Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-458 Ravulizumab

Stand: Januar 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Ravulizumab [Myasthenia Gravis] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Thymektomie, Plasmapherese/ Immunadsorption
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Arzneimittel-Richtlinie/Anlage VI - Off-Label-Use: • Beschluss vom 20. Juli 2017: Mycophenolat Mofetil bei Myasthenia gravis; Aktualisierung • Beschluss vom 20. März 2014: Intravenöse Immunglobuline (IVIG) bei Myasthenia gravis (Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Myasthene Krise/schwere Exazerbationen) • Beschluss vom 19. September 2013: Mycophenolat Mofetil bei Myasthenia gravis (Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Langzeittherapie bei generalisierter Myasthenia gravis bei Therapieresistenz unter Behandlung mit den zugelassenen Substanzen oder bei Azathioprin-Unverträglichkeit.)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ravulizumab L04AA43 Ultomiris®	*Generalisierte Myasthenia gravis (gMG)* Ultomiris wird angewendet als Zusatztherapie zu einer Standardbehandlung bei erwachsenen Azetylcholinrezeptor (AChR)-Antikörper-positiven Patienten mit gMG.
Azathioprin L04AX01	[…] Azathioprin Heumann ist angezeigt zur Behandlung der generalisierten Myasthenia gravis. In Abhängigkeit vom Schweregrad der Erkrankung sollte Azathioprin Heumann wegen des langsamen Wirkungseintritts zu Beginn der Behandlung in Kombination mit Glukokortikosteroiden verabreicht und die Glukokortikosteroid-Dosis nach Monaten der Behandlung schrittweise reduziert werden. FI Azathioprin Heumann, Stand: August 2016
Prednisolon H02AB06 generisch	[…] Neurologie (DS: a) • Myasthenia gravis (Mittel der 1. Wahl ist Azathioprin) […] FI Prednisolon-ratiopharm, Stand: August 2017
Prednison H02AB07 generisch	[…] Neurologie (DS: a) • Myasthenia gravis (Mittel der 1. Wahl ist Azathioprin) […] FI Prednison acis, Stand: August 2017
Pyridostigmin bromid N07AA02 Mestinon® 10	Mestinon 10 ist ein Cholinesterasehemmer und wird bei Kindern, Jugendlichen und Erwachsenen bei Myasthenia gravis angewendet. Mestinon 10 kann gemeinsam mit Mestinon 60 (überzogene Tabletten mit 60 mg Pyridostigminbromid) angewendet werden, um eine individuelle Einstellung der erforderlichen Wirkstoffmenge zu erreichen. FI Mestinon® 10, Stand: August 2015
Neostigminmetil-sulfat N07AA01	[…] Myasthenia gravis (Erkrankung mit vorzeitiger Ermüdung der Muskeln bei Belastung). FI Neostigmin-Rotexmedica, Stand: Februar 2017
Distigminbromid N07AA03 Ubretid	Zur Behandlung von – Neurogenen Blasenentleerungsstörungen mit hypotonem Detrusor im Rahmen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	eines therapeutischen Gesamtkonzepts. – Postoperativer Darmatonie. – Myasthenia gravis. FI Ubretid® Injektionslösung, Stand: November 2018
Eculizumab L04AA25 Soliris	[…] Soliris wird angewendet zur Behandlung von Erwachsenen mit – Refraktärer generalisierter Myastheniagravis (gMG) bei Acetylcholinrezeptor (AChR)-Antikörper–positiven Patienten (siehe Abschnitt 5.1) FI Soliris, Stand: Mai 2020

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-458 (Ravulizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	3. Januar 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

aAMR	acute antibody-mediated rejection
AChR	Acetylcholine receptor
ADL	Activities of daily living
aHUS	atypical hemolytic uremic syndrome
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprin
BLM	Belimumab
CCT	Clinical Controlled Trial
ChEI	Cholinesterase inhibitor
CsA	Cyclosporin
CSR	clinical stable remission
CTX	Cyclophosphamid
DFPP	double-filtration plasmapheresis
DGF	delayed graft function
ECZ	Eculizumab
G-BA	Gemeinsamer Bundesausschuss
GC	Current glucocorticoids
GIN	Guidelines International Network
GKS	Glukokortikosteroide
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IS	Immunsuppresive
IVIg	Immunoglobulin
KI	Konfidenzintervall
LoE	Level of Evidence
MG	Myasthenia Gravis
MGFA	Myasthenia Gravis Foundation of America
MMF	Mycophenolat Mofetil
MMT	Manual muscle test
MTX	Methotrexat
MuSK	Muscle-specific tyrosine kinase
MV	mechanical ventilation
NICE	National Institute for Health and Care Excellence

NOS	Newcastle– Ottawa Scale
NRSI	non-randomized studies of the effects of interventions
NTMG	non-thymomatous MG
OR	Odds Ratio
PIS	Post-Intervention Status
PLA	Placebo
PLEX	Plasma Exchange
PNH	paroxysmal nocturnal hemoglobinuria
PR	pharmacological
QMG	Quantitative Myasthenia Gravis score
RAM	RAND/UCLA appropriateness methodology
RCT	Randomized Controlled Trial
rgMG	refractory generalized myasthenia gravis
RR	Relatives Risiko
RTX	Rituximab
SD	Standardabweichung
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standard Mean Difference
SOC	Standard of care.
TAC	Tacrolismus
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WMD	Weighted mean differences

1 Indikation

Anwendungsgebiet laut Beratungsanforderung: zur Behandlung erwachsener Patienten mit Anti-Acetylcholinrezeptor (Anti-AChR)-Antikörper-positiver generalisierter Myasthenia gravis (gMG), bei denen trotz mindestens einer immunmodulatorischen Therapie die Symptomatik bestehen bleibt.

Indikation der Synopse: Behandlung von generalisierter Myasthenia gravis bei Erwachsenen.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Myasthenia gravis* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.startpage.com) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 16.11.2021 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 236 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt sieben Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Zhang J et al., 2021 [7].

Effects of thymectomy on late-onset non-thymomatous myasthenia gravis: systematic review and meta-analysis.

Fragestellung

to conduct a systematic review in order to answer two questions pertinent to late-onset NTMG: (1) do patients with late-onset NTMG experience the same effects from thymectomy as their earlyonset counterparts? (2) Compared with conservative treatment, does thymectomy have any benefits for late-onset NTMG patients?

Methodik

Population:

- NTMG patients who received thymectomy, regardless of surgical method

Intervention/Komparator:

- thymectomy versus conservative treatment (anticholinesterase, corticosteroids, or immunosuppressants administered either alone or in combination) in late-onset NTMG patients, or early-onset versus late-onset NTMG patients after thymectomy

Endpunkte:

- clinical stable remission/pharmacological remission (CSR/PR) and improvement rates

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library databases for studies published from January 1, 1950 to March 10, 2021

Qualitätsbewertung der Studien:

- RCTs: five-point Jadad scale / Obervational studies: Newcastle– Ottawa Scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 observational articles representing the best evidence answering the questions of our study objective

Charakteristika der Population / Qualität der Studien:

Table 1 Demographic data of studies comparing early-onset with late-onset NTMG after thymectomy

Author/year/country	Study design	Study period	Follow-up (y) mean/range	Age (y) (cutoff/range)	Early-onset (events/all)		Late-onset (events/all)		Thymic histology hyperplasia/involution/normal	Anti-AChR-ab (+/−/ND)	Preoperative classification	Surgical procedures	Medical treatment	NOS score
					CSR	Improved	CSR	Improved						
Liu/2015/China [20]	Single-center retrospective	2007–2011	5.2/3.1–7.2	40/NA	27/57	NA	21/46	NA	68/35/0	54/21/28	I 25/IIa 25/IIb 15/IIIa 17/IIIb 18/IV 3 MGFA	Bilateral/Right VATS	Anticholinesterase; corticosteroid; Ig	8
Lin/2010/Taiwan [12]	Single-center retrospective	1995–2004	3.6/1–11	40/5–78	16/42	NA	4/18	NA	42/14/4	39/10/11	I 22/II 30/III 4/IV 1/V 3 MGFA	Right-VATS/TS	anticholinesterase; corticosteroid	8
Zieliński/2004/Poland [21]	Single-center retrospective	1996–1999	NA/3.5–6.5	40/14–70	25/52	NA	2/6	NA	33/15/10	NA	I 5/IIa 19/IIb 34 Osserman	TS	Anticholinesterase; corticosteroid; immunosuppressant	8
Mantegazza/2003/Italy [22]	Single-center prospective	NA	NA 1–6	40/NA	72/185	NA	2/21	NA	130/76/0	169/37/0	I 19/IIIa 63/IIIb 99/IVb 25 MGFA	Bilateral VATET/TS	Anticholinesterase; immunosuppressant	8
Mack/1996/USA [23]	Multi-center retrospective	1992–1995	NA/0.3–3.9	40/9–84	5/21	14/21	1/6	3/6	19/2/6	NA	I 2/II 23/III 2 Osserman	VATS	Anticholinesterase; steroids	7
Frist/1994/USA [24]	Single-center retrospective	1971–1992	NA/0.8–21	45/2–67	12/33	19/33	2/9	3/9	NA	20/8/14	I 2/II 7/III 11/IV 19/V 3 Oosterhuis	TS	Anticholinesterase; corticosteroid	7
Maggi/1989/Italy [25]	Single-center retrospective	1973–1987	NA/5–10	40/NA	137/326	152/326	31/117	67/117	NA	NA	I 27/IIa 256/IIb 200/III 17 own classification	TC/TC + TS	Anticholinesterase; corticosteroid; immunosuppressant; plasmapheresis	8
Monden/1985/Japan [26]	Single-center retrospective	NA	5/NA	50/16–59	21/32	9/32	2/4	2/4	NA	NA	I 5/IIa 29/IIb 67/III 1 Oosterhuis	TS	NA	8
Rubin/1981/USA [27]	Single-center retrospective	1961–1982	NA/0.5–15	40/9–54	9/18	9/18	1/3	2/3	13/3/5	6/15/0	II 6/III 6/IV 8/V 1 Osserman	TS	Anticholinesterase; corticosteroid; plasmapheresis	7

NTMG non-thymomatous myasthenia gravis, *Anti–AChR-ab* anti-acetylcholine receptor antibody, *CSR* complete stable remission, *TS* trans-sternal thymectomy, *TC* transcervical thymectomy, *VATS* video-assisted thoracoscopic surgery, *MGFA* Myasthenia Gravis Foundation of America, *NOS* Newcastle–Ottawa scale, *NA* not available, *ND* not determined, *IG* immunoglobulin

Studienergebnisse:

- Nine studies, which included 896 patients overall (766 early-onset and 230 late-onset), compared postoperative outcomes between early- and late-onset NTMG.
- The remaining three articles, which included 216 patients (75 in the thymectomy group and 141 in the conservative-treatment group), compared thymectomy with conservative treatment for late-onset NTMG. The early- versus late-onset NTMG studies demonstrated that patients in the former category were 1.95× likelier than their late-onset counterparts to achieve clinical remission (odds ratio [OR] 1.95; 95% confidence interval [CI] 1.39–2.73; I2 = 0%).
- No difference was seen in improvement or remission + improvement rates between these two groups.
- When comparing thymectomy with conservative treatments in late-onset NTMG patients, neither did we observe any difference in CSR/PR.

Fazit der Autoren

We observed that late-onset NTMG patients had a lower chance of achieving CSR after thymectomy than early-onset patients, but no difference was seen in improvement or in CSR+ improvement rates. Moreover, late-onset NTMG patients did not obtain any benefits from thymectomy versus conservative treatments. Thymectomy in late-onset NTMG patients should therefore be performed with caution, and further investigation into cutoff ages is needed to deliver specific therapeutic strategies.

Liu C et al., 2021 [3].

Efficacy and safety of double-filtration plasmapheresis treatment of myasthenia gravis: a systematic review and meta-analysis.

Fragestellung

To evaluate the efficacy of double-filtration plasmapheresis (DFPP) treatment of myasthenia gravis (MG) through a systematic review and meta-analysis.

Methodik

Population:

- Patients with MG

Intervention:

- Patients who had been treated with DFPP.

Komparator:

- Healthy volunteers treated with DFPP or MG patients treated with IVIG, PE, or IA

Endpunkte:

- Clinical efficacy rate, reduced quantitative MG (QMG) score, rate of adverse reactions and number of respiratory supports, duration of hospital stay, time to MG remission, serum antibody levels

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), and Wanfang databases were searched for randomized controlled trials (RCTs) and clinical controlled trials (CCTs) on DFPP for MG from database establishment to June 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven RCTs and 2 CCTs were found comprising 329 patients

Charakteristika der Population:

Study and year	Patients (T/C)	Male (T/C)	Mean age (T/C)	Mean duration of symptoms, month (T/C)	Osserman class (T/C)			Interventions		Means of DFPP intervention	Outcome measures
					IIA	IIB	III	Treatment group	Control group		
Chien, 2011	20/16	5/9	45.2/38.0	60.6/NA	10/NA	7/NA	3/NA	DFPP	Healthy controls	The course of treatment consisted of 3 consecutive DFPP sessions every other day.	②,⑤
Zhang, 2014	15/20	9/10	54.1/50.2	NA	6/NA	5/NA	4/NA	DFPP	NA	DFPP was performed 3 times within 1 week using an apheresis monitor.	①②⑥⑦
Yeh, 2009	19/6	7/2	46	174.6/NA	4/NA	8/NA	7/NA	MG patients with DFPP	Healthy volunteers with DFPP	Each course of treatment consisted of a mean of 4.7 consecutive DFPP sessions every other day.	②⑤
Yeh, 1999	8/8	4/4	38.5/49	NA	NA	4/3	0/1	DFPP	IA	Each course of treatment consisted of 5 sessions of apheresis every other day with 1 plasma volume processed for each patient.	②
Liu, 2010A	15/10	9/6	55.2/57.2	NA	5/2	3/5	7/3	DFPP	IA	Each patient received 3 treatments every 24–48 h.	①②③⑥⑦
Liu, 2010B	15/15	9/8	55.2/53.2	NA	5/6	3/4	7/5	DFPP	IVIg	Each patient received 3 treatments every 24–48 h.	①②③⑤⑦
Okada, 1997	4/8	NA	42/41.5	NA	NA	NA	NA	DFPP	PE	DFPP treatment was administered with ~1 plasma volume at each session for 3 d.	②⑤
Gong, 2005	26/23	11/9	42.3/38.2	12.5/10	0	19/17	7/6	DFPP	NA	The course of treatment consisted of 3 consecutive DFPP sessions every other day.	②④
Han, 2015	26/20	16/13	45.6/43.9	NA	NA	NA	NA	DFPP	NA	Each patient received 3 treatments every 48 h.	①②④⑥⑦
Zang, 2015	35/35	16/17	37.8/38.6	13.9/14.3	NA	NA	NA	DFPP	IA	Every 3 d for a course of treatment.	②④

C = control group, DFPP = double-filtration plasmapheresis, IA = immunoadsorption, IVIg = intravenous immunoglobulin, MG = myasthenia gravis, NA = not available, PE = plasma exchange, QMG = the quantitative MG, T = trial group.
① QMG score ② acetylcholine receptor (AChR) removal rate ③ titin-ab ④ clinical absolute and relative scores ⑤ MG score ⑥ duration of hospital stay ⑦ time to MG remission.

Qualität der Studien:

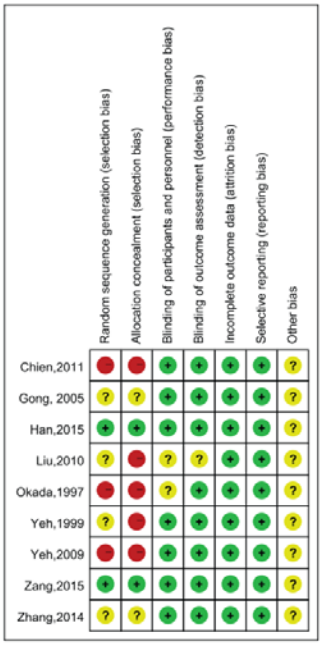


Figure 2. Risk of bias summary based on the review authors' judgement for each included study.

Studienergebnisse:

- Clinical MG remission rate after DFPP treatment was significantly higher (OR=4.33; 95% confidence interval [CI], 1.97–9.53; P<.001) and the serum levels of antititin antibody was significantly decreased (standardized mean difference [SMD]=9.30; 95% CI, 7.51–11.08; P<.001)
- The quantitative MG (QMG) score, hospital stay and time to remission of MG symptoms, and acetylcholine receptor antibody (AchRAb) decreased in the DFPP treatment group; however, these outcomes had high heterogeneity among the studies.
- Only one study has reported on the adverse effects, including hypotension and hematoma.

Fazit der Autoren

The meta-analysis and systematic review supply evidence that DFPP treatment can effectively eliminate autoantibodies and has adefinite clinical effect on MG patients. It may also significantly reduce AChRAb levels, QMGS, duration of hospital stay, and time to MG remission. DFPP treatment may be a beneficial option for treating MG.

Bernuy-Guevara C et al., 2020 [1].

The Inhibition of Complement System in Formal and Emerging Indications: Results from Parallel One-Stage Pairwise and Network Meta-Analyses of Clinical Trials and Real-Life Data Studies.

Fragestellung

This manuscript presents quantitative findings on the actual effectiveness of terminal complement component 5 (C5) inhibitors and complement component 1 (C1) esterase inhibitors through their formal and common “off-label” (compassionate) indications.

Methodik

Population:

- Adult and pediatric individuals affected by or at higher risk of developing PNH attacks, aHUS, rgMG, aAMR episodes, or DGF.

Intervention:

- Commercial C5 inhibitors (e.g., eculizumab, ravulizumab) and C1-inhibitors (e.g., Berinert®, Cinryze®, Haegarda®, Ruconest®).

Komparator:

- Placebo, pre-/o -treatment state, historical cohorts that did not receive the interventions, and any other therapeutic strategy (e.g., SOC) including active drugs when it was considered as comparators in the eligible studies

Endpunkte:

- K.A.

Recherche/Suchzeitraum:

- MEDLINE via PubMed, Ovid and Web of Science, EMBASE via Elsevier’s Scopus, and Cochrane Controlled Register of Trials (CENTRAL), will be searched to June 2019.

Qualitätsbewertung der Studien:

- Risk of bias in RCTs will be assessed using the standard tool produced by the Cochrane Collaboration
- Risk of bias in NRSI studies will be assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 28 pharmaceutical industry-sponsored clinical trials corresponding to phases 1 to 3 evaluation of various complement inhibitors, and 15 real-life NRSI reflecting uses of these medicines in real-world settings were found to be eligible: these studies assess outcomes in PNH (No. of clinical trials/real-life NRSI: 7/7), aHUS (7/8), rgMG (3/0), aAMR (6/0), and DGF (5/0), and included a total population of 7484 participants

Charakteristika der Population:

Information from clinical trial (R/NR)[e] / NRSI study in:	Study participant characteristics:
gMG	Age (range in yr), disease duration (range in yr), previous/concomitant treatments (%):
(p) Eculizumab pilot study (1/0)	30–72, 1–30, 50.0
(q) REGAIN (1/0) & ECU-MG-302 (0/1)	20–57, 1–18, 96.0

Qualität der Studien:

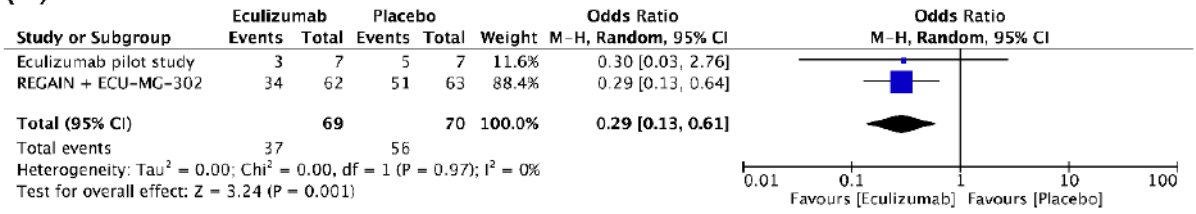
(b) the risk of bias in clinical trials,

Trials	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
pilot rgMG (p)	L	L	L	U	U	U	H
REGAIN & extension (q)	L	L	L	U	H	H	U

Studienergebnisse:

- Forest and funnel plots showing effect estimates of complement inhibition (clinical trials) corresponding to (a) the treatment of rgMG crises

(a)



Anmerkung/Fazit der Autoren

Our results include a total of 7484 participants and confirmed that C5 inhibitors are effective (i) to treat PNH, aHUS, and rgMG crises, and (ii) to prevent aAMR episodes. The two available C5 inhibitors eculizumab and ravulizumab are similar regarding their effect. The evidence on the inhibition of C1 esterase is still scarce, and data from our analysis showed no effects.

Wang L et al., 2019 [6].

Immunosuppressive and monoclonal antibody treatment for myasthenia gravis: a network meta-analysis.

Fragestellung

To perform a network meta-analysis (NMA) of all relevant immunotherapies to comprehensively compare and rank strategies for MG treatment.

Methodik

Population:

- Patients with myasthenia gravis

Intervention und Komparator:

- All the relevant immunosuppressive agents and monoclonal antibodies
- The treatment strategies of high-dose methylprednisolone (HDMP), intravenous immunoglobulin (IVIg), plasmapheresis, thymectomy, tirasemtiv, and terbutaline were excluded for their short-term interventions

Endpunkte:

- Primary: MG Foundation of America (MGFA) quantitative MG score (QMGS)
- Secondary: steroid-sparing effect measured by GC reduction and safety measured by drug-related adverse events (AEs)

Recherche/Suchzeitraum:

- up to August 31, 2018 in Medline, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and clinicaltrials.gov

Qualitätsbewertung der Studien:

- Grading: Oxford hierarchy of evidence 2011
- Risk of Bias: Cochrane

Ergebnisse

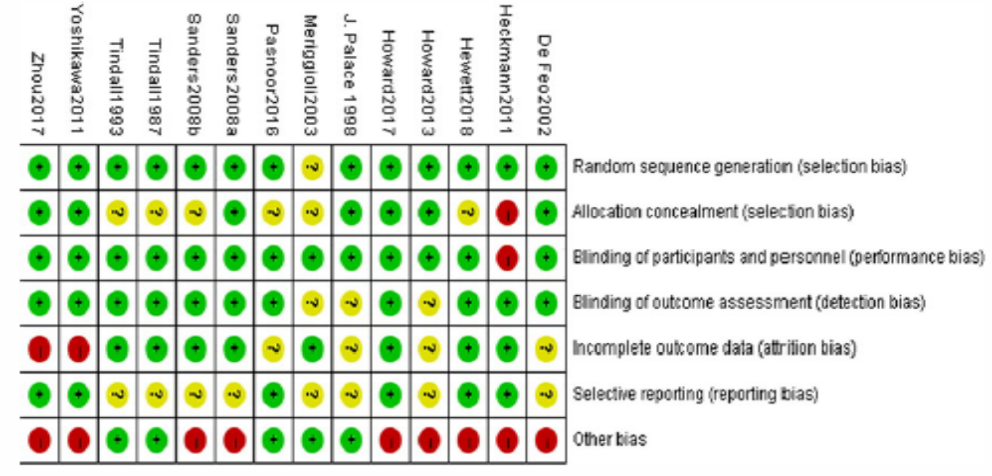
Anzahl eingeschlossener Studien:

- 14 studies with 808 MG patients
- The anti-AChR antibody serostatus was displayed in 725 patients, with 684 (94.3%) seropositive samples

Charakteristika der Population:

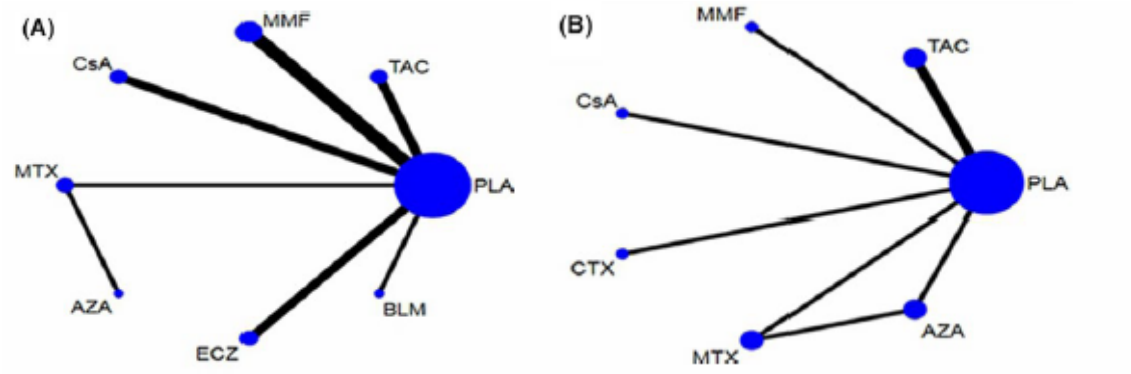
- Thymectomy was performed in 245 of 769 (31.9%) reported participants while thymoma was found in 48 of 390 (11.8%) reported participants.
- The anti-AChR antibody serostatus was displayed in 725 patients, with 684 (94.3%) seropositive samples.

Qualität der Studien:



Studienergebnisse:

- A, Network of treatment comparisons for the primary outcome of quantitative myasthenia gravis score. B, Network of treatment comparisons for the secondary outcome of glucocorticoid reduction. The size of nodes is in proportion to the number of trials that assessed the same intervention and the thickness of lines corresponds to the number of trials which have a direct comparison. AZA, azathioprine; BLM, belimumab; CsA, cyclosporine A; CTX, cyclophosphamide; ECZ, eculizumab; MMF, mycophenolate mofetil; MTX, methotrexate; PLA, placebo; TAC, tacrolimus



- QMGS:
  - There were 12 studies involving eight interventions including immunosuppressive agents and monoclonal antibodies evaluating the reduction of QMGS.
  - With traditional pairwise mean-analysis, statistical significances were calculated in CsA of −1.19 (−1.75, −0.63) vs PLA, ECZ of −0.80 (−1.37, −0.23) vs PLA, and TAC of −0.41 (−0.72 to −0.096) vs PLA. According to SUCRA, CsA was hierarchically the best, with statistical significances of −1.18 (−1.81, −0.59) vs PLA, −0.98 (−1.72, −0.23) vs MMF, and −0.77 (−1.57, −0.032) vs TAC. ECZ was ranked second with statistical significances of −0.75 (−1.33, −0.30) vs PLA while TAC was ranked third of −0.41 (−0.88, 0.065; Figure 3A). BLM, MTX, AZA, and MMF were not demonstrated to be efficacious. Additionally, improved muscle strength with statistical significance ($P < 0.025$) was reported using CTX although QMGS was not conducted. For the loop was not formed in the primary outcome, there was no source of inconsistency. Comparison-adjusted funnel plot was shown in Figure 4A and revealed possible small-study effects for the QMGS.
  - Network meta-regression was further conducted. When the follow-up months were controlled, ECZ of −1.50 (−2.81, −0.18) vs PLA and CsA of −1.23 (−1.81, −0.64) vs PLA reached a statistical significance in the QMGS.

TABLE 2 Estimated differences in the efficacy of interventions on quantitative myasthenia gravis score

Standardized mean difference using traditional pairwise meta-analysis								
Standardized mean difference with network meta-analysis	Cyclosporine A	—	—	—	—	—	—	−1.19 (−1.75, −0.63)
	−0.42 (−1.19, 0.40)	Eculizumab	—	—	—	—	—	−0.80 (−1.37, −0.23)
	−0.77 (−1.57, −0.032)	−0.34 (−1.11, 0.29)	Tacrolimus	—	—	—	—	−0.41 (−0.72, −0.096)
	−0.78 (−1.85, 0.22)	−0.37 (−1.36, 0.59)	−0.014 (−0.95, 0.95)	Belimumab	—	—	—	−0.40 (−1.08, 0.28)
	−0.79 (−1.78, 0.14)	−0.37 (−1.31, 0.47)	−0.024 (−0.90, 0.85)	−0.012 (−1.14, 1.09)	Methotrexate	—	—	−0.39 (−0.94, 0.18)
	−0.86 (−2.18, 0.49)	−0.45 (−1.73, 0.86)	−0.090 (−1.34, 1.24)	−0.084 (−1.52, 1.45)	−0.058 (−0.98,0.92)	Azathioprine	0.041 (−0.75, 0.83)	—
	−0.98 (−1.72, −0.23)	−0.56 (−1.24, 0.062)	−0.22 (−0.80, 0.45)	−0.19 (−1.10, 0.74)	−0.19 (−0.99, 0.67)	−0.12 (−1.41, 1.13)	Mycophenolate mofetil	−0.17 (−0.41, 0.066)
	−1.18 (−1.81, −0.59)	**−0.75 (−1.33, −0.30)**	−0.41 (−0.88, 0.065)	−0.39 (−1.23, 0.43)	−0.38 (−1.11, 0.36)	−0.32 (−1.56, 0.83)	−0.19 (−0.64, 0.17)	Placebo

Median values of standardized mean differences with 95% confidence intervals (column vs row) of the efficacy of interventions are exhibited on the lower left part of the table while standardized mean differences with 95% confidence intervals using metan command are exhibited on the upper right of the table. Values lower than zero favor the column-defining intervention. Interventions are ordered in accordance with efficacy ranking. Numbers in bold with darker shades show statistically significant results.

- Reduction of GC:
  - Eight studies evaluating the reduction of GC with seven immunosuppressive agents were included in this NMA. Figure 2B revealed the network plot while Table 3 listed the estimated SMDs of the relative efficacy with median value and 95% CI, agent by agent. Compared with PLA, only AZA therapy lasting 36 months demonstrated to be statistically efficacious (P = 0.009) while a correlation trend was shown in CTX (P = 0.086). When using SUCRA (Figure 3B), AZA was ranked the best treatment while CTX was hierarchically the second. However, inconsistency existed in AZA vs PLA with the design-by-treatment interaction model (P = 0.032) while not significant in the node-splitting model (P = 0.104). Besides, Figure 4B exhibited the absence of small-study effects for GC reduction. We further employed network meta-regression to control the intervention periods. However, compared with PLA, the statistical differences were not significant in any immunosuppressive agents.

TABLE 3 Estimated differences in the efficacy of interventions on glucocorticoid reduction

Standardized mean difference using traditional pairwise meta-analysis							
Standardized mean difference with network meta-analysis	Azathioprine	—	0.35 (−0.44, 1.15)	—	—	−1.39 (−2.44, −0.35)	—
	−0.072 (−1.97, 1.73)	Cyclophosphamide	—	—	—	−0.74 (−1.59, 0.11)	—
	−0.20 (−1.36, 0.99)	−0.13 (−1.89, 1.72)	Methotrexate	—	—	−0.19 (−0.75, 0.36)	—
	−0.41 (−1.92, 1.03)	−0.33 (−2.05, 1.37)	−0.20 (−1.70, 1.16)	Tacrolimus	—	−0.38 (−0.92, 0.17)	—
	−0.51 (−2.32, 1.23)	−0.44 (−2.43, 1.55)	−0.31 (−2.10, 1.38)	−0.10 (−1.73, 1.51)	Cyclosporine A	−0.28 (−0.91, 0.35)	—
	−0.79 (−1.98, 0.34)	−0.71 (−2.14, 0.72)	−0.58 (−1.75, 0.48)	−0.38 (−1.29, 0.55)	−0.27 (−1.60, 1.09)	Placebo	−0.16 (−0.46, 0.13)
	−0.94 (−2.67, 0.73)	−0.87 (−2.77, 1.04)	−0.75 (−2.47, 0.89)	−0.54 (−2.09, 1.01)	−0.44 (−2.25, 1.41)	−0.17 (−1.43, 1.09)	Mycophenolate mofetil

Median values of standardized mean differences with 95% confidence intervals (column vs row) of the efficacy of interventions are exhibited on the lower left part of the table while standardized mean differences with 95% confidence intervals using metan command are exhibited on the upper right of the table. Values lower than zero favor the column-defining intervention. Interventions are ordered in accordance with efficacy ranking. Numbers in bold with darker shades show statistically significant results.

- Adverse Events: Adverse events were counted during the intervention combined with the number of participants, respectively. Relative median values with 95% CI were exhibited using HR with random effects Poisson model to control the time and number. BLM and ECZ ranked the most tolerable therapies causing the least counts of AEs while CsA of 2.41 (0.58, 10.01) ranked the last vs PLA, implicating the most counts of AEs. Additionally, the counts of AEs in the other immunotherapies did not differ significantly. Although the exact number of AEs could not be acquired from the study about CTX, the incidence between CTX and PLA groups did not show statistical difference.

Anmerkung/Fazit der Autoren

This comprehensive NMA concluded ECZ represented the most effective therapeutic alternative to improve QMGS with good tolerability, which could be recommended in the refractory MG patients. TAC may be a beneficial therapy to extensively treat MG with relatively favorable results while the efficacy of CsA and CTX could be limited by their multiple or severe AEs. The efficacy of AZA, MMF, MTX, and BLM may not be significant for MG treatment.

Kommentare zum Review

- Die Autoren schränken die Interventionen ein: “The treatment strategies of high-dose methylprednisolone (HDMP), intravenous immunoglobulin (IVIg), plasmapheresis, thymectomy, tirasemtiv, and terbutaline were excluded for their short-term interventions”. Somit sind Arzneimittel, die bei Myasthenia Gravis insbesondere zur kurzzeitigen Bedarfsbehandlung eingesetzt werden, nicht von der vorliegenden Meta-Analyse umfasst.
- The anti-AChR antibody serostatus was displayed in 725 patients, with 684 (94.3%) seropositive samples

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Cataneo AJM et al., 2018 [2].

Thymectomy in nonthymomatous myasthenia gravis: systematic review and meta-analysis.

Fragestellung

the objective of our study is to evaluate the efficacy of surgical treatment (thymectomy) as compared to non-surgical in non-thymomatous MG, conducting a systematic review of experimental or observational studies.

Methodik

Population:

- generalized MG in patients without thymoma

Intervention:

- simple or extended thymectomy

Komparator:

- Anticholinesterasic drugs (prostigmine, pyridostigmine), immunosuppressive agents (azathioprine), plasmapheresis, corticosteroids.

Endpunkte:

- Remission rates (asymptomatic without medication) and improvement rates (reducing medication or asymptomatic with medication)

Recherche/Suchzeitraum:

- Pubmed (1966 to December 2016); Embase (1980 to December 2016); Lilacs (1982 to December 2016); www.clinicaltrials.gov (assessed December 2016).

Qualitätsbewertung der Studien:

- RCTs: 'Risk of bias' tool for Cochrane reviews
- In order to quantify the inconsistencies of the studies included in the meta-analysis, the heterogeneity test (I2) was used

Ergebnisse

Anzahl eingeschlossener Studien:

- 2 RCTs and 17 observational studies (case-control)

Qualität der Studien:

- Only two RCTs were found, one of them used the time-weighted average Quantitative MG score as the outcome, and randomized the patients to thymectomy + prednisone or only prednisone (14). The risk of bias for this study was considered low, since randomization was done by a computer program, with the professionals as well as the outcomes assessors blind to the procedure. Another RCT (23) was considered as with moderate risk of bias, because although the selection was random, there was no blindness of the outcome assessors, since the surgical scar was visible.

14 Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016; 375(6):511–22.
23 Lorenzana P, Casallas A, Vega D, Aguirre C, Hedmont D, Posso H, et al. Miastenia gravis IIa. Timectomia vs tratamento medico. Act Med Colomb. 1999;24:151–8.

Studienergebnisse:

Ausschließlich deskriptive Darstellung der Ergebnisse

- Wolfe et al (14) compared the surgical and clinical treatment of MG by conducting a multicenter RCT (36 centers, 32 in USA). A total of 126 patients between 2006 and 2012 were enrolled with 66 patients in the surgical group (thymectomy plus prednisone) and 60 in the non-surgical group (prednisone alone). Patients 18 to 65 years of age with disease duration of less than 5 years, Myasthenia Gravis Foundation of America (MGFA) clinical class II to IV and elevated circulating concentrations of acetylcholine-receptor antibody were included. The primary outcomes were the time-weighted average Quantitative MG score and the average dose of prednisone required over a period of 3 years. The surgical group had a lower time-weighted average Quantitative MG score than the non-surgical group (6.15 vs. 8.99, $p < 0.001$). The average dose of prednisone required was also lower in the surgical group as compared to the non-surgical group (44 mg vs. 60 mg, $p < 0.001$). Furthermore, in the thymectomy patients, the use of azathioprine (17% vs. 48% $p<0.001$), and hospital admission for exacerbations (9% vs. 37%, $p < 0.001$) were lower.
- Lorenzana et al. (23), in a RCT performed at a single center in Colombia, analyzed the results by comparing muscle strength and fatigue measured at intervals that varied from 3 months to 24 months; patients aged 15–50 years with illness duration of less than 5

years. In the surgical group (n = 11) strength improved 2.1 in the strength scale, statistically significant (95% CI 0.86 to 3.35; ρ = 0.004), while in the non-surgical group (n = 18) the improvement was 0.25 (95% CI 0.80 to 1.30; ρ = 0.612). For fatigue, the non-surgical group had an average gain of 2.2 s (95% CI 0.81 to 5.2; p = 0.138), and the surgical group had average gain of 9.1 s (95% CI 0.37 to 17.82; p = 0.043).

Anmerkung/Fazit der Autoren

We concluded that thymectomy is effective in the treatment of nonthymomatous MG with remission rates greater than non-surgical treatment. At the moment we need studies that show which subgroups would most benefit from the treatment.

The main limitation of this review is the fact that only two RCTs were found and all other studies were case-control. Another limitation was the inability to conduct subgroup analyzes.

Kommentare zum Review

- Es wurden ausschließlich die Ergebnisse der identifizierten RCTs dargestellt. Laut Autoren konnten die RCTs nicht meta-analystisch zusammengefasst werden. Ein Grund hierfür wurde nicht genannt.
- Keine Angabe über AChR-Status

rials investigating the use of RTX in patients with myasthenia gravis are thus warranted.

Reis TA et al., 2019 [5].

Clinical usefulness of prethymectomy plasmapheresis in patients with myasthenia gravis: a systematic review and meta-analysis

Fragestellung

Our goal was to evaluate, through a systematic review, the efficacy of plasmapheresis in the preoperative preparation of the patient for a thymectomy for the treatment of myasthenia gravis.

Methodik

Population:

- Patients included those with MG and candidates for thymectomy

Intervention:

- surgical treatment with plasmapheresis during the preoperative period

Komparator:

- surgical treatment without plasmapheresis during the preoperative period

Endpunkte:

- Myasthenic crisis, mortality, pneumonia, bleeding, use of mechanical ventilation, length of hospital stay and intensive care unit (ICU) stay

Recherche/Suchzeitraum:

- MEDLINE via PubMed, LILACS (Latin American and Caribbean Literature in Health Sciences), Scopus, Embase, CENTRAL (Cochrane Central Register of Controlled Trials)

and additional sources of published and unpublished trials. We also searched the Experimental Clinical Trials database (http://clinicaltrials.gov) for data from any ongoing studies.

- Keine Angabe über Suchzeitraum

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7
- The 7 studies that met the previously defined inclusion criteria involved 360 patients operated on between 1975 and 2011. There were 2 prospective randomized and 5 observational studies.

Charakteristika der Population:

Table 1: Main features of included studies

Author (year of publication)		Intervention/ control	d'Empaire *et al.* [18] (1985)	Iváñez *et al.* [19] (1994)	Seggia *et al.* [20] (1995)	Nagayasu *et al.* [21] (2005)	Kamel and Essa [3] (2009)	Nishtar *et al.* [22] (2012)	Saeteng *et al.* [6] (2013)
Country			USA	Spain	Brazil	Japan	Egypt	Pakistan	Thailand
Type of study			RTP	RCT	RTP	RTP	RCT	RTP	RTP
Centre (uni-/multicentric)			Uni	Uni	Uni	Uni	Uni	Multi	Uni
Period of study		PPG	1975–1983	NA	1984–1993	1980–1997	2004–2008	2002–2009	2005–2011
		NPPG			1975–1983				
Postoperative follow-up time (months)		PPG	NA	12	12	100.2 ± 41.2	19.8 ± 7.5	12	NA
		NPPG				125.1 ± 77.5	18.9 ± 10.2		
Participants		PPG	11	12	40	19	19	20	33
		NPPG	26	12	40	32	16	27	53
Osserman, *n* (%)	I	PPG	0	0	0	0	0	0	2 (6)
	IIA		0	0	0	8 (42.1)	6 (31.6)	0	6 (18.2)
	IIB		11 (100)	12 (100)	19 (47.5)	11 (57.9)		8 (40)	21 (63.3)
	III		0	0	16 (40)	0	9 (47.4)	8 (40)	4 (12.1)
	IV		0	0	5 (12.5)	0	4 (21.1)	4 (20)	0
	I	NPPG	0	0	0	0	0	0	5 (9.4)
	IIA		0	0	0	20 (62.5)	8 (50)	0	14 (25.9)
	IIB		26 (100)	12 (100)	18 (45)	12 (37.5)		17 (63)	31 (58.4)
	III		0	0	20 (50)	0	6 (37.5)	5 (18.5)	3 (5.7)
	IV		0	0	2 (5)	0	2 (12.5)	5 (18.5)	0

NA: not available; NPPG: no plasmapheresis in the preoperative period group; PPG: plasmapheresis during the preoperative period group; RCT: randomized clinical trial; RTP: retrospective.

Qualität der Studien:

Table 2: Risk of bias in case-control studies

Bias domains	Author (year of publication)				
	d'Empaire *et al.* [18] (1985)	Seggia *et al.* [20] (1995)	Nagayasu *et al.* [21] (2005)	Nishtar *et al.* [22] (2012)	Saeteng *et al.* [6] (2013)
Confounding	Low	Low	Serious	Low	Low
Selection of participants	Serious	Serious	Critical	Serious	Serious
Classification of interventions	Low	Moderate	Low	Low	Low
Deviations from intended interventions	Moderate	Low	Low	Low	Low
Missing data	Low	Low	Low	Low	Low
Measurement of outcomes	Low	Moderate	Low	Low	Low
Selection of the reported result	Low	Low	Low	Low	Low
Overall bias	Serious	Serious	Critical	Serious	Serious

Table 3: Risk of bias in randomized controlled trials

Author (year)	Domain of biases					
	Random sequence generation	Allocation concealment	Blinding of participants and professionals	Outcome evaluator blinding	Incomplete outcomes	Report of selective outcome
Iváñez *et al.* [19] (1994)	Uncertain	Uncertain	Uncertain	Uncertain	Low	Uncertain
Kamel and Essa [3] (2009)	Uncertain	Uncertain	Uncertain	Uncertain	Low	Uncertain

Studienergebnisse:

- myasthenic crisis
  - Five studies involving 243 people evaluated myasthenic crisis in the postoperative period. Plasmapheresis during the preoperative period did not decrease the myasthenic crisis in the postoperative period (RR 0.36, 95% CI 0.08–1.66; I2 = 44%; P = 0.13; Fig. 2A).
- mortality rate
  - Three studies involving 172 people evaluated the mortality rate. Plasmapheresis during the preoperative period did not alter the mortality rate (RR 0.7, 95% CI 0.11–4.62; I2 = 0%; P = 0.44; Fig. 2B).
- pneumonia
  - Five studies involving 272 people evaluated pneumonia. Plasmapheresis during the preoperative period did not reduce the risk of pneumonia in the postoperative period (RR 0.28, 95% CI 0.07–1.09; I2 = 27%; P = 0.25), but plasmapheresis tended to reduce this risk (Fig. 2C).
- bleeding
  - Two studies involving 121 people evaluated bleeding. Plasmapheresis during the preoperative period increased bleeding in the patients who had it compared to those in the control group (mean difference 34.34 ml; 95% CI 24.93–43.75; I2 = 0%; P = 0.57; Fig. 2D).

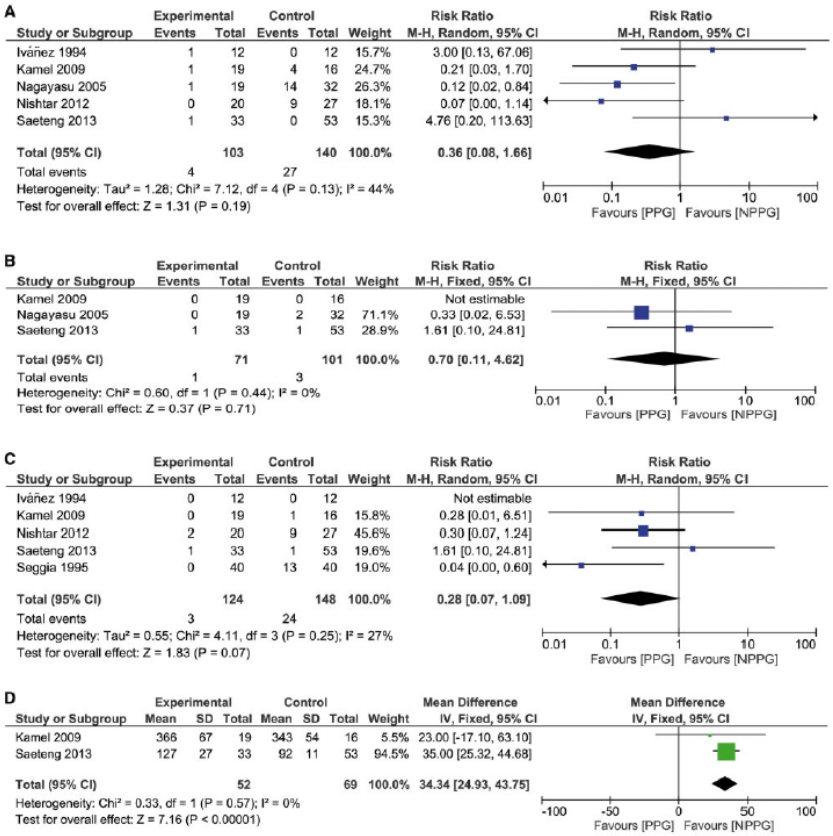

Figure 2: (**A**) Forest plot of the risk ratio (RR) for myasthenic crisis in the postoperative period of patients who underwent PPG compared to those who did not. Meta-analysis applying random effect in 5 studies (RR 0.36, 95% CI 0.08–1.66; I^2 = 44%; P = 0.13). (**B**) Forest plot of the RR for death of patients who underwent plasmapheresis compared to those who did not: meta-analysis applying fixed effect in 3 studies (RR 0.70, 95% CI 0.11–4.62; I^2 = 0%; P = 0.44). (**C**) Forest plot of the RR for pneumonia in patients who underwent plasmapheresis compared to those who did not: meta-analysis applying random effect in 5 studies (RR 0.28, 95% CI 0.07–1.09; I^2 = 27%; P = 0.25). (**D**) Forest plot of mean bleeding difference: patients who underwent plasmapheresis bled about 34 ml more than those who did not (DM = 34.34 ml; 95% CI 24.93–43.75; I^2 = 0%; P = 0.57). CI: confidence interval; df: degree of freedom; M-H: Mantel–Haenszel; NPPG: control: no plasmapheresis during the preoperative period; PPG: experimental: plasmapheresis during the preoperative period; SD: standard deviation.

- mechanical ventilation: Three studies with 213 people evaluated the need for MV in postoperative period. Due to the high degree of heterogeneity, the meta-analysis for this outcome was considered inappropriate. In 2 studies, the need for MV was lower in the group that underwent plasmapheresis, but in 1 study there was no difference between the groups (Fig. 3A).
- length of hospital stay: Two studies involving 121 people evaluated length of hospital stay. Due to the high degree of heterogeneity, a meta-analysis for this outcome was considered inappropriate. In 1 study, there was a shorter hospital stay in patients who had plasmapheresis, but in the other there was no difference (Fig. 3B).
- length of stay in the ICU: Three studies involving 158 people evaluated length of stay in the ICU. Due to the high degree of heterogeneity, the metaanalysis for this outcome was considered inappropriate. In 2 of these studies, the patients who underwent plasmapheresis had a shorter stay in the ICU, but in the other there was no difference (Fig. 3C).
- MV time: Two studies involving 72 people evaluated MV time. Due to the high degree of heterogeneity, the meta-analysis for this outcome was considered inappropriate. In both studies, patients who had plasmapheresis had shorter MV times (Fig. 3D).

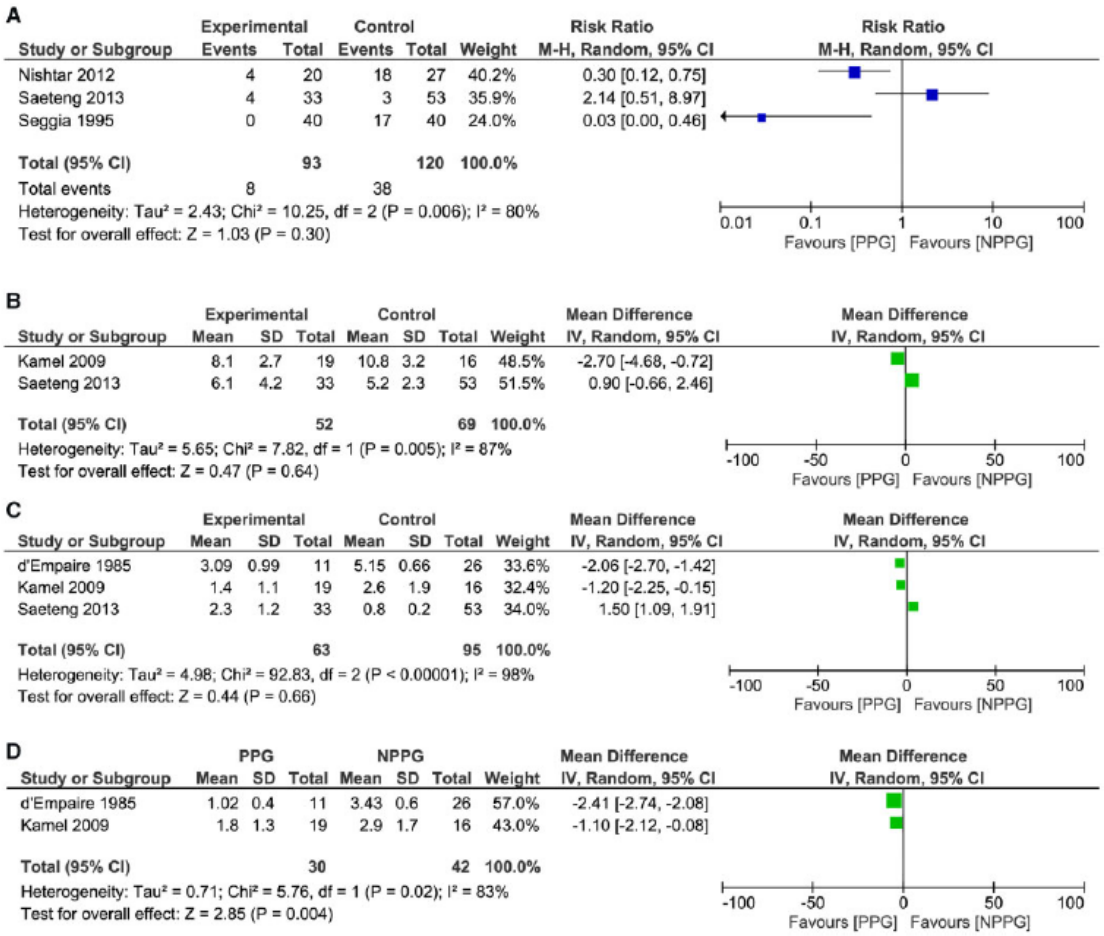

Figure 3: (**A**) Forest plot of the risk ratio for the need for mechanical ventilation in the postoperative period of patients who underwent plasmapheresis in the preoperative period compared to those who did not: meta-analysis not performed due to high heterogeneity (I^2 = 80%). (**B**) Forest plot of the mean difference in hospitalization time between patients who underwent plasmapheresis and those who did not: meta-analysis not performed due to high heterogeneity (I^2 = 87%). (**C**) Forest plot of the mean difference in length of stay in the intensive care unit between patients who underwent plasmapheresis and those who did not: meta-analysis not performed due to high heterogeneity (I^2 = 98%). (**D**) Forest plot of the mean mechanical ventilation time difference between patients who underwent plasmapheresis and those who did not: meta-analysis not performed due to high heterogeneity (I^2 = 83%). CI: confidence interval; df: degree of freedom; M-H: Mantel–Haenszel; NPPG: control: no plasmapheresis during the preoperative period; PPG: experimental: plasmapheresis during the preoperative period; SD: standard deviation.

- Subgroup analysis
  - It was not possible to separate young women with MG for <2 years and elderly men with the disease for more than 2 years. Because the studies did not separate patients' progress according to the Osserman classification, the subgroups were divided as follows: subgroup 1 (less advanced disease) included studies with 80–100% of patients in stage II; subgroup 2 (more advanced disease) included studies with 40% or more of the patients in stages III and IV. For the subgroups, only a meta-analysis of the primary outcomes was performed because of the limited number of studies that separated the more severe patients from the less severe ones.
  - Three studies involving 161 people evaluated myasthenic crisis in the postoperative period in subgroup 1. Plasmapheresis during the preoperative period did not decrease the myasthenic crisis in the postoperative period in this subgroup (RR 0.93, 95% CI 0.07– 12.14; I2 = 63%; P = 0.07; Fig. 4A).
  - Two studies involving 82 people evaluated myasthenic crisis in the postoperative period in subgroup 2. Plasmapheresis during the preoperative period decreased the myasthenic crisis in the postoperative period in this subgroup (RR 0.12, 95% CI 0.02–0.65; I2 = 0%; P = 0.51; Fig. 4B).

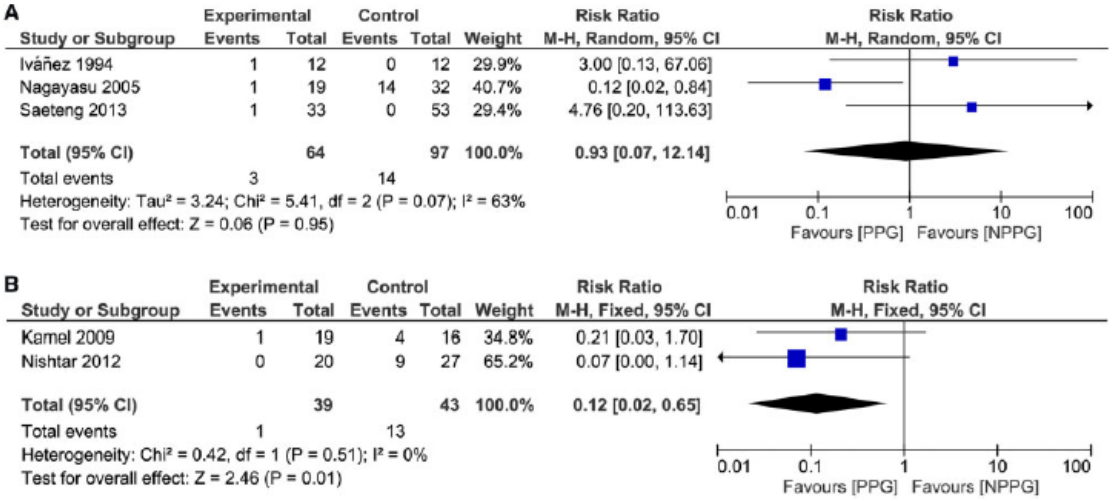

Figure 4: (**A**) Forest plot of the risk ratio (RR) for myasthenic crisis in the postoperative period of the patients who underwent plasmapheresis in the preoperative period compared to those who did not in the subgroup with more than 80% of the patients in the Osserman II group: meta-analysis applying random effect in 3 studies (RR 0.93, 95% CI 0.07–12.14; $I^2 = 63\%$; $P = 0.07$). (**B**) Forest plot of the RR for myasthenic crisis in the postoperative period of patients who underwent plasmapheresis in the preoperative period compared to those who did not in the subgroup with more than 40% of patients in the Osserman III group: meta-analysis applying fixed effect in 2 studies (RR 0.12, 95% CI 0.02–0.65; $I^2 = 0\%$; $P = 0.51$). CI: confidence interval; df: degree of freedom; M-H: Mantel–Haenszel; NPPG: control: no plasmapheresis during the preoperative period; PPG: experimental: plasmapheresis during the preoperative period.

Anmerkung/Fazit der Autoren

Five of the 7 included studies evaluated the myasthenic crisis in the postoperative period. Only 1 study demonstrated the efficacy of plasmapheresis in reducing the crisis [21], but in that study, plasmapheresis was used in the best patients, that is, in those who exhibited symptoms for a shorter time. Thus, we performed a sensitivity test, withdrawing this study and obtaining a combination with the rate of risk approaching even closer to the nullity line. In the other studies, there was no difference between the 2 groups. According to the meta-analysis, plasmapheresis did not reduce the risk of a myasthenic crisis postoperatively. In the analysis of subgroups of patients with more advanced disease, we noted a protective effect of plasmapheresis, i.e. it reduced the risk of a myasthenic crisis in these patients. But the same result was not observed in the subgroup of patients with less advanced disease in whom plasmapheresis did not alter the risk of myasthenic crisis.

Plasmapheresis during the preoperative period prior to a thymectomy may reduce myasthenic crisis postoperatively in patients with more advanced disease (Osserman III and IV) but may make little or no difference in patients with less advanced disease (Osserman II).

Kommentare zum Review

- 5 der 7 eingeschlossenen Studien sind Beobachtungsstudien. Eine Sensitivitätsanalyse allein für die randomisierten Studien gibt es nicht.
- Keine Angabe über AChR-Status

3.3 Leitlinien

Narayanaswami P et al., 2020 [4].

International Consensus Guidance for management of Myasthenia Gravis: 2020 Update.

Zielsetzung/Fragestellung

To update the 2016 formal consensus-based guidance for the management of myasthenia gravis (MG) based on the latest evidence in the literature.

To develop formal consensus-based guidance for the management of myasthenia gravis (MG).

Methodik

Die Leitlinie erfüllt nicht die methodischen Anforderungen einer hochwertigen Leitlinie. Aufgrund fehlender höherwertiger Evidenz wurde die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium. Keine Patientenbeteiligung.
- Interessenkonflikte und finanzielle Unabhängigkeit wurden erfasst und es wurde angegeben, wie mit COI umgegangen wurde.
- Es wurde angegeben, dass eine Literaturrecherche durchgeführt wurde, jedoch nicht systematisch.
- Keine systematische Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse dargelegt. Externes Begutachtungsverfahren über peer-Review Verfahren der veröffentlichenden Zeitschrift.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist im Hintergrundtext dargestellt.
- Regelmäßige Überprüfung der Aktualität unklar.

Recherche/Suchzeitraum:

- Nicht angegeben

LoE

- Nicht angegeben

GoR

- The panel rated each recommendation for appropriateness on a nine point scale (1-3: inappropriate, 4-6: uncertain, and 7-9: appropriate). Median and range were calculated for each recommendation to assess appropriateness and agreement per the RAM method.

Empfehlungen

Thymectomy

- 1a. In non-thymomatous, generalized MG patients with AChR-Ab, aged 18-50 years, thymectomy should be considered early in the disease to improve clinical outcomes and to minimize immunotherapy requirements and need for hospitalizations for disease exacerbations. (Median 9, range 2-9)

- 1b. Thymectomy should be strongly considered in patients with AChR-Ab+ generalized MG if they fail to respond to an initial adequate trial of immunotherapy or have intolerable side effects from that therapy. (Median 9, range 5-9)
- 2. Thymectomy for MG is an elective procedure and should be performed when the patient is stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function. (Median 9, range 9)
- Recommendations 4 and 5 below are unchanged from the 2016 consensus guidance.1
- 3. Endoscopic and robotic approaches to thymectomy are increasingly performed and have a good track record for safety in experienced centers. Data from randomized, controlled comparison studies are not available. Based on comparisons across studies, less invasive thymectomy approaches appear to yield similar results to more aggressive approaches.(Median 9, range 4-9)
- 4. Thymectomy may be considered in generalized MG patients without detectable AChR-Ab if they fail to respond adequately to immunosuppressive (IS) therapy, or to avoid/minimize intolerable adverse effects from IS therapy. Current evidence does not support an indication for thymectomy in patients with MuSK, low-density lipoprotein receptor-related protein 4 (LRP4) or agrin antibodies. (Median 9, range 6-9)

The multicenter, randomized, rater-blinded MGTX trial enrolled patients < 65 years of age with acetylcholine receptor antibody positive (AChR-Ab+) generalized non-thymomatous MG of < 5 years duration.3 Sixty-six subjects underwent extended transsternal thymectomy and received prednisone using a standard dosing schedule, while 60 subjects received the standardized prednisone dosing schedule alone. An effect favoring thymectomy was seen in both of the coprimary outcome measures: reductions in the time-weighted average Quantitative MG (QMG) score and the time-weighted average alternate-day prednisone dose. Secondary outcome measures including azathioprine use, intravenous immunoglobulin (IVIg) use and hospitalizations for MG exacerbations, also favored thymectomy plus prednisone. Benefits were seen within the first year and were sustained through year 3. In a post-hoc analysis, neither the prednisone dose nor QMG scores were significantly different between the two treatment groups in patients 50 years or older.3 An extension of the MGTX trial followed 68 (61%) participants from the original trial for two additional years. At 60 months, lower time-weighted average QMG scores and a reduction in average time-weighted prednisone dose favored thymectomy plus prednisone.4 A recent AAN Practice Advisory recommended that clinicians should discuss thymectomy with patients with AChR Ab+ generalized MG and should counsel patients considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches (Level B).5

Ocular MG:

- 1. Ophthalmoparesis or ptosis in ocular MG that is not responding to anti-cholinesterase agents should be treated with immunosuppressant agents if symptoms are functionally limiting or troublesome to the patient. (Median 9, range 7-9)
- 2. Corticosteroids should be used as the initial IS agent in ocular MG. Steroid-sparing IS agents may be needed when corticosteroids alone are ineffective, contraindicated or not tolerated. (Median 9, range 6-9)
- 3. Data from a single small RCT suggest that low-dose corticosteroids may be effective for ocular MG and may avoid side effects associated with high-dose corticosteroids. (Median 9, range 4-9)
- 4. AChR Ab+ patients with ocular MG who do not respond adequately to acetylcholinesterases
- and who either prefer not to take IS therapy or have contraindications to or are refractory to
- IS agents may be offered thymectomy. (Median 8, range 5-9)

A small RCT comparing prednisone to placebo in 11 ocular MG patients who had previously failed to achieve minimal manifestation (MM) status after 4-6 weeks of pyridostigmine, found that five of six participants (83%) in the prednisone group achieved the primary end-point of sustained MM status at a median of 14 weeks on prednisone (median dose 15mg/day), compared to none of 5 in the placebo group.6 Three of the five placebo participants switched to prednisone

(60 mg/day) with rapid taper; two attained sustained MM status. A prospective cohort study of 13 consecutive ocular and 76 generalized MG patients evaluated the effect of immunosuppressive (IS) agents on ophthalmoparesis.7 Fifty-nine percent of patients had complete resolution of ophthalmoparesis within 12±2 months of initiation of IS agents. Patients with milder ophthalmoparesis had greater odds of symptom resolution in the first year of treatment. Median time to resolution was 7 months after IS agents were started.

Evidence for the efficacy of thymectomy in ocular MG is limited by the retrospective design of most published studies. In a case control study of 47 patients with non-thymomatous ocular MG who underwent thymectomy matched to 67 patients who refused surgery, there was no difference in the proportion of patients achieving stable remission at a median follow-up of 100-116 months.8 A retrospective analysis of 236 patients with thymomatous and non-thymomatous MG reported no improvement after thymectomy in 25 patients, of whom 17 (68%) were ocular or predominantly ocular, over 12 months of follow-up. 9 In another retrospective case series of 52 patients with MG, only 2 of 11 patients with ocular MG (18%) achieved remission post thymectomy, in contrast to 28%-50% of generalized MG patients.10

A retrospective case series of 110 patients with ocular MG who underwent extended transsternal thymectomy reported that at a median follow up of 33.5 months, 26% achieved complete remission (defined as asymptomatic without medications for 12 months).11 Five patients had a thymoma.11 A retrospective case series of 49 non-thymomatous ocular MG and 12 ocular MG with thymoma undergoing thymectomy followed for a mean duration of 9 years reported a cure defined as asymptomatic without need for medications in 51%.12 In yet another retrospective case series of transcervical thymectomy in MG, 57% of 12 patients with ocular MG achieved MGFA post-intervention status (PIS) of complete stable remission (CSR)13 at 5 years. 14 A subsequent case series of 151 patients with MG who underwent transcervical thymectomy followed for 5 years showed a higher odds ratio for remission in ocular MG compared to generalized MG without controlling for other variables (analysis performed by PN).15 In 12 patients with ocular MG undergoing thymectomy because of an abnormal chest CT scan, all but one required additional immunosuppression after thymectomy; 6 achieved remission at mean follow-up of 81 months.16 In a retrospective analysis of 50 juvenile MG patients undergoing thymectomy, of whom 46% were ocular, 50% showed improved PIS at a mean of 3.5 years follow-up.17 There was no difference between ocular and generalized MG. In a meta-analysis of 26 studies of thymectomy in non-thymomatous MG, the pooled CSR rate was 0.51.18 There was high heterogeneity in the meta-analysis model, indicating substantial differences among the included studies.

Rituximab:

Recommendation 1 is unchanged from the 2016 consensus guidance.1

- 1. Rituximab should be considered as an early therapeutic option in patients with MuSKAb+ MG who have an unsatisfactory response to initial immunotherapy. (Median 9, range 4-9)
- 2. The efficacy of rituximab in refractory AChR-Ab+ MG is uncertain. It is an option if patients fail or do not tolerate other IS agents. (Median 8, range 4-9)

Most studies of rituximab (RTX) are retrospective and some combine patients with AChR-Ab, MuSK-Ab and seronegative MG. A multicenter blinded prospective review of MuSK-Ab+ MG patients demonstrated that 14 of 24 (58%) of patients treated with RTX achieved MM status and required only low dose IS therapy, compared to 5 of 31 (16%) of the non-RTX group.19 In a prospective open label study of 22 refractory AChR-Ab+, MuSK-Ab+, and seronegative MG, MG Manual Muscle testing (MMT) scores revealed significant improvement from baseline at mean follow-up of 29± 19 months in the AChR-Ab+ and MuSK-Ab+ groups.20 Another prospective open label study of 14 patients with refractory AChR-Ab+, MuSK-Ab+ and seronegative MG reported improvement in MMT scores at mean follow-up of 22 months.21 The time to peak response after a single cycle of RTX was 4.5± 1 months. A retrospective multicenter study of MuSK-Ab+ MG reported that RTX given in the dose of 375 mg/m2 weekly for 4 weeks and then monthly for the next 2 months was associated with lower relapse rates (18%) compared to a regimen of two 1 gm infusions separated by 2 weeks (80%).22 A retrospective Austrian nationwide study of 56 patients with AChR-Ab+ and MuSK-Ab+ MG reported that 26% of patients were in remission 3 months after treatment with varying dosing protocols of RTX. At a median of 20 months, 43% were in remission and 25% achieved MM status.23 A single center retrospective study of 21 AChR-Ab+, 3 MuSK-Ab+ and 4 double seronegative MG patients found that muscle strength improved significantly from baseline at 6 months, and then stabilized up to 36 months, and PIS was improved in 43% at 6 months.24 A retrospective combined analysis of previously published case reports of 169 patients between January 2000 and August 2015 reported that 72% of MuSK-Ab+ MG and 30% of AChR-Ab+ MG patients treated with RTX achieved MM status or better.25 The number of cycles of RTX varied but did not have an effect on the response. A recent systematic review of previous studies of 165 patients with AChR-Ab+ MG treated with RTX concluded that despite heterogeneous outcome measures, significant clinical improvement was seen in 113 patients (68%), with 36% achieving remission.26 A Phase II RCT of RTX (Beat-MG) enrolled 52 patients with generalized non-thymomatous AChR-Ab+ MG on a stable regimen of prednisone for 4 weeks or prednisone plus another IS agent for 6 months.27 Two cycles of RTX 6 months apart were compared to placebo with the primary outcome being a steroid-sparing effect (≥ 75% reduction in mean daily prednisone requirements in the 4 weeks prior to week 52 compared to the 4-week period prior to randomization). The study was designed to assess futility (non-superiority). Preliminary results reported that the area under the curve for prednisone was not significantly different between RTX and placebo groups, with 60% on RTX and 56% on placebo achieving the primary outcome. There were no significant differences in mean QMG or MG- composite (MGC) changes between the groups. The study suggests that in mildly to

moderately symptomatic generalized AChR-Ab+ MG, RTX is unlikely to have a clinically meaningful steroid-sparing effect over 12 months.

Three cases of progressive multifocal leukoencephalopathy (PML) have been reported in MG. One was RTX related, although the patient had previously received other IS agents,28 another patient was on azathioprine and prednisone29 and the third patient was on prednisolone, IVIg and azathioprine.30

Methotrexate:

- 1. While evidence from RCTs is lacking, oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents that are better supported by RCT data. (Median 9, range 5-9)

Studies on the use of methotrexate (MTX) in MG are limited and the available data do not provide convincing evidence of efficacy. In a retrospective case series of 16 patients with MG treated with MTX, (abstract only) 8 patients reduced pyridostigmine doses and 6 showed "clinical improvement."31 A prospective open-label case series published only as an abstract reported that 14 of 16 MG patients treated with MTX had an improved PIS on mean follow-up of 20.6 months.32 In a single-blinded trial, 24 patients with generalized MG on prednisone were randomized to MTX (11) or azathioprine (13).33 At 24 months the average prednisone dose required to achieve and maintain MM status was lower in both MTX and azathioprine treated patients but was not different between the groups. At months 10 and 12, the prednisone dose was lower in the MTX group but the confidence interval includes clinically meaningful and nonmeaningful effects. Similar proportions of both groups achieved MM status, and there were no differences in QMG or MG-activity of daily living (MG-ADL) scores between the groups.33 An RCT enrolled 50 patients with AChR-Ab+ MG taking prednisone at a dose of ≥10mg/day. 34 Patients were randomized 1:1 to MTX 20 mg/week or placebo. There was no difference in the primary outcome measure, the area under the prednisone dose-time curve between months 4 and 12, and the mean 12-month change in QMG, MMT, MG-Quality of life (MG-Qol), MG-ADL and MGC were no different between treatment groups.

Eculizumab:

- 1. Eculizumab should be considered in the treatment of severe, refractory, AChR-Ab+ generalized MG. (Median 9, range 2-9)
- 2. The role of eculizumab in the treatment of MG is likely to evolve over time. Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. (Median 9, range 5-9)
- 3. Recommendations of the Advisory Committee on Immunization Practice (ACIP) or other local guidelines regarding immunization against meningococcal meningitis should be followed prior to treatment with eculizumab. (Median 9, range 8-9)
- 4. Future research should include assessment of the duration of eculizumab therapy necessary to achieve and maintain treatment goals, its efficacy in other MG populations (MG with thymoma, seronegative MG), and in other stages of disease (MG crises, exacerbations, early therapy in non-refractory AChR-Ab+ MG). (Median 8, range 4-9)

Eculizumab is a humanized monoclonal antibody against the terminal C5 complement molecule.35 Eculizumab prevents the formation of the membrane attack complex (MAC) and reduces damage caused by complement-fixing AChR antibodies.36 In a Phase II crossover RCT of 14 patients with refractory generalized AChR-Ab+ MG, at the end of the first treatment period, 6/7 (86%) of eculizumab-treated patients achieved the primary endpoint of a 2-point reduction in the QMG score, compared to 57% with placebo.37 A repeated measures mixed model of data from all visits revealed significant differences in QMG score favoring eculizumab. Eculizumab was well tolerated. In a phase III international multicenter RCT of 125 patients with refractory generalized non-thymomatous AChR-Ab+ MG (REGAIN), the primary outcome measure of change in MG-ADL score from baseline to week 26, measured by worst-rank ANCOVA, was not significantly different (p=0·0698) between eculizumab and placebo arms.38 However, QMG score change on worst-rank ANCOVA, all pre-specified secondary endpoints (changes in QMG, MGC and MG-QOL15 scores and responder analyses of QMG and MG-ADL scores) and multiple sensitivity analyses showed a significant benefit for eculizumab. Participants who completed the 26-week REGAIN study were followed in an open label extension (OLE) within 2 weeks of completing REGAIN.39 A pre-planned interim analysis of the OLE at 22.7 months median follow-up found a reduction in MG exacerbations by 75% compared to the year before REGAIN. In addition, 56% (65/116) of patients achieved MM status or pharmacologic remission. The magnitude of response on all clinical measures for the placebo patients in REGAIN who crossed over to receive eculizumab in the OLE was similar to the eculizumab treated patients in REGAIN. A clinically meaningful response in MG-ADL and QMG scores was seen in 55% and 39.7% of patients, respectively. Eculizumab was well tolerated. One case of meningococcal meningitis occurred despite vaccination in the OLE and the patient was successfully treated.

Vaccination against Neisseria meningitidis (both meningococcal conjugate MenACWY and serogroup B or MenB) is required at least 2 weeks prior to starting treatment with eculizumab. The conjugate ACWY vaccines available in the USA include Menveo® (1 dose, GlaxoSmithKline Biologicals, Inc.) and Menactra® (1 dose, single booster 4 years after initial dose if needed, Sanofi Pasteur, Inc.). The two brands of MenB vaccine are Bexsero® (2 dose series, GlaxoSmithKline Biologicals, Inc.) and Trumenba® (3 dose series, Pfizer, Inc.). The brands are not interchangeable, and a course should be completed with the same brand of the vaccine for all doses. The vaccine does not confer absolute protection against meningococcal meningitis. Antibiotic coverage, for at least 4 weeks after immunization is recommended if eculizumab is started prior to the two-week period post-vaccination. The recommendations for antibiotic coverage vary. Penicillin VK 250-500 mg every12 hours is usually the first line chemoprophylaxis. 40, 41 Erythromycin 500 mg twice daily, Azithromycin 500 mg daily or Ciprofloxacin 500 mg daily are alternatives for penicillin allergic patients.40-42 However, both fluoroquinolones and macrolides can worsen MG. Chemoprophylaxis of meningococcal infections in penicillin allergic patients can therefore be challenging, and infectious disease consultation may be required.

Immune Checkpoint Inhibitors (ICIs):

- 1. The risk of MG and other immune-mediated neurologic illnesses should be discussed with patients who are candidates for ICIs. (Median 9, range 5-9)
- 2. At this time, there is no evidence to either support or refute the utility of AChR antibody testing in patients without MG prior to starting ICIs. (Median 8, range 7-9)
- 3. MG associated with ICIs is generally severe, with a high rate of respiratory crises. (Median 8, range 5-9)
- 4. Pre-existing MG does not constitute an absolute contraindication to the use of ICIs, at least in patients with well-controlled disease (MM status or better). However, in these patients:
  - a. It may be prudent to avoid combined therapy (anti-CTLA-4 plus anti-PD1/PD-L1 monoclonal antibodies), given the higher potential for severe irAEs.
  - b. Close clinical monitoring, particularly of respiratory and bulbar function, is mandatory.
  - c. Although the therapeutic response to ICIs seems to be less satisfactory in patients receiving immunosuppressants, MG treatment should be maintained and may even be restarted in patients whose MG is in remission prior to treatment with ICIs. (Median 8, range 5-9)
- 5. Early aggressive treatment with high-dose steroids in combination with plasma exchange or IVIg may be required in patients who develop overt MG while on ICIs. The decision to withdraw ICIs is determined by the oncologic status. (Median 8, range 7-9)

Immune checkpoints (ICPs) are most often inhibitory molecules expressed on the surface of Tcells, which modulate the immune response and prevent host tissue damage due to uncontrolled responses to foreign or self-antigens. The immune inhibitory cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PDL1) are the best-characterized ICPs and are targeted in cancer immunotherapy. CTLA-4 reduces T-cell activation, competing with CD28 in binding B7 molecules (CD80 and CD86) on antigen-presenting cells. PD-1 binds its ligands (PD-L1 and PD-L2) and reduces activated T-cell proliferation through the inhibition of specific phosphorylation pathways.43, 44 Monoclonal antibodies against CTLA-4, PD-1 and PD-L1 act by blocking these inhibitory ICP molecules in order to stimulate antitumor immunity (immune checkpoint inhibitors, ICIs). These include the CTLA-4 inhibitor ipilimumab, PD-1 inhibitors pembrolizumab, nivolumab and cemiplimab, and the PDL-1 inhibitors atezolizumab, durvalumab, and avelumab. Because of the up-regulation of the immune response, multisystem immune-related adverse events (irAEs) such as skin rash, thyroid dysfunction, pneumonitis, colitis, hepatitis, nephritis, hypophysitis, and neurologic disorders including MG have been reported in patients receiving checkpoint inhibitors. The literature on irAEs of these drugs is rapidly evolving. De novo MG has been reported in patients treated with anti-CTLA-4 agents (ipilimumab), 45 PD1 inhibitors (nivolumab or pembrolizumab) 45-47 and with combined (anti-CTLA-4 plus anti-PD-1 or PD-L1) therapy.45 The estimated frequency of MG among patients treated with PD-1 inhibitors ranges from 0.12% to 0.2%.48-52 Exacerbation of pre-existing MG and subclinical AChR-Ab+ MG has been reported in patients treated with PD-1 inhibitors.45, 53, 54

MG onset or exacerbation varies in severity and generally occurs in the early phase of treatment. MG can overlap with other immune-mediated peripheral and central neurological syndromes.48, 55 In a review of the literature combined with a single center experience, of 63 patients with MG due to ICIs, 52 had new onset MG and 11 had a flare of preexisting MG. Most received PD1 therapy. Concurrent myositis was diagnosed in 24 patients (37%), and myocarditis in five (8%); two had the triad of MG/myositis/myocarditis. Median time from ICI initiation to developing MG was 4 weeks (6 days- 16 weeks). Respiratory failure requiring mechanical ventilation occurred in 29 patients (45%). Patients with

MG/myositis/myocarditis developed respiratory failure more frequently than those with MG alone (54% vs. 42%). AChR-Ab titers were elevated in 37/56 (66%) of tested patients. Three patients had AChR-Ab when tested before ICI initiation and antibody titers increased at least 2-fold after ICI initiation. Intravenous corticosteroids were used in 59/63 patients. Thirty-eight patients received steroids as first line therapy and 24 (63%) improved. Four patients with ocular MG developed respiratory insufficiency after corticosteroid treatment. MG symptoms completely resolved in 12 patients (19%), improved in 34 (55%), and worsened in 16 (26%).51 In a review of 1834 patients receiving ICIs, four had MG, of whom one was AChR- Ab+. Three were associated with myositis. Three MG patients received combined CTLA-4 and PD1 ICIs and one received a CTLA4 ICI. Concurrent occurrence of MG with myocarditis and thyroiditis was also noted.50 The diagnosis of ICI related MG can be challenging. Many cancer patients have fatigue or generalized weakness. The recognition of underlying neuromuscular disease may be delayed by the focus on the oncologic illness. Concurrent myositis may make MG difficult to diagnose especially when associated with ocular and bulbar weakness. Seronegative MG appears to be more frequent in these patients, making the diagnosis even more challenging.50 The severity of the illness may be the result of multiple concurrent conditions including MG, myositis and myocarditis. Central nervous system involvement may occur in conjunction with MG or MG-myositis overlap.50 Corticosteroid therapy appears to result in favorable outcomes.50

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2021) am 09.11.2021

#	Suchfrage
1	[mh "myasthenia gravis"]
2	myastheni*:ti,ab,kw
3	(musk AND mg):ti,ab,kw
4	(Erb-Goldflam OR oppenheim*)):ti,ab,kw
5	[mh ^"muscle weakness"]
6	((muscle* OR muscular) AND (weakness*)):ti
7	[mh ^"neuromuscular disease"]
8	((neuromuscular OR neuro-muscular) AND (disease* OR disorder*)):ti
9	(((foley* AND denny* AND brown*) OR (fasciculation* AND cramp*)) AND (syndrom*)):ti
10	{OR #1-#4}
11	{OR #5-#9}
12	{AND #11, #2}
13	{OR #10, #12}
11	#13 with Cochrane Library publication date from Nov 2016 to present

Systematic Reviews in Medline (PubMed) am 09.11.2021 [1,2]

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	myasthenia gravis[mh]
2	myastheni*[tiab] OR (MuSK[tiab] AND MG[tiab])
3	Erb[tiab] AND (Goldflam*[tiab] OR Oppenheim*[tiab])
4	#1 OR #2 OR #3

[1] Das Enddatum der Recherche in Pubmed/Medline wird seit 01/2018 auf „3000“ durch TIM festgelegt. Begründung: das Aufnahme bzw. Erscheinungsdatum neuerer Publikationen sind in der Datenbank (PM/ML) des öfteren vordatiert, so dass sie durch die Einschränkung des Suchzeitraums nicht miterfasst werden. Zur Abhilfe wird das Enddatum des Suchzeitraums heraufgesetzt.

2 Recherche in New PubMed gültig ab 18.05.2020

#	Suchfrage
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	((#5) AND ("2016/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 15.11.2021 [3]

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	myasthenia gravis[mh]
2	Myastheni*[tiab] OR (MuSK[tiab] AND MG[tiab])
3	Erb[tiab] AND (Goldflam*[tiab] OR Oppenheim*[tiab])
4	muscle weakness[mj]
5	(muscle*[ti] OR muscular[ti]) AND weakness*[ti]
6	Neuromuscular Diseases[mj:noexp]
7	(Neuromuscular[ti] OR "Neuro-muscular"[ti] OR oppenheim*[ti]) AND (disease*[ti] OR disorder*[ti])
8	((foley*[ti] AND denny*[ti] AND brown*[ti]) OR (Fasciculation*[ti] AND cramp*[ti])) AND syndrom*[ti]
	"Amyotonia Congenita"[ti] → veraltet keine Publ seit 1986
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
11	(((#10) AND ("2016/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

[3] Das Enddatum der Recherche in Pubmed/Medline wird seit 01/2018 auf „3000“ durch TIM festgelegt. Begründung: das Aufnahme bzw. Erscheinungsdatum neuerer Publikationen sind in der Datenbank (PM/ML) des Öfteren vordatiert, so dass sie durch die Einschränkung des Suchzeitraums nicht miterfasst werden. Zur Abhilfe wird das Enddatum des Suchzeitraums heraufgesetzt.

Referenzen

1. **Bernuy-Guevara C, Chehade H, Muller YD, Vionnet J, Cachat F, Guzzo G, et al.** The Inhibition of Complement System in Formal and Emerging Indications: Results from Parallel One-Stage Pairwise and Network Meta-Analyses of Clinical Trials and Real-Life Data Studies. Biomedicines 2020;8(9).

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO