501. Bredare antikroppsmönster; titin, ryanodin
3. Tymom-associerad MG. Medelålders personer. Tymektomi. Bredare antikroppsmönster; titin, ryanodin
4. MuSK+ MG. Oftare ursprung från medelhavet. Bulbära symptom. Svarar bra på rituximab. Ej tymektomi.
5. LRP4+ MG. Sämre karaktäriserad. Mildare sjukdom? Tymektomi?
6. Trippel seronegativ MG. Vanligare hos okulär MG.

De flesta kan debutera som okulär MG.
Ca 70% konverterar till generaliserad sjukdom inom 2 år.

Antikroppsmedierad modulering av NMJ funktion

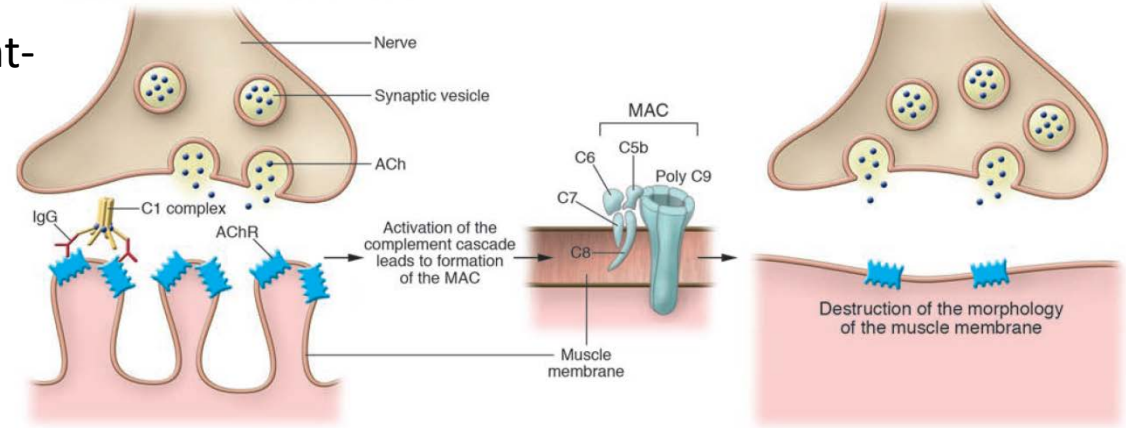
Bindning, återupptag





Blockering

Komplement-fixation



> Rimlig orsak till tidsmässigt varierande svar på på terapi

J. Clin. Invest. 116:2843–2854 (2006).

Hur kvantifiera symptom objektivt - QMG

13 domäner

Max 39 poäng

Milda spt <6

Måttliga 6-12

Svåra >12

Kvantitativt MG status — 13 domäner poängsätts 0-3

Cirkla korrekt ruta och skriv uppmätt värde i rutan

	0p	1p	2p	3p
1. Dubbelseende vid blick uppåt	120s	91-119s	11-90s	<11s
2. Ptos vid blick uppåt	120s	91-119s	11-90s	<11s
3. Grimasera (alt ansiktsmuskulatur): Sluter ögonlock	20ggr	11-19ggr	5-11ggr	<5ggr
	Normalt	Reducerad kraft	Ej mot motstånd	Kan ej sluta
4. Tuggning (alt sväljfunktion vatten)	20ggr	11-19ggr	5-11ggr	<5ggr
	Normalt	Minimal hosta	Kraftig hosta	Kan ej svälja
5. Räkning till 100 - Dysartri	100	41-100	5-40	<5
6. Armlyft höger (alt Framsträckta armar höger)	40ggr	25-39ggr	10-24ggr	<10ggr
	180s	60-179s	10-59s	<10s
7. Armlyft vänster (alt Framsträckta armar vänster)	40ggr	25-39ggr	10-24ggr	<10ggr
	180s	60-179s	10-59s	<10s
8. PEF % normalt för ålder, kön (se bild baksida)	76-140%	51-75%	26-50%	<26%
9. Fingerextension höger	70ggr	40-69ggr	10-39ggr	<10ggr
10. Fingerextension vänster	70ggr	40-69ggr	10-39ggr	<10ggr
11. Huvudlyft	30ggr	15-29ggr	5-14ggr	<5ggr
12. Benlyft höger dynamiskt (alt Benlyft höger statiskt 45 grader)	35ggr	21-34ggr	10-20ggr	<10ggr
	60s	40-59s	15-39s	<15s
13. Benlyft vänster dynamiskt (alt. Benlyft vänster statiskt 45 grader)	35ggr	21-34ggr	10-20ggr	<10ggr
	60s	40-59s	15-39s	<15s

Ev. Kommentarer:

Patient-rapporterade utfall: MG-ADL

MG-skala över aktiviteter i dagliga livet

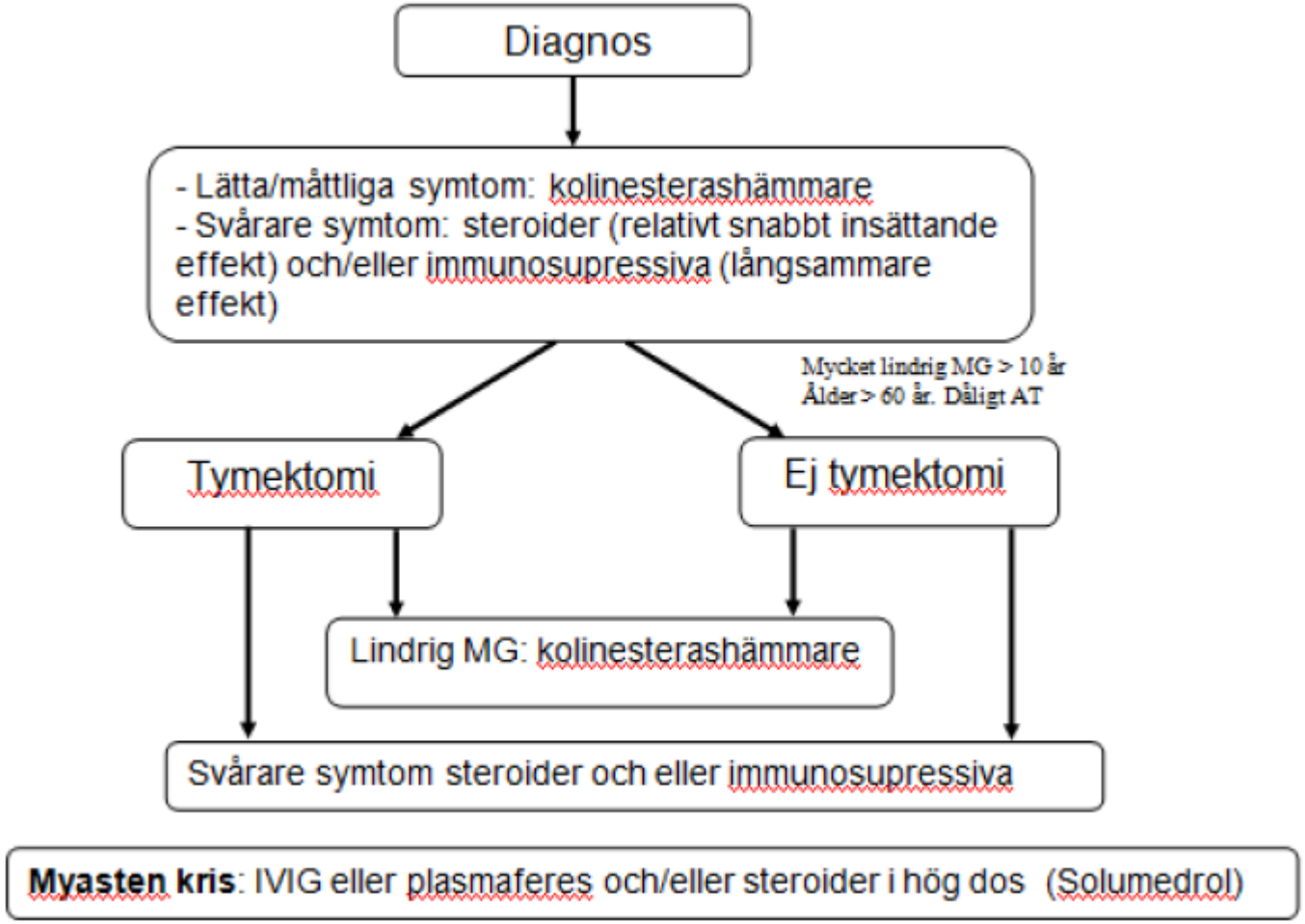
Poster	Grad 0	Grad 1	Grad 2	Grad 3	Poäng (0,1,2,3)
1. Tal	Normalt	Intermittent sluddrigt eller nasalt tal	Konstant sluddrigt eller nasalt tal, men kan förstås	Svårighet att förstå tal	
2. Tuggning	Normal	Tröttsamt med fast föda	Tröttsamt med mjuk föda	Ventrikelsond	
3. Sväljning	Normal	Sällan förekommande kvävnings-händelse	Ofta förekommande kvävnings-händelse som kräver ändrad kost	Ventrikelsond	
4. Andning	Normal	Andfåddhet vid ansträngning	Andfåddhet vid vila	Respirator-beroende	
5. Nedsatt förmåga att borsta tänder eller kamma håret	Ingen	Extra ansträngning, men inget behov av viloperioder	Behov av viloperioder	Kan inte göra någon av dessa funktioner	
6. Nedsatt förmåga att resa sig från en stol	Ingen	Lätt, använder ibland armarna	Måttlig, använder alltid armarna	Uttalad, behöver hjälp	
7. Dubbelseende	Inget	Förekommer, men inte dagligen	Dagligen, men inte konstant	Konstant	
8. Hängande ögonlock	Inget	Förekommer, men inte dagligen	Dagligen, men inte konstant	Konstant	

Patient-rapporterade utfall: MG-QoL

Ange hur väl varje påstående stämde för dig (under de senaste 4 veckorna).

	Inte alls	Lite	Något	Ganska mycket	Väldigt mycket
	0	1	2	3	4
1. Jag är frustrerad över mitt tillstånd					
2. Jag har svårigheter med att använda ögonen					
3. Jag har svårigheter med att äta					
4. Jag har begränsat mina sociala aktiviteter på grund av mitt tillstånd					
5. Mitt tillstånd begränsar min förmåga att finna nöje i fritidsintressen och roliga aktiviteter					
6. Jag har svårigheter med att uppfylla min familjs behov					
7. Jag måste planera med hänsyn till mitt tillstånd					
8. Min yrkesskicklighet och min arbetssituation har påverkats negativt					
9. Jag har svårigheter att tala					
10. Jag har svårigheter med att köra bil					
11. Jag är deprimerad över mitt tillstånd					
12. Jag har svårigheter med att gå					
13. Jag har svårigheter med att ta mig runt på allmänna platser					
14. Jag känner mig överväldigad av mitt tillstånd					
15. Jag har svårigheter med att sköta mina kroppsvårdsbehov					

SNEMA behandlingsalgoritm v2 (2016)



http://www.snema.se/dokument_files/MGkonsensus160412.pdf

Tymektomi

The NEW ENGLAND JOURNAL of MEDICINE

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Randomized Trial of Thymectomy in Myasthenia Gravis

G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.-C. Kuo, A. Marx, P. Ströbel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A.A. Amato, A.I. Shaibani, B. Katirji, B.R.F. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J.G.M. Verschuuren, J.M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, R. Tandan, T. Mozaffar, R. Conwit, J. Odenkirchen, J.R. Sonett, A. Jaretzki, III, J. Newsom-Davis, and G.R. Cutter, for the MGTX Study Group*

BACKGROUND

Thymectomy has been a mainstay in the treatment of myasthenia gravis, but there is no conclusive evidence of its benefit. We conducted a multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone.

METHODS

We compared extended transsternal thymectomy plus alternate-day prednisone with alternate-day prednisone alone. Patients 18 to 65 years of age who had generalized nonthymomatous myasthenia gravis with a disease duration of less than 5 years were included if they had Myasthenia Gravis Foundation of America clinical class II to IV disease (on a scale from I to V, with higher classes indicating more severe disease) and elevated circulating concentrations of acetylcholine-receptor antibody. The primary outcomes were the time-weighted average Quantitative Myasthenia Gravis score (on a scale from 0 to 39, with higher scores indicating more severe disease) over a 3-year period, as assessed by means of blinded rating, and the time-weighted average required dose of prednisone over a 3-year period.

QMG score ca 10 = måttliga symptom
Bättre effekt <40 åå

Annan studie* visat extremt få fall med hyperplasi >60 åå (kvinnor, höga AChR ak)

*Uzawa, J Neurol (2015) 262:1019–1023

Immunmodulerande/-suppressiv behandling

Evidensgrad 2b;
-Azatioprin
-Ciklosporin
-Cyklofosfamid
-Metotrexat
-Takrolimus

Aza add-on reduces maintenance dose of prednisolone. 34 MG patients followed for 3 years (!) Neurology 1998 50(6):1778-83.

No evidence of effect of methotrexate in gMG Neurology 2016 87(1):57-64

Evidensgrad 3a;
-Rituximab
-Mykofenolatmofetil

MMF not superior to placebo during prednisone tapering Neurology 2008;71:400–406

Immunmodulerande/-suppressiv behandling

- Kortison är vanligen en bra behandling, men problem med biverkningar på sikt
- Plasmabyte / Immunoglobuliner är effektiva, men problematiska vid långtidsbehandling
- Riktigt starka behandlingsdata (klass 1) saknas för p.o immunosuppressiva
- Vanligt att börja med azatioprin, vid behandlingssvikt byta till ciklosporin eller mykofenolat
- Starkt motiv för att utveckla bättre algoritmer?

Nya behandlingar: Vad fanns på horisonten för 5 år sedan?

1) T cell Intracellular Signaling Pathways associated with T cell activation,
   such as monoclonal antibodies against CD52, Interleukin 2-receptor (IL-2 R),
   co-stimulatory molecules or compounds inhibiting Janus tyrosine kinases JAK1, JAK3;
2) B cells, against key B cell-surface molecules or trophic factors B cell activation factor (BAFF)
   and a proliferating inducing ligand (APRIL);
3) Complement, against C3 or C5 that intercept membranolytic attack complex formation;
4) Cytokines and cytokine receptors, including IL-6, IL-17, the p40 subunit of IL12/1L-23, and GM-CSF; and
5) Lymphocyte migration molecules.

Dalakas, Autoimmun Rev. 2013 Jul;12(9):936-41.

Vad har hänt ?

1) Alemtuzumab (anti-CD52) – case report tillsammans med HSCT
   Daclizumab (anti-IL2R) – indragen
   Tofacitinib (oral JAK hämmare) – ej testad

2) Belimumab (anti-BLyS)– ingen effekt (NCT01480596; BEL115123: Neurology. 2018 90(16):e1425-e1434)

3) Eculizumab (anti-C5) – positiva RCT III data

4) Tocilizumab (anti-IL6) – case report
   Secukinumab (anti-IL17) – ej testad
   Ustekinumab (anti-p40 IL12/23) – ej testad
   GM-CSF – case report

5) Fingolimod (S1P blockerare) – ej testad

Eculizumab (Soliris™): humaniserad monoklonal AK mot C5 – förhindrar terminala komplement-kaskaden.

Indikation: Paroxysmal nokturnal hemoglobulinemi och Atypiskt hemolytiskt syndrome.

Ges i.v. varannan vecka

Positive CHMP opinion "Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive (see section 5.1)."

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

*James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group**

Summary

Background Complement is likely to have a role in refractory generalised myasthenia gravis, but no approved therapies specifically target this system. Results from a phase 2 study suggested that eculizumab, a terminal complement inhibitor, produced clinically meaningful improvements in patients with anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis. We further assessed the efficacy and safety of eculizumab in this patient population in a phase 3 trial.

Methods We did a phase 3, randomised, double-blind, placebo-controlled, multicentre study (REGAIN) in 76 hospitals and specialised clinics in 17 countries across North America, Latin America, Europe, and Asia. Eligible patients were aged at least 18 years, with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or more, Myasthenia Gravis Foundation of America (MGFA) class II–IV disease, vaccination against *Neisseria meningitides*, and previous treatment with at least two immunosuppressive therapies or one immunosuppressive therapy and chronic intravenous immunoglobulin or plasma exchange for 12 months without symptom control. Patients with a history of thymoma or thymic neoplasms, thymectomy within 12 months before screening, or use of intravenous immunoglobulin or plasma

Findings Between April 30, 2014, and Feb 19, 2016, we randomly assigned and treated 125 patients, 62 with eculizumab and 63 with placebo. The primary analysis showed no significant difference between eculizumab and placebo (least-squares mean rank 56·6 [SEM 4·5] *vs* 68·3 [4·5]; rank-based treatment difference –11·7, 95% CI –24·3 to 0·96; p=0·0698). No deaths or cases of meningococcal infection occurred during the study. The most common adverse events in both groups were headache and upper respiratory tract infection (ten [16%] for both events in the eculizumab group and 12 [19%] for both in the placebo group). Myasthenia gravis exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group. Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy.

Lancet Neurol 2017; 16: 976–86

	Ecu	Plc	Totalt
Previous use of immunosuppressive treatments			
≥3	31 (50%)	34 (54%)	65 (52%)
≥2	61 (98%)	62 (98%)	123 (98%)
Types of immunosuppressive treatments used before study enrolment			
Corticosteroids	58 (94%)	62 (98%)	120 (96%)
Azathioprine	47 (76%)	47 (75%)	94 (75%)
Mycophenolate mofetil	27 (44%)	29 (46%)	56 (45%)
Cyclosporine	18 (29%)	18 (29%)	36 (29%)
Tacrolimus	9 (15%)	11 (17%)	20 (16%)
Rituximab	7 (11%)	7 (11%)	14 (11%)
Methotrexate	6 (10%)	8 (13%)	14 (11%)
Cyclophosphamide	3 (5%)	3 (5%)	6 (5%)

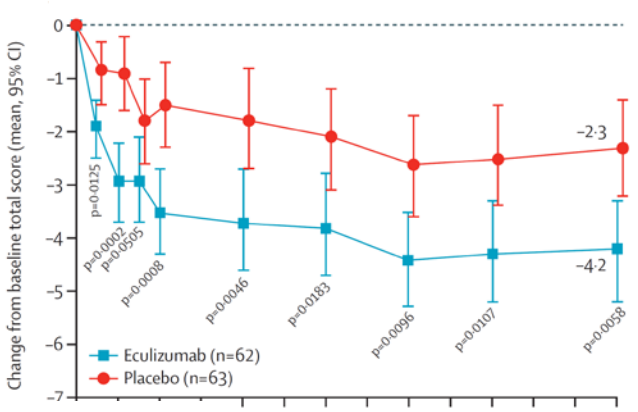
	Ecu	Plc	Totalt
Immunosuppressive treatments at baseline (day 1)			
Corticosteroids	47 (76%)	51 (81%)	98 (78%)
Azathioprine	20 (32%)	21 (33%)	41 (33%)
Mycophenolate mofetil	18 (29%)	16 (25%)	34 (27%)
Cyclosporine	8 (13%)	9 (14%)	17 (14%)
Tacrolimus	5 (8%)	6 (10%)	11 (9%)
Methotrexate	5 (8%)	4 (6%)	9 (7%)
Rituximab	0	0	0
Cyclophosphamide	2 (3%)	0	2 (2%)
Previous thymectomy	37 (60%)	31 (49%)	68 (54%)
Mean time from thymectomy to first dose in REGAIN (years)	11 (8·51)	11·3 (9·67)	11·1 (8·99)
Previous long-term intravenous immunoglobulin therapy	18 (29%)	17 (27%)	35 (28%)
Previous long-term plasma exchange therapy	4 (6%)	10 (16%)	14 (11%)
History of myasthenia gravis exacerbations	46 (74%)	52 (83%)	98 (78%)
History of myasthenia gravis crisis	13 (21%)	10 (16%)	23 (18%)

Lancet Neurol 2017; 16: 976–86

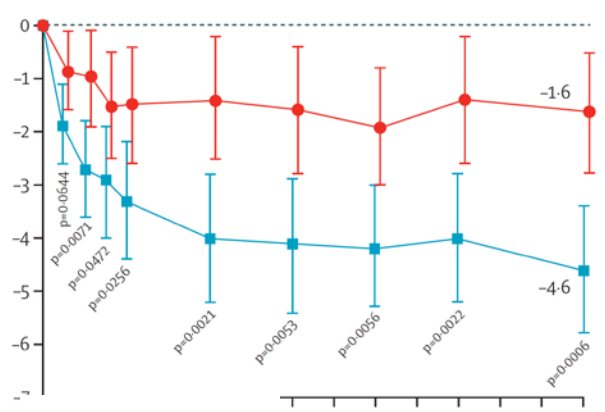
Ecu Plc

	Eculizumab (n=62)	Placebo (n=63)	Difference (95% CI)	p value*
Prespecified worst-rank ANCOVA score†				
MG-ADL‡	56·6 (4·5)	68·3 (4·5)	−11·7 (−24·3 to 0·96)	0·0698
QMG	54·7 (4·5)	70·7 (4·5)	−16·0 (−28·5 to −3·4)	0·0129
MGC	57·3 (4·5)	67·7 (4·5)	−10·5 (−23·1 to 2·1)	0·1026
MG-QOL15	55·5 (4·6)	69·7 (4·5)	−14·3 (−27·0 to −1·6)	0·0281
Prespecified sensitivity repeated-measures model analysis with immunosuppressive treatments as covariate§				
MG-ADL	−4·1 (0·5)	−2·3 (0·5)	−1·8 (−3·2 to −0·5)	0·0077
QMG	−4·6 (0·6)	−1·7 (0·6)	−2·9 (−4·6 to −1·2)	0·0007
MGC	−7·9 (1·0)	−4·6 (1·0)	−3·3 (−5·9 to −0·6)	0·0168
MG-QOL15	−13·8 (1·6)	−6·7 (1·6)	−7·1 (−11·3 to −3·0)	0·0009
Post-hoc sensitivity worst-rank ANCOVA score¶				
MG-ADL	54·8 (4·5)	70·2 (4·4)	−15·4 (−27·8 to −2·9)	0·0160
QMG	53·9 (4·5)	71·6 (4·4)	−17·7 (−30·1 to −5·3)	0·0055
MGC	56·1 (4·5)	69·0 (4·4)	−12·9 (−25·4 to −0·5)	0·0414
MG-QOL15	54·6 (4·5)	70·6 (4·5)	−16·0 (−28·6 to −3·4)	0·0134

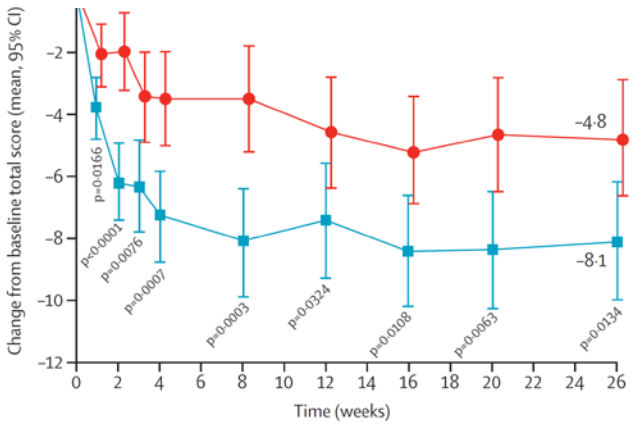
MD-ADL



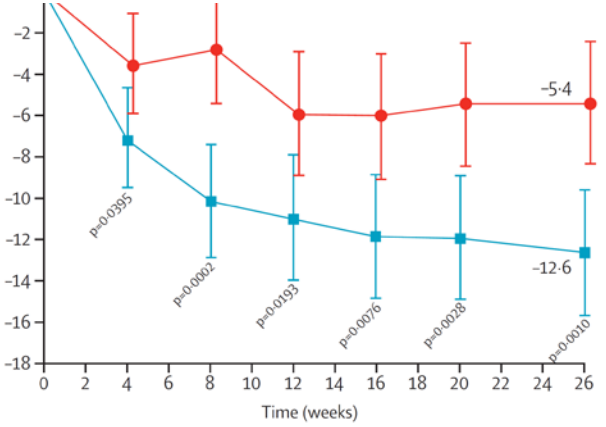
QMG



MGC



MG-QoL



Lancet Neurol 2017; 16: 976–86

Eculizumab

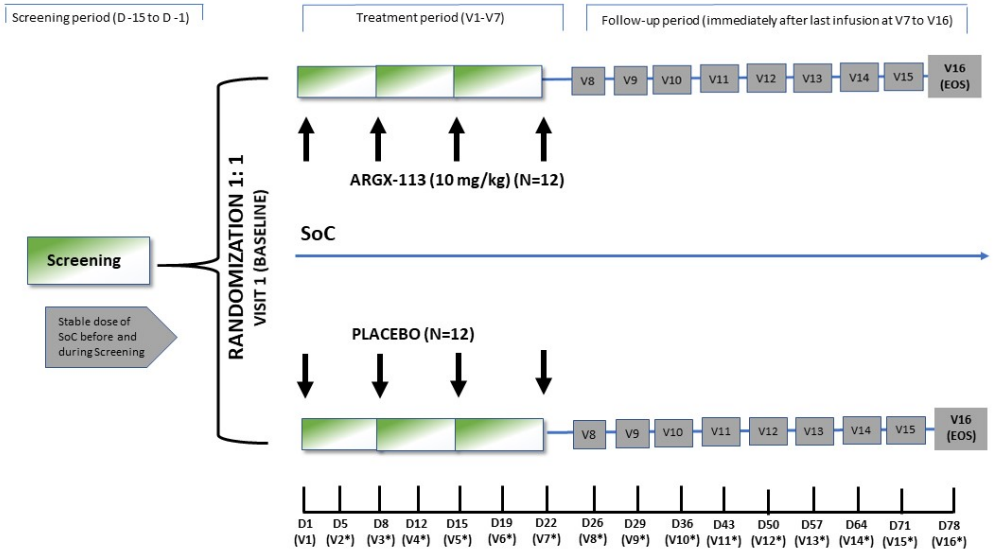
Kraftigt ökad risk meningokockinfektioner, ökad risk för andra infektioner

Mycket höga behandlingskostnader, behov av frekventa infusioner

A randomized, double-blind, placebo-controlled Phase 2 study of FcRn antagonist *efgartigimod* in generalized myasthenia gravis

Efgartigimod blockerar neonatala Fc receptorn > selektiv minskning patogena antikroppar

Prövningen inkluderade n=24 MG patienter med AChR^{+} MG-ADL ≥5



*Visit window: ± 1 day
Only blood sampling at V9-V16. Optional intermediate blood sampling at V2, V4, V6 and V8.
ARGX-113: Investigational Medicinal Product; D: Day; EoS: End of Study; N: sample size; SoC: Standard of Care; V: Visit

Submitted

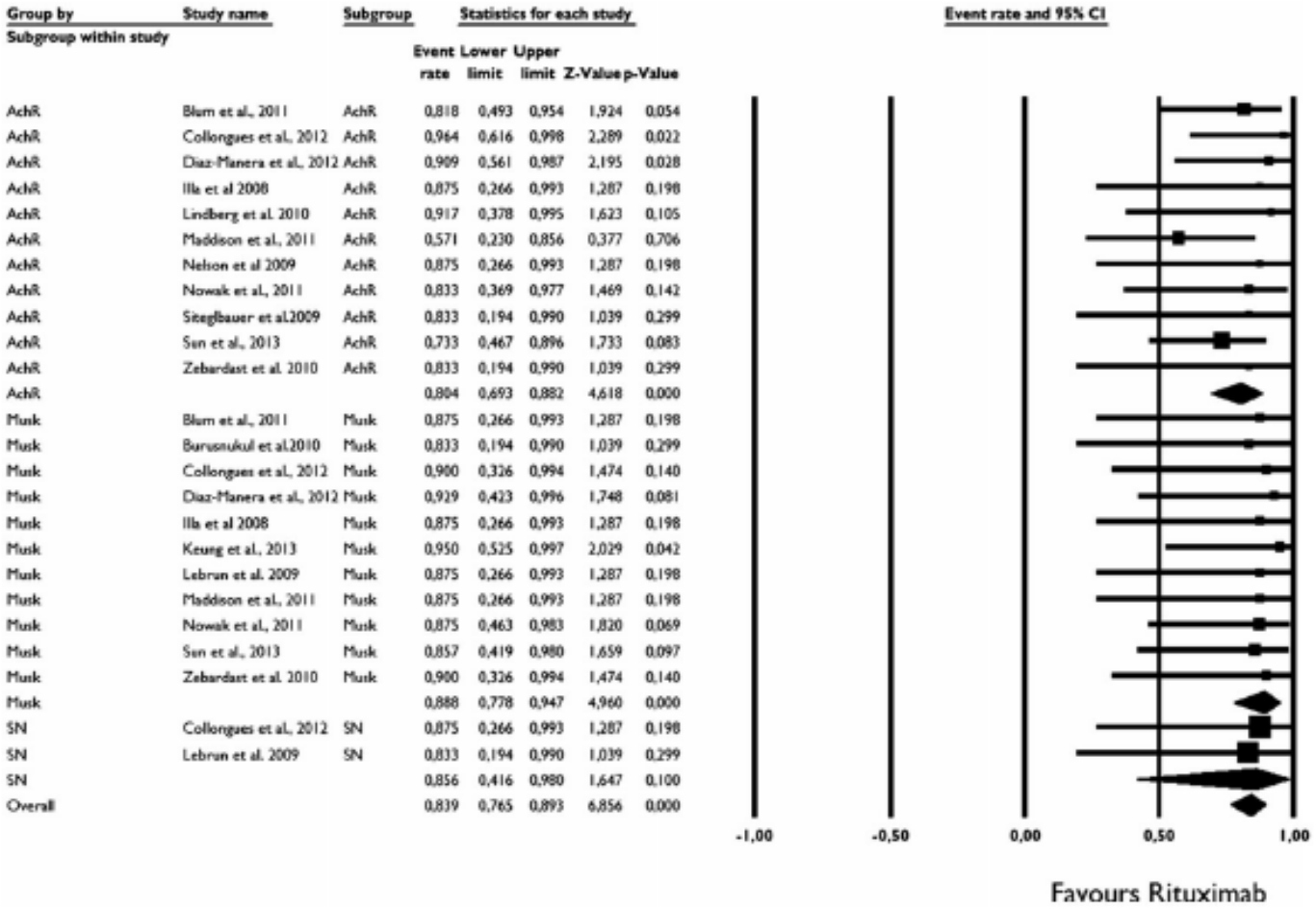
Det mest använda biologiska LM vid MG: Rituximab

Meta-analys RTX i MG

MG subtype	No. of studies	Pts	Gender M/F	Age at treatment	Refractory MG	Disease severity	MG duration years (mean, range)
AChR-Ab+	24	91	30/61	Range 9–81 Mean 43 Median 40	81 (89 %)	Severe 71 (78 %) M/M 20	9.2 (0.5–45)
MuSK-Ab+	23	70	10/60	Range 16–69 Mean 43 Median 43	68 (97 %)	Severe 53 (76 %) M/M 17	7 (1–27)
SN-MG	4	7	3/4	Range 5–78 Mean 38 Median 39	6 (86 %)	Severe 5 (71 %) M/M 1 n/r 1	12.8 (0.5–44)

J Neurol 2015 262:1115-1119

Meta-analys RTX i MG



Group by Subgroup within study	Study name	Subgroup	Event rate	Lower limit	Upper limit	Z-Value	p-Value
AchR	Blum et al., 2011	AchR	0,818	0,493	0,954	1,924	0,054
AchR	Collongues et al., 2012	AchR	0,964	0,616	0,998	2,289	0,022
AchR	Diaz-Manera et al., 2012	AchR	0,909	0,561	0,987	2,195	0,028
AchR	Illa et al 2008	AchR	0,875	0,266	0,993	1,287	0,198
AchR	Lindberg et al. 2010	AchR	0,917	0,378	0,995	1,623	0,105
AchR	Maddison et al., 2011	AchR	0,571	0,230	0,856	0,377	0,706
AchR	Nelson et al 2009	AchR	0,875	0,266	0,993	1,287	0,198
AchR	Nowak et al., 2011	AchR	0,833	0,369	0,977	1,469	0,142
AchR	Stieglbauer et al.2009	AchR	0,833	0,194	0,990	1,039	0,299
AchR	Sun et al., 2013	AchR	0,733	0,467	0,896	1,733	0,083
AchR	Zebardast et al. 2010	AchR	0,833	0,194	0,990	1,039	0,299
AchR			0,804	0,693	0,882	4,618	0,000
Musk	Blum et al., 2011	Musk	0,875	0,266	0,993	1,287	0,198
Musk	Burusnukul et al.2010	Musk	0,833	0,194	0,990	1,039	0,299
Musk	Collongues et al., 2012	Musk	0,900	0,326	0,994	1,474	0,140
Musk	Diaz-Manera et al., 2012	Musk	0,929	0,423	0,996	1,748	0,081
Musk	Illa et al 2008	Musk	0,875	0,266	0,993	1,287	0,198
Musk	Keung et al., 2013	Musk	0,950	0,525	0,997	2,029	0,042
Musk	Lebrun et al. 2009	Musk	0,875	0,266	0,993	1,287	0,198
Musk	Maddison et al., 2011	Musk	0,875	0,266	0,993	1,287	0,198
Musk	Nowak et al., 2011	Musk	0,875	0,463	0,983	1,820	0,069
Musk	Sun et al., 2013	Musk	0,857	0,419	0,980	1,659	0,097
Musk	Zebardast et al. 2010	Musk	0,900	0,326	0,994	1,474	0,140
Musk			0,888	0,778	0,947	4,960	0,000
SN	Collongues et al., 2012	SN	0,875	0,266	0,993	1,287	0,198
SN	Lebrun et al. 2009	SN	0,833	0,194	0,990	1,039	0,299
SN			0,856	0,416	0,980	1,647	0,100
Overall			0,839	0,765	0,893	6,856	0,000

Verkar som om det har effekt…

Flertal fått 375mg/m^2 x 4

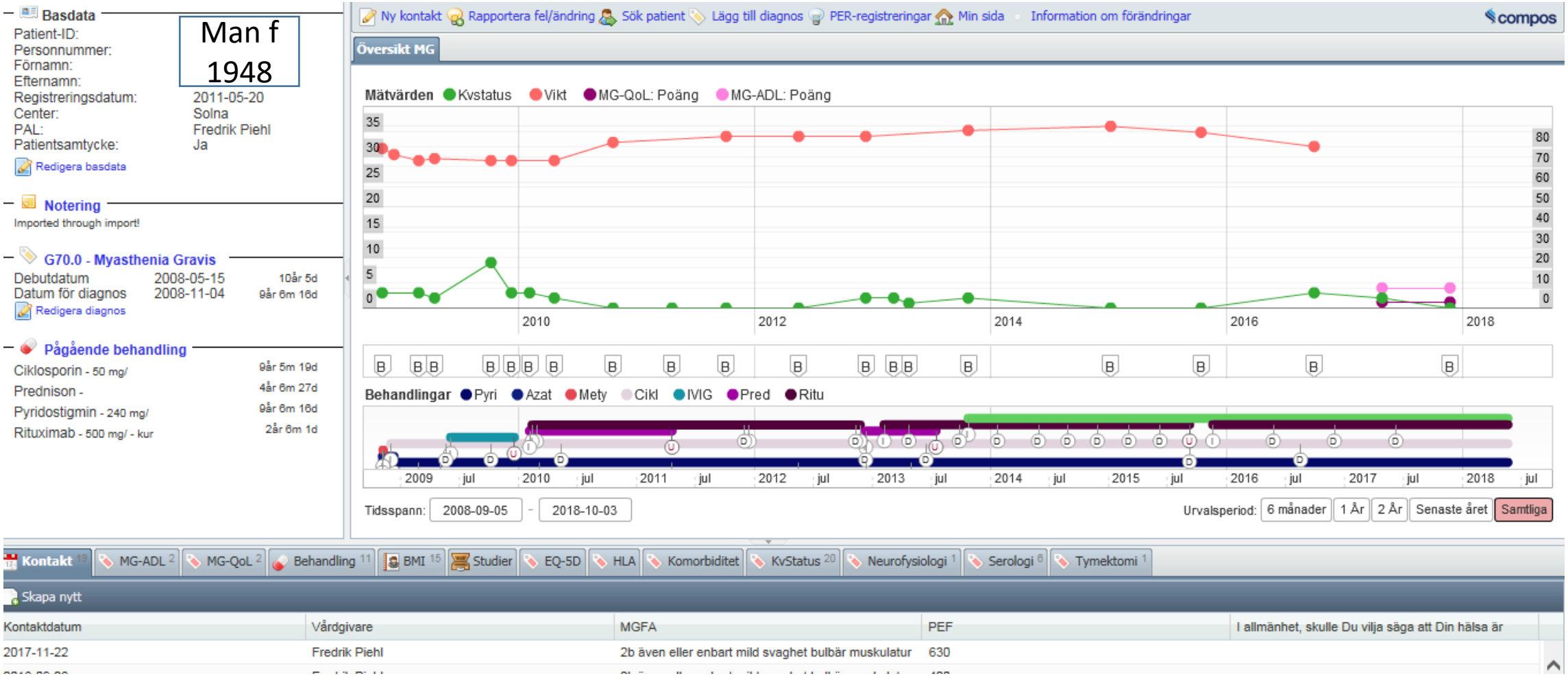
Även, JAMA Neurol. 2017 1;74(1):60-66
ytterligare 16 patienter

Karolinska n=70 (500mg x 1 dosering)

-refraktära
-nydebuterade

J Neurol 2015 262:1115-1119

Exempel



Dubbelseronegativ, tymektomi = atrofi

Amerikansk retrospektiv komparativ effektstudie MuSK+ MG

RTX n=24, kontroller n=31 valda med liknande sjukdomskaraktäristik

Median uppföljning >3.5 å.

Primärt utfall: antal/dos immunosuppressiva och kliniskt status

58% RTX och 16% av kontroller uppnådde förbättring (p = 0.002)

29% RTX hade Prednisolon (medel 4.5 mg/d) jämfört med 74% av kontroller (medel 13 mg/d)

Neurology. 2017 89(10):1069-1077.

Pågående RCT med RTX för MG

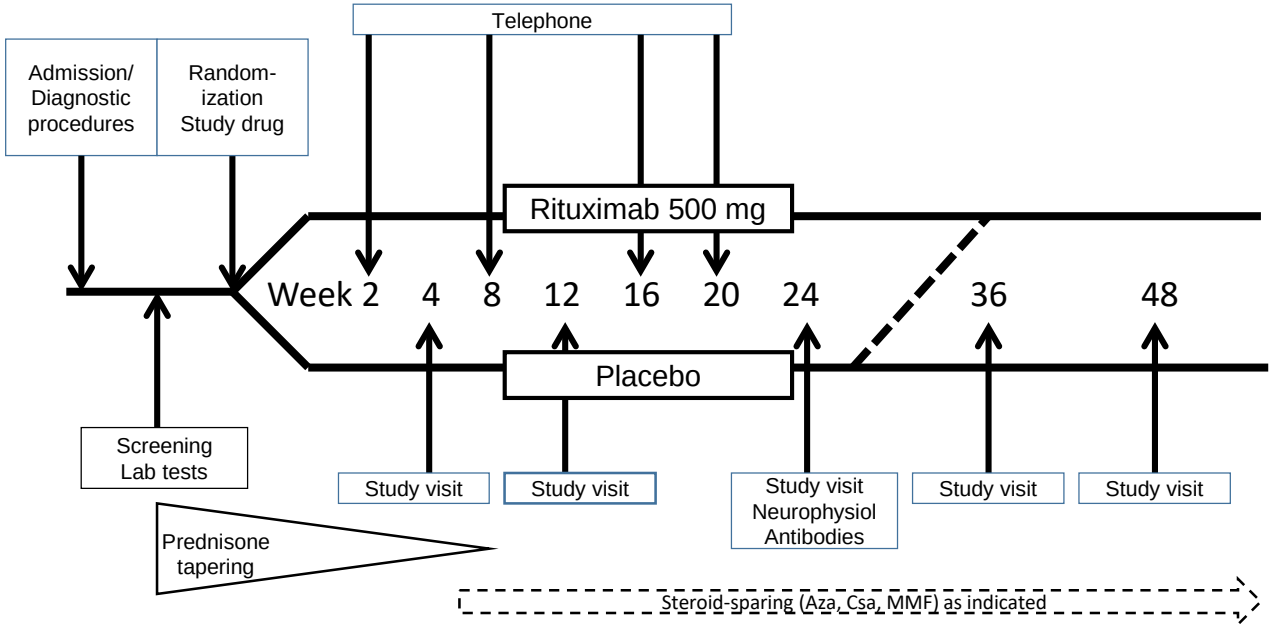
Placebo-kontrollerade (add-on)

BeatMG: Phase II Trial of Rituximab In Myasthenia Gravis
(USA, refractory MG, 375mg/m^2x4, n=50)

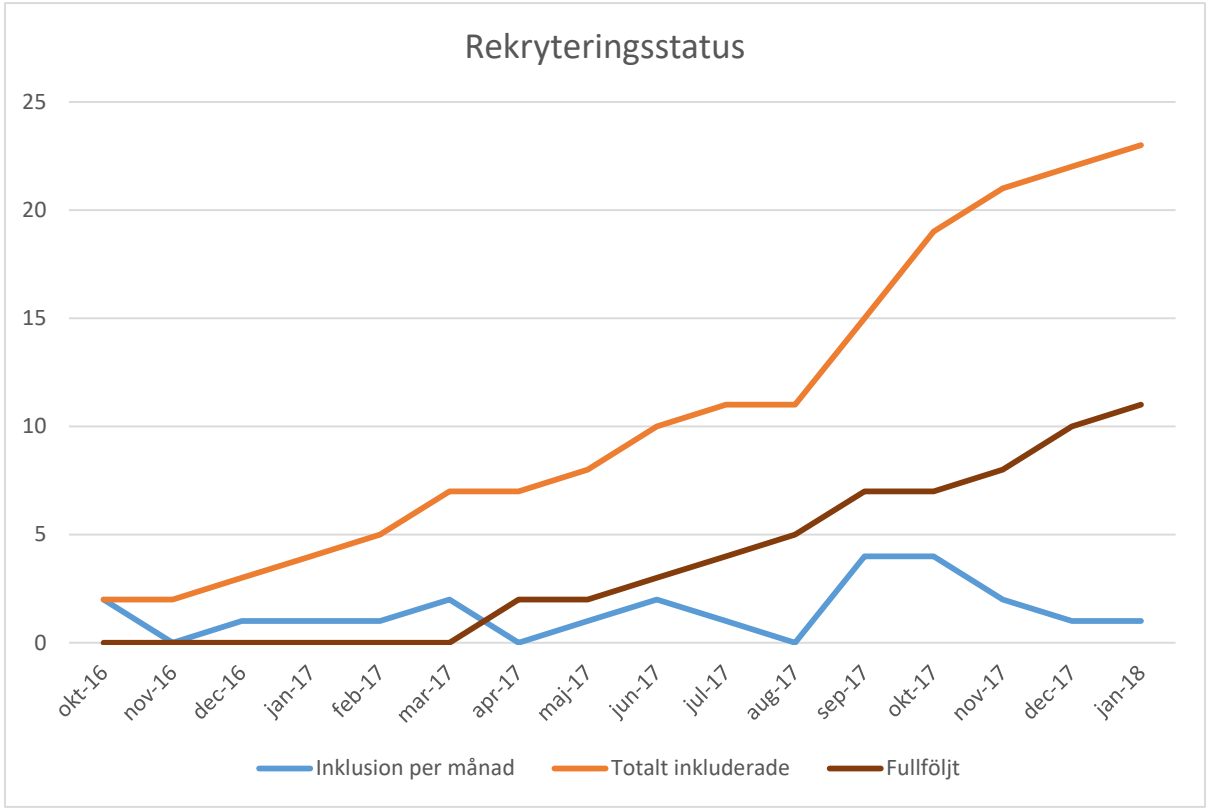
Rinomax: Rituximab for new onset Myasthenia Gravis
(Sweden, all university clinics + 2 regional clinics,
new onset MG, 500 mg single dose, n=50 (19))
Rationale: impede build up of plasma cell pool

- *Importance of treating effectively early vs stepped approach*

RINOMAX: Mabthera-studie vid nydebuterad MG

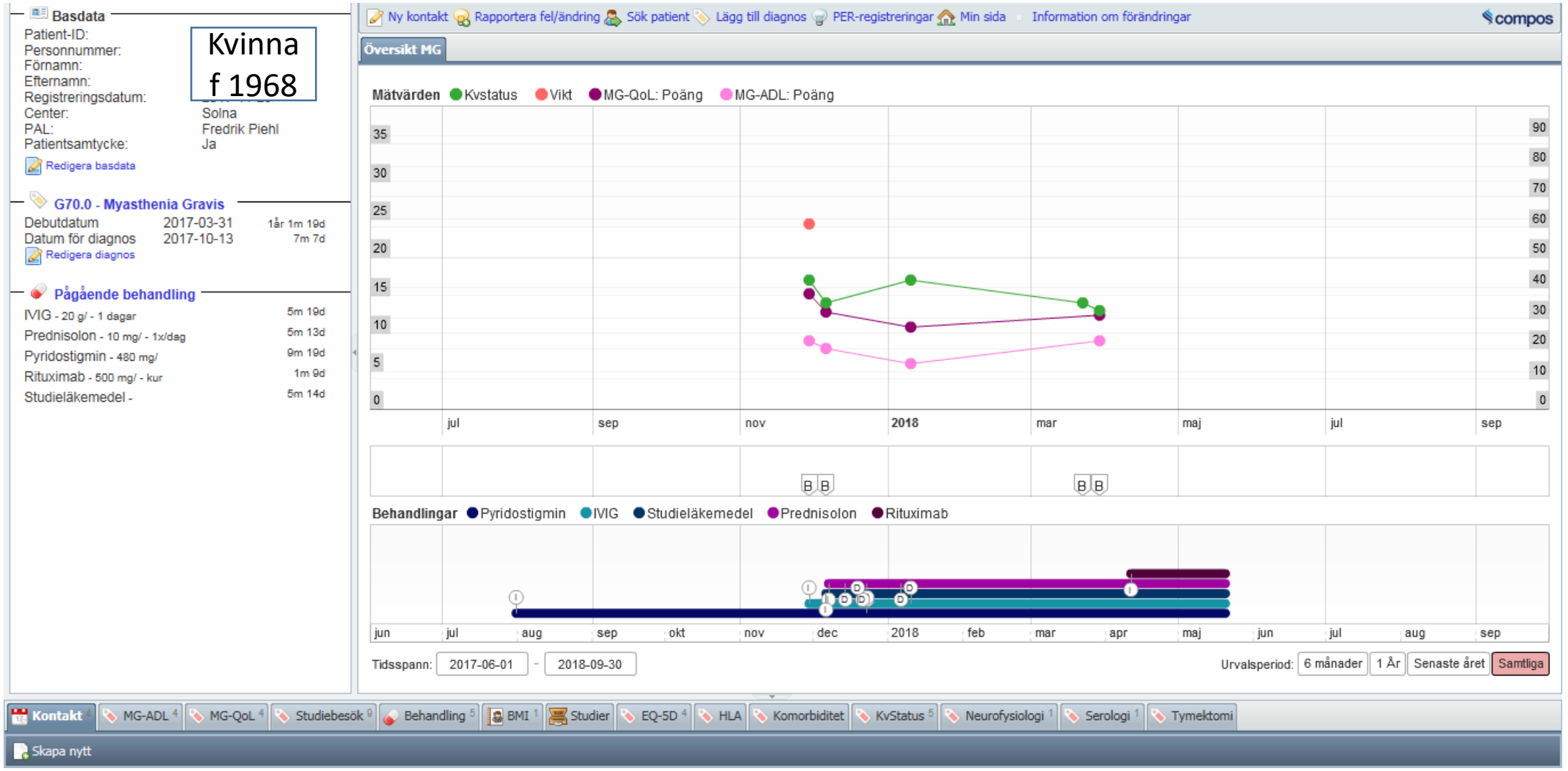


RINOMAX: Mabthera-studie vid nydebuterad MG



PatientId	Rinomax-MS inklusion (datum)	Enhet
24153	2016-10-20 10:49:13	Solna
24105	2016-10-25 11:05:11	Solna
25128	2016-12-16 10:38:47	Huddinge
25512	2017-01-04 08:02:43	Umeå
25861	2017-02-21 14:27:25	Sahlgrenska
25306	2017-03-07 16:00:25	Huddinge
26114	2017-03-09 14:41:32	Sahlgrenska
26502	2017-05-23 15:42:53	Ryhov
27112	2017-06-01 16:31:57	Huddinge
27065	2017-06-15 14:42:39	Sahlgrenska
27534	2017-07-12 12:01:51	Solna
27544	2017-09-07 15:47:36	Sahlgrenska
28045	2017-09-12 10:56:04	Solna
28069	2017-09-15 11:05:51	Huddinge
28085	2017-09-19 10:50:45	Karlstad
28178	2017-10-02 10:05:12	Neurologiska kliniken Linköping
28198	2017-10-02 12:39:08	Solna
27636	2017-10-04 18:23:25	Solna
28536	2017-10-17 08:52:40	Uppsala
28709	2017-11-07 14:38:59	Solna
28994	2017-11-29 09:27:54	Solna
28758	2017-12-13 10:58:16	Sahlgrenska
29343	2018-01-09 14:40:21	Solna
30366	2018-04-11 09:13:23	Solna

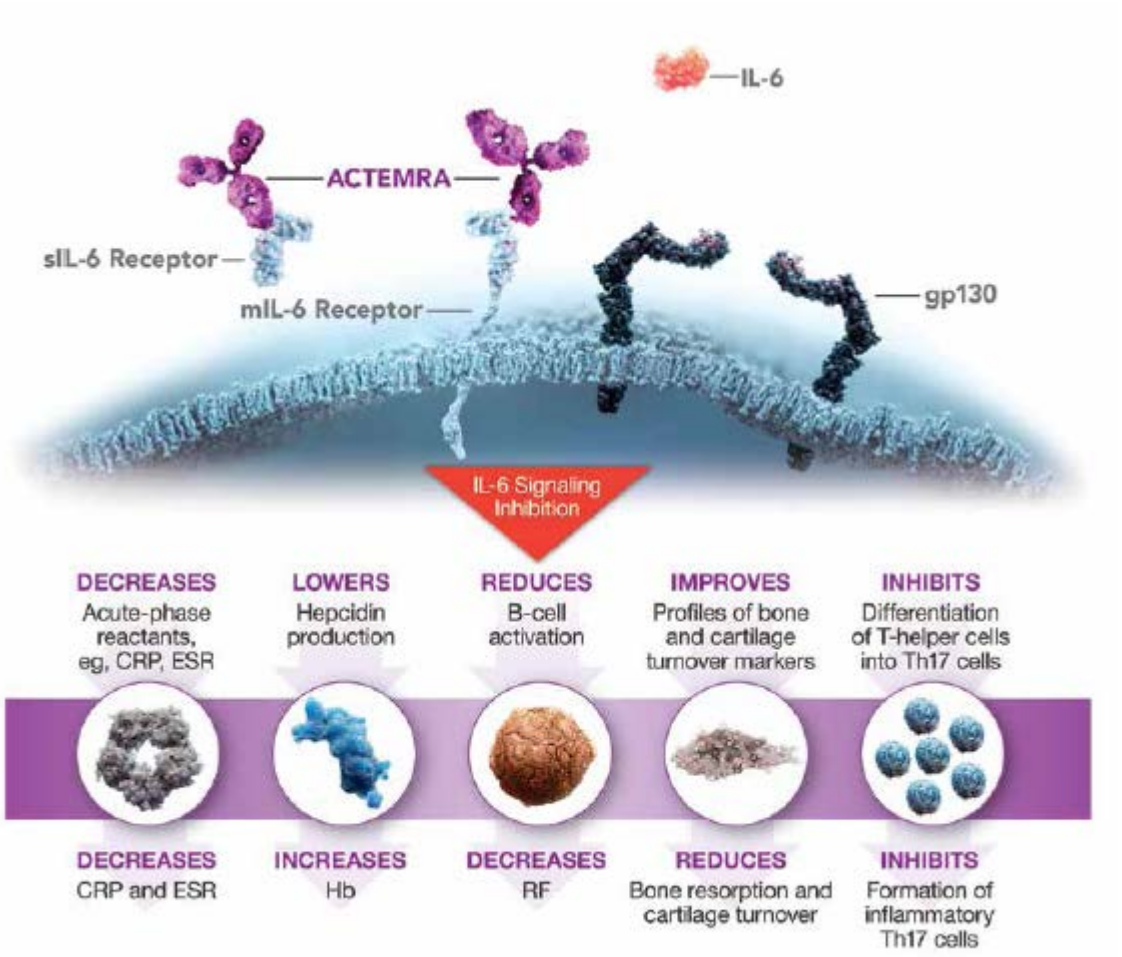
Exempel


Basdata
Patient-ID:
Personnummer:
Förnamn:
Efternamn:
Registreringsdatum:
Center: Solna
PAL: Fredrik Piehl
Patientsamtycke: Ja
Kvinna f 1968
Redigera basdata
G70.0 - Myasthenia Gravis
Debutdatum 2017-03-31 1år 1m 19d
Datum för diagnos 2017-10-13 7m 7d
Redigera diagnos
Pågående behandling
IVIG - 20 g/ - 1 dagar 5m 19d
Prednisolon - 10 mg/ - 1x/dag 5m 13d
Pyridostigmin - 480 mg/ 9m 19d
Rituximab - 500 mg/ - kur 1m 9d
Studieläkemedel - 5m 14d
Ny kontakt
Rapportera fel/ändring
Sök patient
Lägg till diagnos
PER-registreringar
Min sida
Information om förändringar
compos
Översikt MG
Mätvärden Kvstatus Vikt MG-QoL: Poäng MG-ADL: Poäng
jul sep nov 2018 mar maj jul sep
Behandlingar Pyridostigmin IVIG Studieläkemedel Prednisolon Rituximab
jun jul aug sep okt nov dec 2018 feb mar apr maj jun jul aug sep
Tidsspann: 2017-06-01 - 2018-09-30
Urvalsperiod: 6 månader 1 År Senaste året Samtliga
Kontakt
MG-ADL
MG-QoL
Studiebesök
Behandling
BMI
Studier
EQ-5D
HLA
Komorbiditet
KvStatus
Neurofysiologi
Serologi
Tymektomi
Skapa nytt

Om inte RTX fungerar...

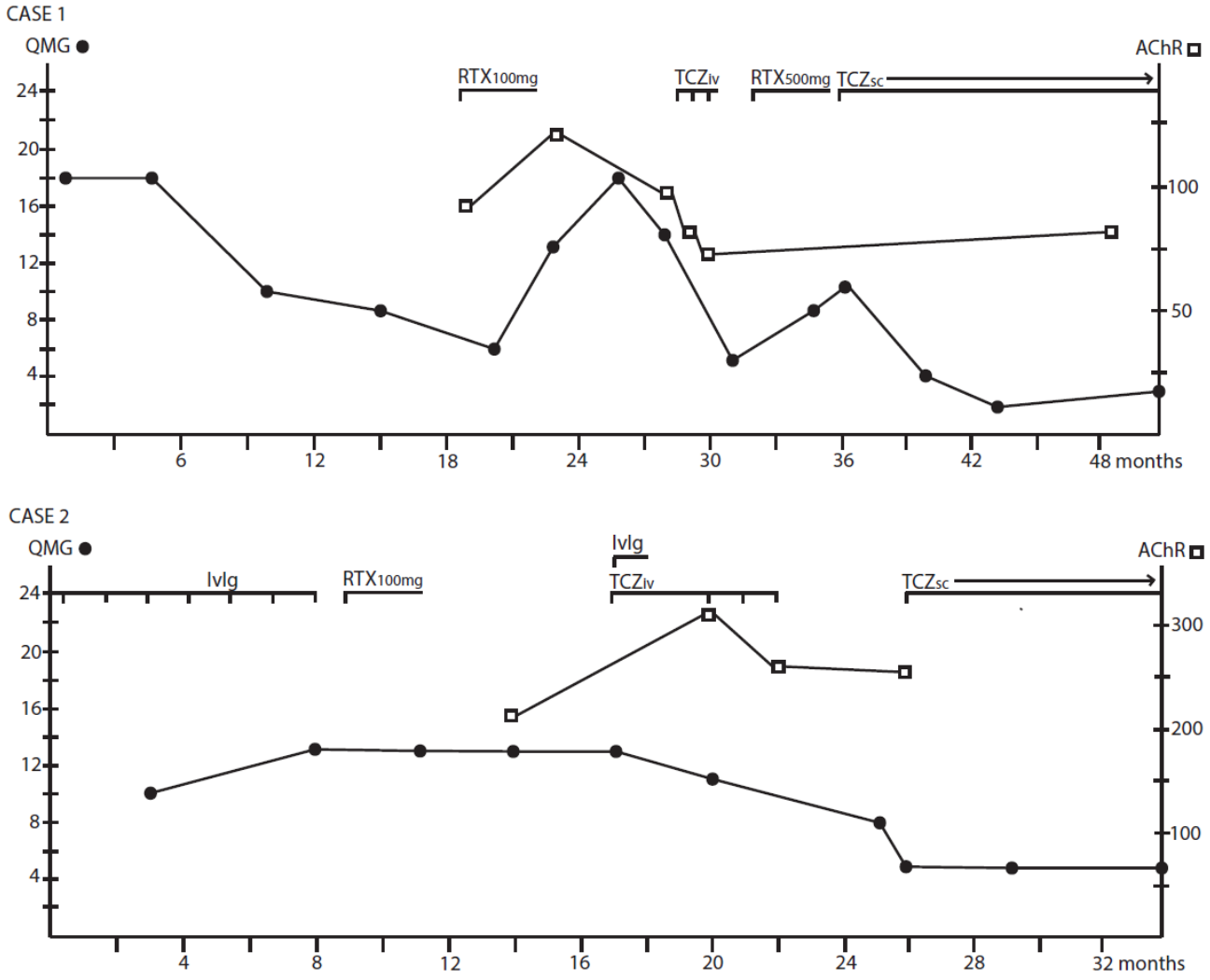
RoActemra är godkänt för
RA (nydebuterad, svår) eller minst
måttligt svår RA med
bristande effekta på DMARD/
TNF-blockerare.

Ges i infusion 1gg/mån alt
s.c. en gång/vecka



IL-6 driver antikroppsproduktion hos plasmablaster vid NMO
Två fas III studier i NMO pågår

Magert evidens hittills: Två fall av RTX refraktär MG



Jónsson, Neuromuscular Disorders 27 (2017) 565–568

För riktigt svåra nötter: Autolog hematogen stamcellstransplnatation (HSCT)

Original Investigation

Myasthenia Gravis Treated With Autologous Hematopoietic Stem Cell Transplantation

Adam Bryant, MD; Harold Atkins, MD, FRCPC; C. Elizabeth Pringle, MD; David Allan, MD, MSc; Grizel Anstee, MD; Isabelle Bence-Bruckler, MD, FRCPC; Linda Hamelin, MScN; Michael Hodgins, MD; Harry Hopkins, RPh, FCSHP; Lothar Huebsch, MD, FRCPC; Sheryl McDiarmid, MBA; Mitchell Sabloff, MD, FRCPC; Dawn Sheppard, MD, MSc, FRCPC; Jason Tay, MD, MSc, FRCPC; Christopher Bredeson, MD, MSc, FRCPC

IMPORTANCE Some patients with myasthenia gravis (MG) do not respond to conventional treatment and have severe or life-threatening symptoms. Alternate and emerging therapies have not yet proved consistently or durably effective. Autologous hematopoietic stem cell transplant (HSCT) has been effective in treating other severe autoimmune neurologic conditions and may have similar application in MG.

Editorial

Supplemental content at jamaneurology.com

RESULTS Seven patients underwent autologous HSCT, 6 for MG and 1 for follicular lymphoma with coincident active MG. Mean (SD) ages at MG diagnosis and at autologous HSCT were 37 (11) and 44 (10) years, respectively. Five patients (71%) had concurrent autoimmune or lymphoproliferative illnesses related to immune dysregulation. All patients had distinct clinical and electromyographic evidence of MG (MGFA clinical classification IIIb-V). All patients achieved durable MGFA complete stable remission with no residual MG symptoms and freedom from any ongoing MG therapy (MGFA postintervention status of complete stable remission). Three patients (43%) experienced transient viral reactivations, and 1 (14%) developed a secondary autoimmune disease after autologous HSCT, all of which resolved or stabilized with treatment. There were no treatment- or MG-related deaths.

JAMA Neurol. doi:10.1001/jamaneurol.2016.0113

Svensk erfarenhet av HSCT: Sveriges mest refraktära MG ?
-strålande effekt av HSCT

Table 1
Treatment for MG before AHSCT.

Drug	Dose	Administration	Effect
Pyridostigmine	360–840 mg/day	Age 27 to 64[1]	Moderately positive
Terbutaline	7.5–15 mg/day	Age 35 to 64[2]	No effect*
Methylprednisolone	3–4 g total dose	Three times, at age 38, 46 and 51	No effect
Azathioprine	150 mg/day	Eight months[3], age 51	No effect
Prednisolone	10–60 mg/day	Several times, for weeks to months	No effect
Sirolimus	2 mg/day	Two months[3], age 53	No effect
Rituximab	2 g total dose	Age 54	No effect
Cyclosporin	350 mg/day	Nine months[3], age 54	No effect
Mycofenolat mofetil	2 g/day	Ten months at age 57 and 12 months at age 61[3]	No effect
Bortezomib	25 mg total dose[4]	Age 59	No effect
Cyclophosphamide	10.6 g total dose	Age 61	No effect
IvIg	20–30 g	Numerous treatment series with 20–30 g × 1 × III-V and several periods of 20–30 g given every third or fourth week during the last 13 years before AHSCT.	Varying from none to good but short lasting.
Plasmapheresis	Usually three to five exchanges	Numerous treatment series during the last 13 years before AHSCT.	Varying from slightly positive to very good but short lasting.

Bortezomib (Velcade™) – multiplelt myelom, proteasom-hämmare, slår ut plasmaceller, risk bl a polyneuropati

Håkansson, Neuromuscular Disorders 27 (2017) 90–93

Olika verkningsmekanismer vid autoantikroppsmedierade sjukdom

-fördel kombinera ?

Sveinsson et al, J Neuroimmunol 2017

Reducerade livskvalitetsmått vid generaliserad MG; incitament förbättra behandlingen?

An up-date on health-related quality of life in myasthenia gravis -results from population based cohorts

M. I. Boldingh[1,4*], L. Dekker[2], A. H. Maniaol[1], C. Brunborg[1,3], A. F. Lipka[2], E. H. Niks[2], J. J. G. M. Verschuuren[2] and C. M. E. Tallaksen[1,4]

Abstract

Current available therapies control Myasthenia gravis (MG) reasonably well, but Health Related Quality of life (HRQOL) remains lower than expected. The aim was provide insights in how HRQOL in MG stands across borders and time, compare the scores to general population controls and other chronic disorders and assess the impact of potential predictors for quality of life such as a) clinical characteristics b) antibodies c) thymoma and d) treatment in a population-based cohort.

Methods: We designed a population-based cross-sectional study including 858 patients, 373 from Norway and 485 from the Netherlands. The Short Form Health Survey 36 (SF-36) and a cross-cultural validated questionnaire were used. Data were in addition compared to the general population, other chronic diseases and previous studies.

Results: Mean physical composite score was 59.4 and mental composite score 69.0 with no differences between the countries. The mean HRQOL score was lower in patients with bulbar and generalized symptoms ($p < 0.001$) compared to sex and age adjusted healthy controls, but not in patients with ocular symptoms or patients in remission. Multivariate analysis revealed that female gender, generalized symptoms and use of secondary immunosuppressive drugs at the time of testing were risk factors for reduced HRQOL.

Conclusions: Remission and absence of generalized symptoms were favorable factors for HRQOL in MG patients. Historically, the HRQOL levels have not changed since 2001 and no new clinical predictors could be detected in this exhaustive population-based study. Further studies should explore the impact of non clinical factors like ethnic variations, socio-economic and hormonal factors on HRQOL.

Keywords: Health-related quality of life, SF-36, Myasthenia gravis, MuSK, Seronegative MG, Acetylcholine receptor, Thymoma, Population based, Burden of disease

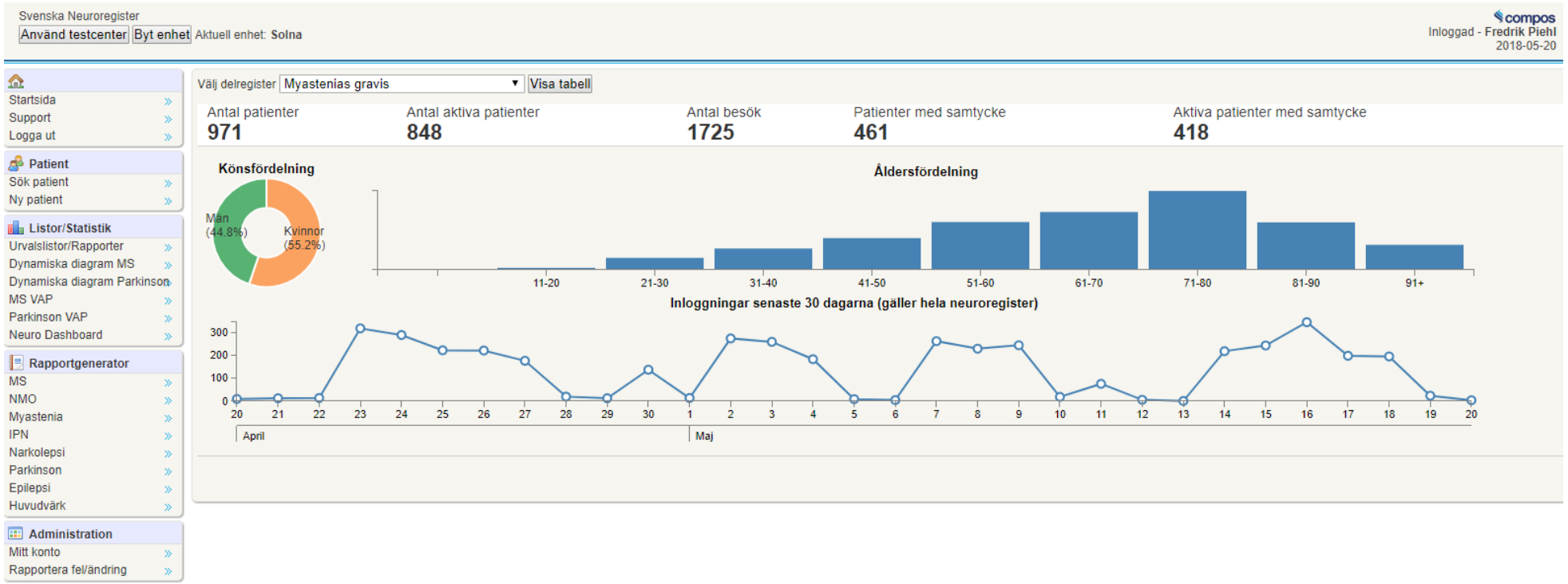
Boldingh et al. Health and Quality of Life Outcomes (2015) 13:115

Sammanfattning

- Signifikant andel med otillräcklig effekt av p.o immunosuppressiva
  - -Värde av att även registrera QoL och ADL funktionsnivå
- Delvis lovande resultat med nyare biologiska LM
  - -Roll för eculizumab (biverkningsrisk, kostnader)?
  - -Rituximab sannolikt lägre risker, olika behandlingsalgoritmer
  - -Tocilizumab?
- Bortezomib eller HSCT vid sjukdom refraktär för biologiska LM behandlingar?
- Bättre effekt av att behandla med biologiska LM tidigt i sjukdomsförloppet?

Nu dags för reklampaus....

MG registret: Hyggligt, men kan bli bättre!



Viktigt ffa nyinsjuknade och de som får biologiska LM
-Viktigt för att utveckla förbättrade behandlingsalgoritmer

Klinik	TotalPatients	AktivaPatienter	AvslutadePatienter	Kvinnor	Men	KvStatus	MG-ADL	MG-QoL	EQ5D	Visits	Behandling	OngoingBehandling
Solna	547	458	89	327	220	744	57	37	20	829	551	304
Huddinge	78	72	6	40	38	89	19	14	14	120	196	110
Umeå	33	29	4	19	14	60	0	1	0	251	156	64
Gävle	18	16	2	5	13	4	1	0	0	10	35	23
Uppsala	15	15	0	8	7	16	0	0	0	32	25	22
Västerås	12	12	0	4	8	2	0	0	0	6	14	8
Östersund	11	11	0	4	7	31	0	0	0	34	29	18
Danderyd	7	7	0	2	5	11	0	0	0	13	14	12
Kristianstad	7	6	1	6	1	15	0	0	0	46	28	10
Sahlgrenska	7	7	0	3	4	18	18	18	16	0	10	10
Karlskrona	6	6	0	2	4	0	0	0	0	34	0	0
Bollnäs	4	3	1	2	2	6	0	0	0	6	7	2
Nyköping	3	3	0	1	2	8	1	1	2	8	2	2
Ryhov	3	3	0	2	1	4	4	4	4	2	0	0
Norrköping	1	1	0	1	0	0	0	0	0	0	9	3
Oskarshamn	1	1	0	1	0	0	0	0	0	1	1	1
Sunderbyn	1	1	0	1	0	0	0	0	0	0	0	0
Västervik	1	1	0	0	1	0	0	0	0	0	0	0
Riket 2017-09-09	755	652	103	428	327	1008	100	75	56	1392	1077	589
Riket 2016-09-24	709			412	297							
Diff2017.2016	46			16	30							

Efter EIRA och EIMS, nu dags för EIMG ?

Sjösätta nationell studie avseende miljöfaktorer och genetik ?

Susanna.brauner@ki.se
Fredrik.piehl@ki.se

Tack till Svenska MG nätverket

Och särskilt de som registrerar i registret och rekryterar till Rinomax

Våra patienter förtjänar det!