# MYASTHENIA GRAVIS: EARLY TREATMENT WITH BIOLOGICS

# PROS

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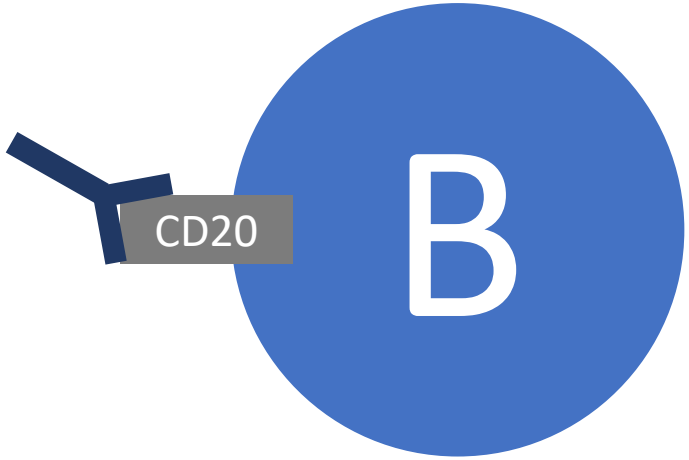
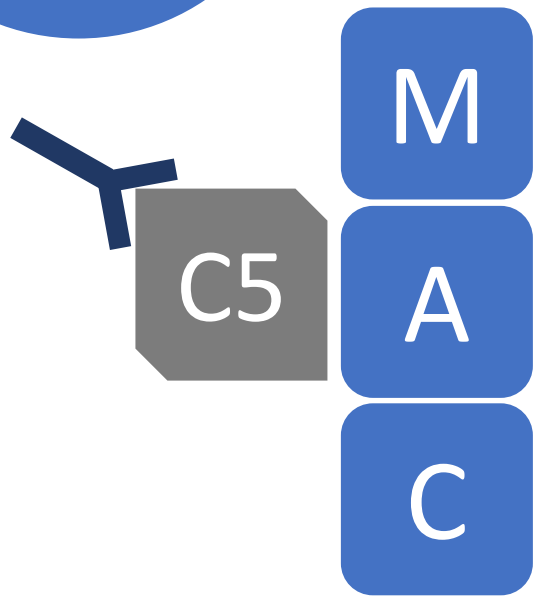
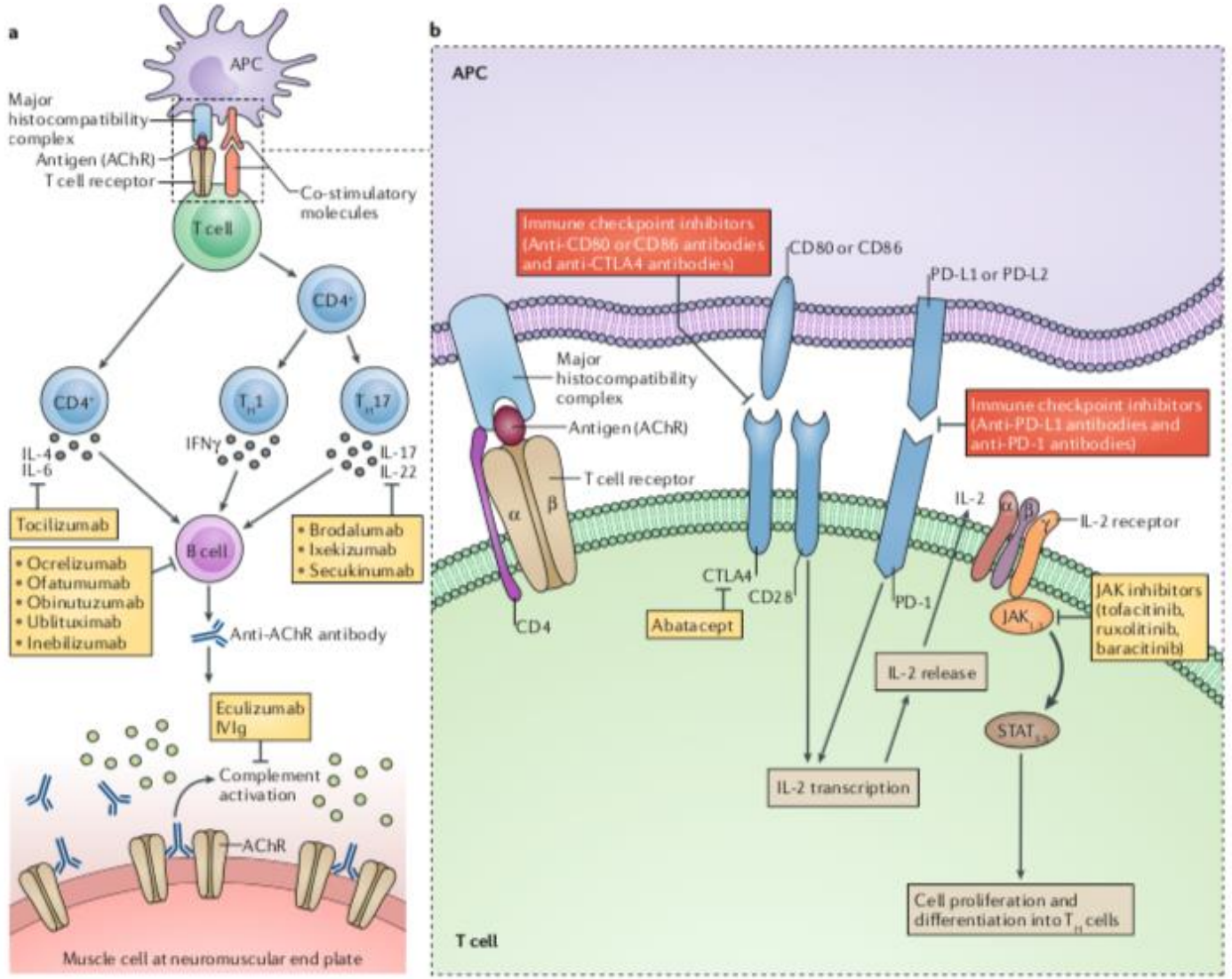
# BIOLOGICS IN MYASTHENIA GRAVIS




**Rituximab**




**Eculizumab**




**Immunotherapy in myasthenia gravis in the era of biologics** Dalakas, 2018 Nature Rev. Neurology

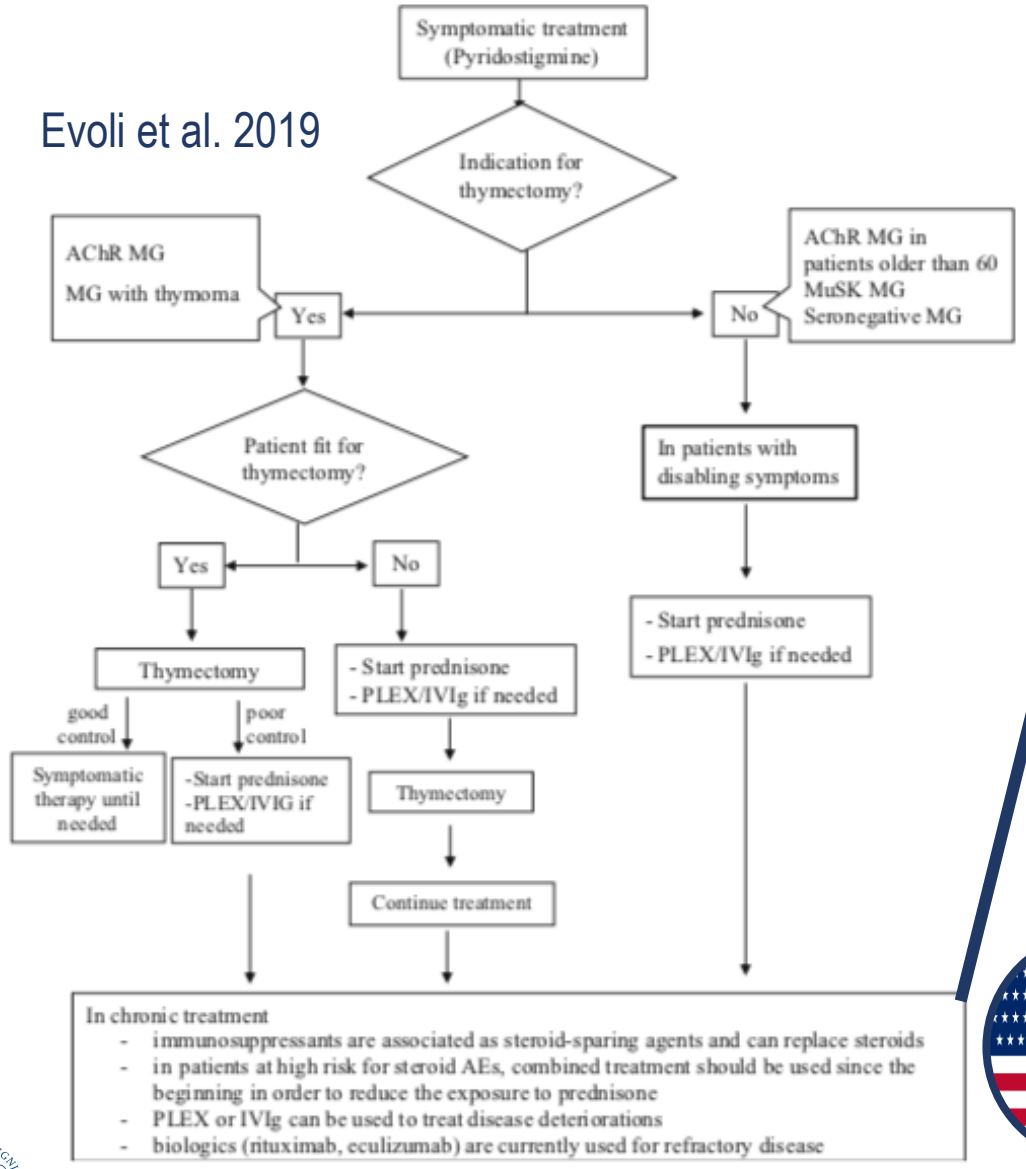
# BIOLOGICS IN MYASTHENIA GRAVIS

| Drug | Mechanism | Current state | Ref |
|---|---|---|---|
| **Rituximab** | CD20 Ab | Approved | Tandan et al 2017 |
| **Eculizumab** | C5 Ab | Approved<br>Phase III (REGAIN) | Howard et al 2017 |
| **Belimumab** | BAFF Ab | Phase II trial | Hewett et al 2018 |
| **Efgartigimod** | FcRn Ab | Phase II trial | Howard et al 2019 |
| **Ravulizumab** | C5 Ab | Future phase III trial | McKeage 2019 |
| **Zilucoplan** | C5 antagonist | Phase II | Beecher et al 2019 |
| **Tocilizumab** | IL6R Ab | Case report | Jonsson et al 2017 |

**Immunotherapy in myasthenia gravis in the era of biologics** Dalakas, 2018 Nature Rev. Neurology

# BIOLOGICS IN THERAPEUTIC ALGORITHM

Evoli et al. 2019




**Biologics (rituximab, eculizumab) are currently used for REFRACTORY DISEASE**

refractory to classical immunosoppressive treatment (Evoli et al 2019)

no specific definition – patients not responding to classical classical immunosoppressive treatment (Melzer et al 2016)

no specific definition – patients not responding to classical classical immunosoppressive treatment (Sussman et al 2015)

PIS3 is unchanged or worse after corticosteroids and at least 2 other IS agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician (Sanders et al 2016)

# RISK FACTOR FOR REFRACTORY MG

1. Failure to respond adequately to conventional therapies
2. Inability to reduce immunosuppressive therapy without clinical relapse or a need for ongoing rescue therapy such as intravenous immuno- globulin G (IVIg) or plasma exchange (PE)
3. Severe or intolerable adverse effects from immunosuppressive therapy
4. Comorbid conditions that restrict the use of conventional therapies
5. Frequent myasthenic crises even while on therapy

| Parameter | Total ($n$ = 128) | Nonrefractory ($n$ = 109) | Refractory ($n$ = 19) | $p$ value* |
|---|---|---|---|---|
| Median age at onset, year (IQR) | 55 (38–69) | 60 (42–72) | 36 (28–51) | <0.001 |
| Female | 51% | 47% | 74% | 0.03 |
| Antibody status available | 90% | 88% | 100% | |
| Anti-AChR positive | 71% | 75% | 53% | 0.05 |
| Anti-MuSK positive | 10% | 2% | 47% | <0.001 |
| Double seronegative | 19% | 23% | 0 | 0.02 |
| Thymectomy | 24% | 17% | 68% | <0.001 |
| Thymoma status available | 60% | 61% | 58% | |
| Thymomatous | 18% | 14% | 45% | 0.02 |
| Non-thymomatous | 82% | 86% | 55% | |

Adapted from Suh *et al.*[11] with permission from The Yale School of Biology and Medicine.
*For comparison between patients with refractory and nonrefractory myasthenia gravis.
Anti-AChR positive, anti-acetylcholine receptor antibody positive; anti-MuSK positive, anti-muscle-specific tyrosine kinase antibody positive; IQR, interquartile range.

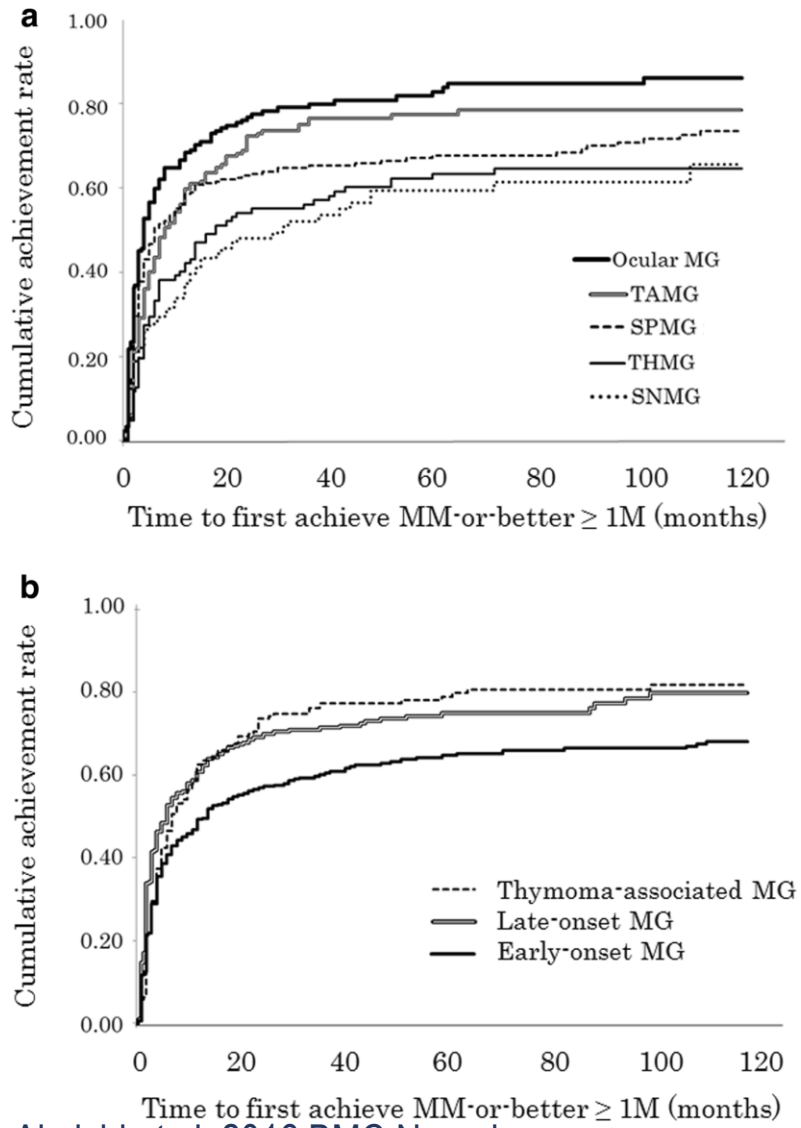
**Female** **Young** **MUSK+**

**When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies** Mantegazza and Antozzi 2018 Therapeutic Advances in Neurological Disorders

# RESPONSE RATE TO CLASSICAL MG THERAPY

**Table 5** Details of past treatment and response to treatment for each of the five subtypes

| | Ocular MG | Thymoma-associated MG | MG with thymic hyperplasia | AChR-Ab-negative MG | (MuSK-Ab -positive) | AChR-Ab-positive MG without thymic abnormalities | Total |
|---|---|---|---|---|---|---|---|
| Past immunotherapy ($n = 923$) | | | | | | | |
| Peak dose of oral PSL, mg/day | 9.2 ± 12.2, 5.0† | 28.5 ± 18.8, 30.0† | 29.7 ± 19.4, 30.0† | 18.8 ± 17.2, 15.0 | 32.6 ± 20.6, 30.0 | 23.7 ± 20.2, 20.0 | 21.5 ± 19.3, 15.0 |
| Duration of PSL ≥20 mg/day, M | 0.0 ± 0.0, 0.0† | 12.0 ± 25.2, 5.0† | 13.0 ± 27.3, 6.0† | 3.8 ± 7.0, 0.0 | 7.2 ± 9.5, 4.0 | 8.2 ± 17.0, 2.0 | 7.9 ± 19.3, 1.0 |
| CNIs,% | 24.0%* | 68.2%* | 54.0% | 67.4% | (72.7%) | 58.1% | 52.9% |
| PP,% | 2.0%* | 48.1%* | 22.1% | 46.0%* | (54.5%) | 37.2% | 27.3% |
| IVIG,% | 6.1%* | 36.1% | 29.9% | 42.5%* | (27.3%) | 24.7% | 15.0% |
| Initial response to treatment ($n = 923$, see Fig. 2a) | | | | | | | |
| Achievement of MM-or-better once,% | 79.8%* | 73.5% | 66.1% | 56.2%* | (75.0%) | 67.8% | 70.2% |
| Months to achieve MM-or-better in 50% of patients | 4.0‡ | 8.0 | 18.0‡ | 31.0‡ | (7.0) | 6.0 | 8.0 |
| Stability of improved status ($n = 923$) | | | | | | | |
| MM-or-better at present,% | 74.0%* | 58.1% | 49.6% | 39.6%* | (55.0%) | 55.4% | 57.6% |
| Maintaining rate of MM-or-better, % | 92.7%* | 79.0% | 75.0% | 70.5% | (73.3%) | 81.7% | 82.1% |




**Response to treatment of myasthenia gravis according to clinical subtype** Akaishi et al. 2016 BMC Neurology

# PRO # 1 - EFFICACY

*INVITED REVIEW*

## RITUXIMAB TREATMENT OF MYASTHENIA GRAVIS: A SYSTEMATIC REVIEW

**RUP TANDAN, MD, FRCP,[1] MICHAEL K. HEHIR II, MD,[1] WAQAR WAHEED, MD,[1] and DIANTHA B. HOWARD, MS[2]**

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*Accepted 28 January 2017*

**Table 3.** Rituximab regimens and treatment effect in myasthenia gravis.

| | All MG ($n = 169$) | AChR MG ($n = 99$) | MuSK MG ($n = 57$) | *P*-value AChR vs. MuSK |
|---|---|---|---|---|
| Rituximab induction regimen | | | | |
| 375 mg/m$^2$ per week × 4 | 135 of 168 (80%) | 77 of 99 (78%) | 48 of 57 (84%) | 0.50 |
| 500 mg days 1 and 14 | 14 of 168 (8%) | 11 of 99 (11%) | 3 of 57 (5%) | |
| Other | 19 of 168 (12%) | 11 of 99 (11%) | 6 of 57 (11%) | |
| Rituximab follow-up regimen | | | | |
| Cycles of rituximab (*n*, % cases) (*n*, range of cycles) | 32 of 168 (19%) (1–4)* | 19 of 98 (19%) (1–2) | 12 of 57 (21%) (1–4) | 0.89 |
| Infusions of rituximab (*n*, %) (*n*, range of infusions, range of intervals in months) | 75 of 131 (57%) (1–8, 1–25) | 46 of 79 (58%) (1–8, 1–25) | 25 of 45 (56%) (1–8, 1–9) | 0.77 |
| Total number of rituximab infusions/case (initial + follow-up) (mean ± SD) | 6.8 ± 3.7 ($n = 167$) | 6.6 ± 3.3 ($n = 98$) | 7.1 ± 4.2 ($n = 57$) | 0.49 |
| Treatment effect | | | | |
| PIS-m MM or better (*n*, %) | 75 of 169 (44%) | 30 of 99 (30%) | 41 of 57 (72%) | <0.001 |
| PIS-m CSR or PR (*n*, %) | 45 of 169 (27%) | 16 of 99 (16%) | 27 of 57 (47%) | <0.001 |
| Any relapse after rituximab (*n*, %) | 26 of 101 (26%) | 21 of 63 (33%) | 4 of 29 (14%) | 0.05 |
| Relapses after rituximab (*n*) (mean ± SD) | 0.4 ± 0.9 ($n = 100$) | 0.5 ± 1.0 ($n = 62$) | 0.2 ± 0.6 ($n = 29$) | 0.04 |
| QMG score (mean ± SD) | | | | |
| Number of cases | 18 | 15 | 3 | |
| Pre-rituximab | 16.8 ± 5.5 | 17.7 ± 0.5 | 12.7 ± 4.5 | 0.15 |
| Post-rituximab | 8.7 ± 6.9 | 9.9 ± 6.7 | 2.3 ± 4.0 | 0.08 |
| Change in score (absolute) | 8.2 ± 5.1 | 7.7 ± 5.4 | 10.3 ± 2.5 | 0.44 |
| Change in score (%) | 52.6 ± 33.1 | 45.9 ± 30.9 | 86.3 ± 23.8 | 0.05 |

*AChR, acetylcholine receptor; CSR, chronic stable remission; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; MG, myasthenia gravis; PIS-m, postintervention scale—modified; PR, pharmacologic remission; QMG, quantitative myasthenia gravis.*

*One patient was noted to have received "several" cycles.

## Eculizumab: A Review in Generalized Myasthenia Gravis

**Sohita Dhillon[1]**

| Analyses | Treatment | LSM rank[a] or LSM change from BL[b] in total scores at week 26[c] | | | |
|---|---|---|---|---|---|
| | | MG-ADL | QMG | MGC | MG-QOL15 |
| *Worst-rank ANCOVA* | | | | | |
| Prespecified | ECU | 56.6[d] | 54.7* | 57.3 | 55.5* |
| | PL | 68.3[d] | 70.7 | 67.7 | 69.7 |
| | | BGD − 11.7 | BGD − 16.0 | BGD − 10.5 | BGD − 14.3 |
| Post hoc sensitivity | ECU | 54.8* | 53.9** | 56.1* | 54.6* |
| | PL | 70.2 | 71.6 | 69.0 | 70.6 |
| | | BGD − 15.4 | BGD − 17.7 | BGD − 12.9 | BGD − 16.0 |
| *Repeated-measures model* | | | | | |
| Prespecified sensitivity analysis with IST as covariate | ECU | − 4.1** | − 4.6*** | − 7.9* | − 13.8*** |
| | PL | − 2.3 | − 1.7 | − 4.6 | − 6.7 |
| | | BGD − 1.8 | BGD − 2.9 | BGD − 3.3 | BGD − 7.1 |
| Prespecified sensitivity analysis without IST as covariate | ECU | − 4.2** | − 4.6*** | − 8.1* | − 12.6*** |
| | PL | − 2.3 | − 1.6 | − 4.8 | − 5.4 |
| | | BGD − 1.9 | BGD − 3.0 | BGD − 3.3 | BGD − 7.2 |

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ARTICLE CLASS OF EVIDENCE

## Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis

James F. Howard, Jr., MD, Vera Bril, MD, Ted M. Burns, MD, Renato Mantegazza, MD, Malgorzata Bilinska, MD, Andrzej Szczudlik, MD, Said Beydoun, MD, Francisco Javier Rodriguez De Rivera Garrido, MD, Fredrik Piehl, MD, PhD, Mariarosa Rottoli, MD, Philip Van Damme, MD, PhD, Tuan Vu, MD, Amelia Evoli, MD, Miriam Freimer, MD, Tahseen Mozaffar, MD, E. Sally Ward, PhD, Torsten Dreier, PhD, Peter Ulrichts, PhD, Katrien Verschueren, MSc, Antonio Guglietta, MD, Hans de Haard, PhD, Nicolas Leupin, MD, and Jan J.G.M. Verschuuren, MD, PhD, on behalf of the Efgartigimod MG Study Group

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0 20 40 60 80 0 20 40 60 80
Study day Study day

# PRO # 2 - SAFETY

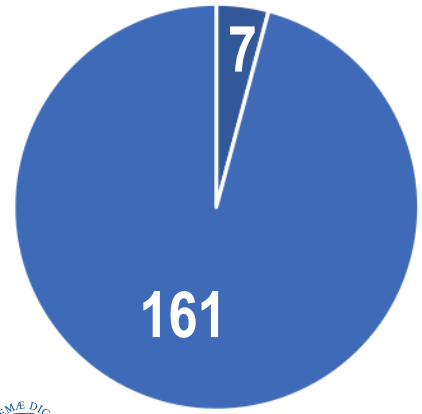
J Neurol
DOI 10.1007/s00415-014-7532-3

REVIEW

## Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis

Raffaele Iorio · Valentina Damato · Paolo Emilio Alboini · Amelia Evoli

| Adverse effect | N° patients |
|---|---|
| Infections | 4 |
| Prolonged B cell depletion | 2 |
| Heart failure | 1 |




Tot: 168 pz
EC: 7 pz
%: 4,2

## 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*

| | Eculizumab (n=62) | Placebo (n=63) | Total (n=125) |
|---|---|---|---|
| Patients with any treatment-emergent serious adverse event* | 9 (15%) | 18 (29%) | 27 (22%) |
| Myasthenia gravis | 5 (8%) | 8 (13%) | 13 (10%) |
| Pyrexia | 2 (3%) | 0 | 2 (2%) |
| Upper respiratory tract infection | 0 | 2 (3%) | 2 (2%) |
| Apnoea | 0 | 1 (2%) | 1 (1%) |
| Bacteraemia | 1 (2%) | 0 | 1 (1%) |
| Acute cholecystitis | 0 | 1 (2%) | 1 (1%) |
| Deep-vein thrombosis | 0 | 1 (2%) | 1 (1%) |
| Diverticulitis | 1 (2%) | 0 | 1 (1%) |
| Endocarditis | 1 (2%) | 0 | 1 (1%) |
| Gastritis | 0 | 1 (2%) | 1 (1%) |
| Gastroenteritis | 0 | 1 (2%) | 1 (1%) |
| General physical health deterioration | 0 | 1 (2%) | 1 (1%) |
| Hyperglycaemia | 0 | 1 (2%) | 1 (1%) |
| Intentional overdose† | 0 | 1 (2%) | 1 (1%) |
| Intestinal perforation | 1 (2%) | 0 | 1 (1%) |
| Lymphocyte count decreased | 0 | 1 (2%) | 1 (1%) |
| Lymphopenia | 1 (2%) | 0 | 1 (1%) |
| Metastases to bone | 1 (2%) | 0 | 1 (1%) |
| Myasthenia gravis crisis | 1 (2%) | 0 | 1 (1%) |
| Prostate cancer | 1 (2%) | 0 | 1 (1%) |
| Pulmonary embolism | 0 | 1 (2%) | 1 (1%) |
| Tonsillitis | 0 | 1 (2%) | 1 (1%) |
| Bacterial urinary tract infection | 0 | 1 (2%) | 1 (1%) |
| Varicella | 0 | 1 (2%) | 1 (1%) |

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**Table 2** Treatment-emergent safety outcomes in all treated patients (overall reported in ≥2 patients)

| TEAE/patient count | Placebo (n = 12) | Efgartigimod (n = 12) | Total (n = 24) |
|---|---|---|---|
| TEAEs (total) | 10 (83.3) | 10 (83.3) | 20 (83.3) |
| Headache | 3 (25.0) | 4 (33.3) | 7 (29.2) |
| Nausea | 1 (8.3) | 1 (8.3) | 2 (8.3) |
| Diarrhea | 1 (8.3) | 1 (8.3) | 2 (8.3) |
| Abdominal pain upper | 1 (8.3) | 1 (8.3) | 2 (8.3) |
| Arthralgia | 2 (16.7) | 0 (0.0) | 2 (8.3) |
| Total lymphocyte count decrease | 0 (0.0) | 2 (16.7) | 2 (8.3) |
| B-lymphocyte decrease | 0 (0.0) | 2 (16.7) | 2 (8.3) |
| Monocyte count decrease | 0 (0.0) | 2 (16.7) | 2 (8.3) |
| Neutrophil count increase | 0 (0.0) | 2 (16.7) | 2 (8.3) |
| Myalgia | 0 (0.0) | 2 (16.7) | 2 (8.3) |
| Pruritus | 2 (16.7) | 1 (8.3) | 3 (12.5) |
| Rhinorrhea | 1 (8.3) | 1 (8.3) | 2 (8.3) |
| Tooth abscess | 2 (16.7) | 0 (0.0) | 2 (8.3) |
| Toothache | 2 (16.7) | 0 (0.0) | 2 (8.3) |

Abbreviation: TEAE = treatment-emergent adverse event.
Data are n (%).

# PRO # 3 – TIME TO EFFECT

PLEX

IVIG

RITUXIMAB/ECULIZUMAB*

AZATHIOPRINE

MICOPHENOLATE

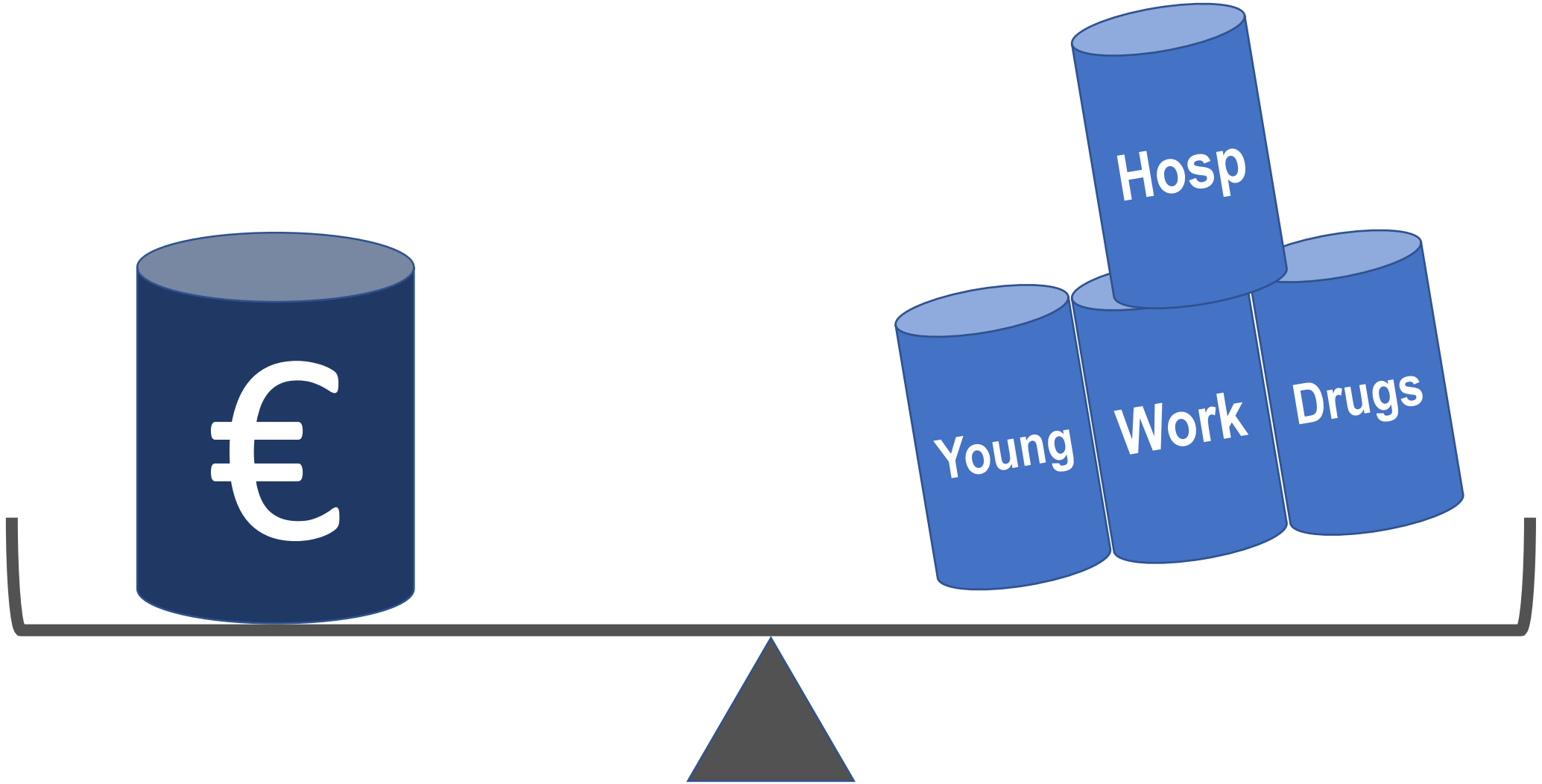
*** Benefits within weeks**

**Days** **Weeks** **Months** **Year**

**Myasthenia Gravis** – Drachman 2016, Seminars in Neurology; **Immunotherapy in myasthenia gravis in the era of biologics** Dalakas, 2018 Nature Rev. Neurology

# COSTS AND BENEFITS

**Estimating the Population Benefits and Costs of Rituximab Therapy in the United States from 1998 to 2013 Using Real-World Data** – Danese et al 2016 Medical Care



# CONCLUSIONS

- A subgroup of patients suffering from MG may benefit from an early treatment with biologics
- This subgroup could be identified considering Ab sub-type (MUSK+), sex (female), age (30 y), disease severity and thymic abnormalities
- Biologics are showing to be effective drugs, producing remission or symptoms relief in a certain percentage of treated patients
- Reduction of MG relapses and myasthenic crisis frequences could be observed with biologics treatment
- The costs/benefits analysis may be in favour for a wider administration of these drugs

# *Thank you for your attention!*

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