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: 2023-B-268 Efgartigimod alfa

Stand: November 2023

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

Efgartigimod alfa
[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	Nutzenbewertung nach §35a SGB V • Efgartigimod alfa; Beschluss vom 17. Februar 2023 • Ravulizumab; Beschluss vom 20. April 2023 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

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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Efgartigimod alfa L04AA58 Vyvgart	Zugelassenes Anwendungsgebiet: „Vyvgart wird zusätzlich zur Standardtherapie zur Behandlung von erwachsenen Patienten mit generalisierter Myasthenia gravis (gMG) angewendet, die Anti-Acetylcholin-Rezeptor (AChR)-Antikörper positiv sind.“
Glukokortikoide	
Prednisolon H02AB06 Prednisolon-ratiopharm	[…] Neurologie (DS: a) • Myasthenia gravis (Mittel der 1. Wahl ist Azathioprin) […]
Prednison H02AB07 Prednison acis	[…] Neurologie (DS: a) • Myasthenia gravis (Mittel der 1. Wahl ist Azathioprin) […]
Nicht-steroidale Immunsuppressiva	
Azathioprin L04AX01 Azathioprin Heumann	[…] 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.

Cholinesterasehemmer	
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.
Neostigminmetil-sulfat N07AA01 Neostigmin-Rotexmedica	[…] Myasthenia gravis (Erkrankung mit vorzeitiger Ermüdung der Muskeln bei Belastung).
Distigminbromid N07AA03 Ubretid® Injektionslösung	Zur Behandlung von – Neurogenen Blasenentleerungsstörungen mit hypotonem Detrusor im Rahmen eines therapeutischen Gesamtkonzepts. – Postoperativer Darmatonie. – Myasthenia gravis.
Sonstige	
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)
Ravulizumab L04AA43 Ultomiris	*[…]* *Generalisierte Myasthenia gravis (gMG)* Ultomiris wird angewendet als Zusatztherapie zu einer Standardbehandlung bei erwachsenen Azetylcholinrezeptor (AChR)- Antikörper-positiven Patienten mit gMG.
Normales Immunglobulin vom Menschen (IVIg) J06BA02 Gamunex 10%	[…] <u>Immunmodulation bei Erwachsenen (mindestens 18 Jahre):</u> • Schwere akute Exazerbationen bei Myasthenia gravis

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-268 (Efgartigimod alfa)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	1. November 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AChR	Acetylcholin-Rezeptor
AChE-I	Acetylcholinesterase-Hemmer
AHSCT	Autologe hämatopoetische Stammzelltransplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprine
BLM	Belimumab
CsA/CSA	Cyclosporine A / Cyclosporin A
CTX	Cyclophosphamide
DFPP	double-filtration plasmapheresis
ECZ	Eculizumab
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GKS	Glukokortikosteroide
gMG	generalisierter Myasthenia gravis
GoR	Grade of Recommendations
HR	Hazard Ratio
IA	Immunadsorption
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IVIG	Intravenöse Immunglobuline
jMG	juvenile Myasthenia gravis
KI	Konfidenzintervall
LoE	Level of Evidence
LRP4	Lipoprotein-related protein 4
MG	Myasthenia gravis
MMF	Mycophenolate mofetil
MTX	Methotrexate
MuSK	Muskelspezifische Kinase
NICE	National Institute for Health and Care Excellence
NTMG	non-thymomatous myasthenia gravis
oMG	okuläre Myasthenia gravis
OR	Odds Ratio
PE	Plasmaaustausch
PLA	Placebo
QMG/S	Quantitative MG/Score

RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TAC	Tacrolimus
TRIP	Turn Research into Practice Database
Thx	Thymektomie
WHO	World Health Organization

1 Indikation

Erwachsene mit generalisierter Myasthenia gravis (gMG), die Anti-Acetylcholin-Rezeptor (AChR)-Antikörper positiv sind.

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), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 15.11.2022 durchgeführt, die folgenden am 19.04.2023 und 19.10.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 354 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 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurde kein relevanter Cochrane Review im AWG identifiziert.

3.2 Systematische Reviews

Zhang J et al., 2021 [5].

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 [2].

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.	②⑤
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:

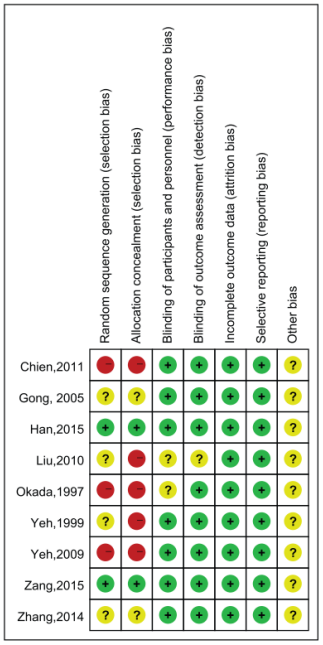


Figure 2. Risk of bias summary based on the review authors' judgement for each included study.

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.

Wang L et al., 2019 [4].

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

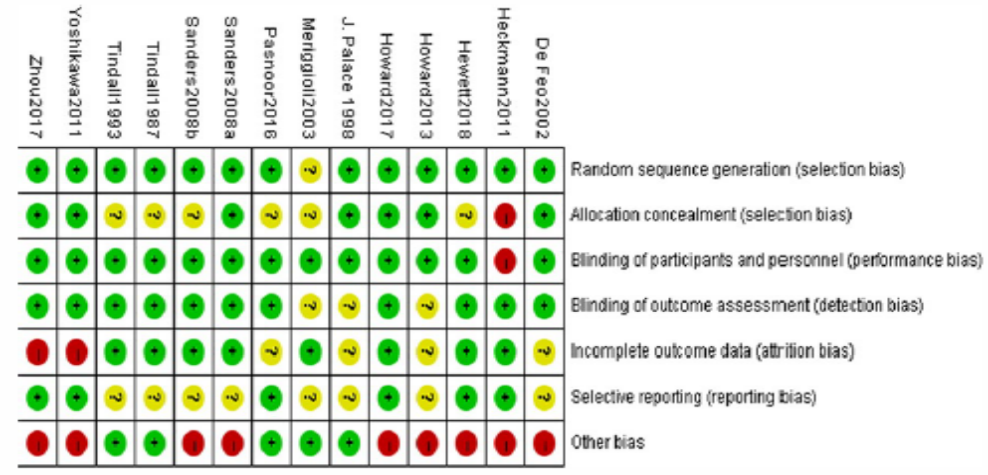
Anzahl eingeschlossener Studien:

- 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:

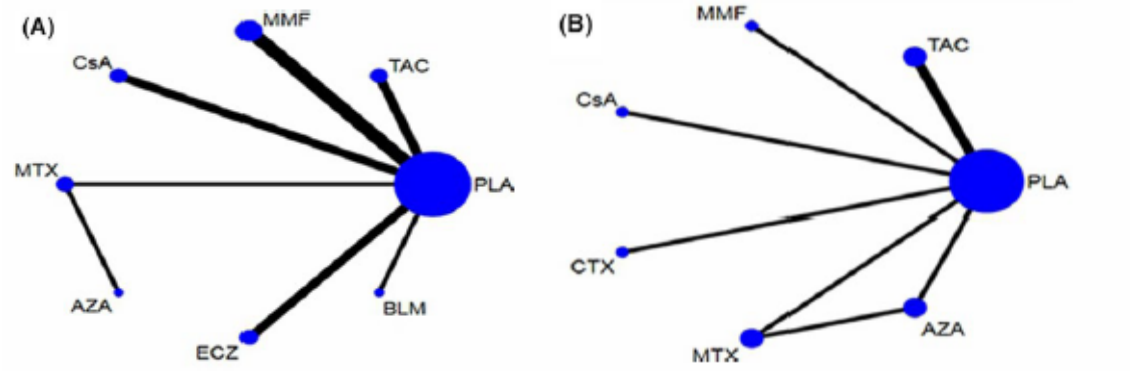
- Thymectomy was performed in 245 of 769 (31.9%) reported participants while thymoma was found in 48 of 390 (11.8%) reported participants.
- The anti-AChR antibody serostatus was displayed in 725 patients, with 684 (94.3%) seropositive samples.

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						
Stand ardized 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

3.3 Leitlinien

Wiendl H et al., 2022 [1].

Deutsche Gesellschaft für Neurologie (DGN).

Diagnostik und Therapie myasthener Syndrome; S2k-Leitlinie, Langfassung, Version 6.2

Zielsetzung/Fragestellung

Die MMG und das Lambert-Eaton-Myasthenie-Syndrom (LEMS) repräsentieren immunvermittelte Störungen der neuromuskulären Übertragung […] Die Autorengruppe möchte daher den aktuellen Stand bzgl. Pathogenese, Diagnostik und Therapie dieser Erkrankungen darlegen.

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;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Keine Systematische Suche, konsensbasierte Leitlinie; Ausgangspunkt der Leitlinienentwicklung waren Kapitel 2–5. Zudem liegen den Erläuterungen und Empfehlungen der Leitlinie Pubmed-Recherchen zur publizierten Evidenz zugrunde (Originalarbeiten und klinische Studien; Suchergebnisse bis zum 26.04.2022). Soweit für die jeweiligen Fragestellungen aus Sicht der Leitliniengruppe keine ausreichende Evidenz zur Verfügung stand, wurde auf Expertenmeinungen aus der Leitliniengruppe und den beteiligten Fachgesellschaften zurückgegriffen…
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Konsensstärke ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert, Gültig bis: 9. November 2025.

Recherche/Suchzeitraum:

- Siehe oben

LoC / GoR

Tabelle 4.5-2: Feststellung der Konsensstärke

Klassifikation der Konsensusstärke	
starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75–95 % der Stimmberechtigten
mehrheitliche Zustimmung	> 50–75 % der Stimmberechtigten
keine mehrheitliche Zustimmung	< 50 % der Stimmberechtigten

Tab. 4.5-1: Empfehlungsgraduierung

Beschreibung	Ausdrucksweise
starke Empfehlung	soll/soll nicht
Empfehlung	sollte/sollte nicht
Empfehlung offen	kann erwogen/verzichtet werden

Sonstige methodische Hinweise

keine

Empfehlungen

Empfehlung 2.4-1	Neu [2022]
Die Therapie **soll** unter Berücksichtigung des Alters, der Thymuspathologie, des Ak-Status (AChR-Ak-, MuSK-Ak-, LRP4-Ak-positive sowie seronegative MG) und der Krankheitsaktivität erfolgen.	
Konsensstärke: starker Konsens	

Schema zur verlaufsmodifizierenden Therapie der MG (Stufentherapieschema)

Verlaufsmodifizierende Therapie	Okulär	Generalisiert			
		AChR-Ak positiv[&]		MuSK-Ak positiv	
		1. Wahl	2. Wahl	1. Wahl	2. Wahl
	• Glukokortikoide[a] **und/oder** • Azathioprin • *Mycophenolat-Mofetil*[c] • *Ciclosporin A* • *Methotrexat*	**Milde/Moderate Krankheitsaktivität/ Krankheitsschwere**: • Glukokortikoide[a] **und/oder** • Azathioprin • Thymektomie[b]	• Glukokortikoide[a] **und/oder** • *Mycophenolat-Mofetil*[c] • *Ciclosporin A* • *Methotrexat* • *Tacrolimus*	• Glukokortikoide[a] **und/oder** • Azathioprin	• Glukokortikoide[a] **und/oder** • *Mycophenolat-Mofetil*[c] • *Ciclosporin A* • *Methotrexat* • *Tacrolimus*
	• Korrektur-OP	**Hohe Krankheitsaktivität/-schwere[#] (inkl. therapierefraktär)**: +/- Glukokortikoide **und/oder** eine zusätzliche Therapieoption aus milder/moderater Krankheitsaktivität/-schwere			
		• Komplement-Inhibitoren (Eculizumab[d], Ravulizumab[d]) • FcRn-Modulatoren (Efgartigimod[e]) • *CD20-Antikörper (z.B. Rituximab)* • Thymektomie[b]	• *IVIG*[f] • *Plasmapherese/ Immunadsorption* • *AHSCT, Bortezomib, Cyclophosphamid*[h]	• *CD20-Antikörper (z.B. Rituximab)*	• *IVIG*[f] • *FcRn-Modulatoren (Efgartigimod*[e]*)* • *Plasmapherese/ Immunadsorption* • *AHSCT, Bortezomib, Cyclophosphamid*[h]
		Krise/Krisenhafte Verschlechterung: • IVIG[f] • Plasmapherese/Immunadsorption • Steroidpulstherapie[g]			

[#] Eine (hoch-) aktive generalisierte MG (inklusive therapierefraktäre MG) kann definiert werden als
moderater/hoher MGFA-Status (≥ MGFA IIb) und/oder mindestens 2 rezidivierende schwere Exazerbationen / Myasthene Krisen mit Notwendigkeit der therapeutischen Intervention (IvIg, PLEX, IA) innerhalb eines Jahres nach Diagnosestellung trotz adäquater verlaufsmodifizierender und symptomatischer Therapie

oder

anhaltende alltagsrelevante Symptomatik (≥ MGFA IIa) und schwere Exazerbation / Myasthener Krise innerhalb des letzten Kalenderjahres trotz adäquater verlaufsmodifizierender und symptomatischer Therapie

oder

anhaltende alltagsrelevante Symptomatik auch vom milden/moderaten Verlaufstyp (≥ MGFA IIa) über mehr als zwei Jahre trotz adäquater verlaufsmodifizierender und symptomatischer Therapie

Anmerkung: Die Bemessung des Schweregrads orientiert sich an der MGFA-Klassifikation. Allerdings berücksichtigt der hier verwendete MGFA-Status nur den Schweregrad zum Zeitpunkt der klinischen Einschätzung und nicht den jemals im Krankheitsverlauf erreichten höchsten Schweregrad.

[&] Seronegative und LRP4-Antikörper-positive MG werden in der Regel wie die AChR-Ak positive MG behandelt.

Kursiv: formal *Off-label*-Therapie

a) Steroide sind nicht als Dauertherapie (zumindest oberhalb der Cushing-Schwelle) indiziert, steroidsparende Strategien sollten frühzeitig angewendet werden

b) Altersfenster (i.d.R. 18 bis 65 Jahre) und Krankheitsdauer (i.d.R. < 5 Jahre) beachten; obligatorisch bei Thymom-Verdacht

c) Mycophenolat-Mofetil ist als Therapie der 2. Wahl nach G-BA-Beschluss im Off-label-Gebrauch erstattungsfähig

d) Eculizumab ist on-label bei therapierefraktärer AChR-Ak-positiver gMG, Ravulizumab ist als Add-on Therapie für die AChR-Ak-positive gMG zugelassen
e) Efgartigimod ist als add-on Therapie für die AChR-Ak-positive gMG zugelassen
f) IVIG sind bei der schweren myasthenen Exazerbation nach G-BA-Beschluss im Off-label-Gebrauch erstattungsfähig; SCIG können anstatt von IVIG in Ausnahmefällen eingesetzt werden, die Erstattungsfähigkeit wird aber nicht durch den G-BA-Beschluss geregelt.
g) cave Steroid-Dip
h) Compassionate Use

Symptomatische Therapie

Empfehlung 2.4-2	Modifiziert [2022]
Zur symptomatischen Therapie der MG **sollen** die AChE-I, vorwiegend Pyridostigmin, verwendet werden. Pyridostigmin **soll** als symptomatische Therapie bei allen MG-Formen in nicht retardierter und/oder retardierter Form in Abhängigkeit von der Krankheitsschwere, von Begleiterkrankungen, Nebenwirkungen und der individuellen therapeutischen Breite in Dosen von bis zu 720 mg eingesetzt werden. Dosen oberhalb von 720 mg p. o. werden nur in Ausnahmefällen vertragen. Bei Kindern und Jugendlichen **soll** auf eine gewichtsadaptierte Dosis geachtet werden.	
Konsensstärke: Konsens	

Empfehlung 2.4-3	Modifiziert [2022]
Die Gabe von Ambenonium, Neostigmin oder Distigmin **kann** bei Patienten mit Unverträglichkeit gegenüber oder Nichtwirksamkeit von Pyridostigmin **erwogen werden.**	
Konsensstärke: starker Konsens	

Therapie für die milde/moderate MG

Empfehlung 2.4-4	Modifiziert [2022]
Orale GKS **sollen** zur Behandlung der milden/moderaten bis (hoch-)aktiven gMG/jMG und der oMG als Basis-Immuntherapeutika in einer der Krankheitsschwere angemessenen Dosierung über einen möglichst kurzen Zeitraum und unter Berücksichtigung von Komorbiditäten, Kontraindikationen und Nebenwirkungen eingesetzt werden.	
Konsensstärke: starker Konsens	

Empfehlung 2.4-5	Neu [2022]
Für die AChR-Ak-positive, LRP4-Ak-positive und seronegative gMG/jMG[1] von milder/moderater Aktivität **sollen** neben der symptomatischen Therapie GKS und/oder AZA (+/– Thx) als die Therapie der ersten Wahl für die Verlaufsmodifikation verwendet werden. Alternativ zu AZA **können** bei der gMG in der zweiten Wahl MMF[2], CSA, Tacrolimus oder MTX **erwogen werden** (Einsatz bei Unwirksamkeit, fehlender Verträglichkeit, Kontraindikationen). Alternativ zu AZA **können** bei der jMG in der zweiten Wahl MMF oder Tacrolimus **erwogen werden.** [1]für die MuSK-Ak-positive MG s. Empfehlung 2.4-9 [2]positives G-BA-Votum (107)	
Konsensstärke: starker Konsens	

Empfehlung 2.4-6	Neu [2022]
Für die oMG **sollen** neben der symptomatischen Therapie als verlaufsmodifizierende Therapie GKS +/– AZA verwendet werden. Alternativ zu AZA **kann** der Einsatz von MMF, MTX, Tacrolimus sowie CSA **erwogen werden.**	
Konsensstärke: starker Konsens	

Intensivierte Therapie

Empfehlung 2.4-7	Neu [2022]
Die symptomatische Therapie der (hoch-)aktiven inklusive der „therapierefraktären" MG ist durch die folgenden verlaufsmodifizierenden Therapien zu ergänzen: ▪ Bei AChR-Ak-positivem Status **sollen** Komplementinhibitoren (Eculizumab[1], Ravulizumab[1,6]) oder FcRn-Modulatoren (Efgartigimod[2,6]) +/– Thx verwendet werden. ▪ Bei LRP4-Ak-positivem[3] oder seronegativem[3] Status **können** Komplementinhibitoren oder FcRn-Modulatoren (Efgartigimod[2]) +/– Thx **erwogen werden.** ▪ Bei AChR-Ak-positivem, LRP4-Ak-positivem[4] oder seronegativem[4] Status **kann** eine CD20-Antikörper-Depletion (Rituximab) +/– Thx als Therapie der ersten Wahl für die Verlaufsmodifikation **erwogen werden.** Der Einsatz von Komplementinhibitoren ist nur bei Nachweis von Verlaufsformen mit einem komplementabhängigen Mechanismus gerechtfertigt. Als Medikamente der zweiten Wahl **sollten** IVIG und PE/IA dienen. In Einzelfällen **können** auch weitere Verfahren **erwogen werden** wie AHSCT, Bortezomib und Cyclophosphamid. Bei der jMG[5] **sollen** IVIG/PE als Therapien der ersten Wahl sowie Rituximab und Eculizumab als Therapien der zweiten Wahl genutzt werden. Efgartigimod[6] und Ravulizumab[6] **können** als Therapien der zweiten Wahl **erwogen werden.** [1]Eculizumab ist nur für die therapierefraktäre AChR-Ak-positive gMG zugelassen, während Ravulizumab als Add-on-Therapie für die AChR-Ak-positive gMG zugelassen ist. [2]Efgartigimod ist nur als Add-on-Therapie nur für die AChR-Ak-positive gMG zugelassen. [3]Eculizumab, Efgartigimod und Ravulizumab sind in dieser Indikation off-label. [4]Rituximab ist in dieser Indikation off-label. [5]Eculizumab, Efgartigimod, Ravulizumab und Rituximab sind in dieser Indikation off-label. [6]in der Schweiz nicht zugelassen
Konsensstärke: starker Konsens	

Antikörperspezifische Besonderheiten der Therapie

Empfehlung 2.4-9	Neu [2022]
Für die MuSK-Ak-positive Myasthenie mit milder/moderater Aktivität **sollen** neben der symptomatischen Therapie mit AChE-I für die Verlaufsmodifikation GKS +/– AZA als Therapie der ersten Wahl verwendet werden, für Patienten mit (hoch-)aktivem Verlauf (inklusive Therapierefraktärität) Rituximab. Die Therapieverfahren der zweiten Wahl **sollen** analog zur AChR-Ak-positiven MG sein/gewählt werden, wobei auch FcRn-Modulatoren (Efgartigimod[1]) **erwogen werden können.** [1]Efgartigimod ist in dieser Indikation off-label.	
Konsensstärke: starker Konsens	

Chirurgische Therapie - Thymektomie

Empfehlung 2.4-10	Modifiziert [2022]
a) Bei Patienten mit AChR-Ak-positiver gMG im Alter zwischen 18 und 65 Jahren **sollte** die Thx (transsternal oder minimalinvasiv) möglichst frühzeitig innerhalb von zwei Jahren und spätestens bis fünf Jahre nach Sicherung der Diagnose durchgeführt werden. b) Die Thx **kann** auch bei seronegativer gMG und LRP4-Ak-positiver gMG mit hoher Krankheitsaktivität nach Möglichkeit in den ersten beiden Krankheitsjahren **erwogen werden.** c) MuSK-Ak-positive MG-Patienten **sollen** nicht thymektomiert werden. d) Die Thx **kann** auch bei der generalisierten AChR-Ak-positiven jMG **in Erwägung gezogen** und individuell entschieden werden. e) Bei Kindern und Jugendlichen im Alter von fünf bis zwölf Jahren **sollte** die Thx erst nach Versagen der medikamentösen Therapie (AChE-I, GKS) erfolgen. Bei Kindern im Alter ab 13 Jahren sollte wie unter a) weiter verfahren werden.	
Konsensstärke: starker Konsens	

Empfehlung 2.4-11	Modifiziert [2022]
a) Jeder MG-Patient **soll** auf das Vorhandensein eines Thymoms hin untersucht werden. Thymome **sollen** in jedem Lebensalter und unabhängig vom Schweregrad der Myasthenie operativ entfernt werden. In Ausnahmefällen **sollte,** in Abhängigkeit vom bildgebenden Befund, eine komplexe Behandlung mittels neoadjuvanter Chemotherapie oder Radiochemotherapie erfolgen. In Abhängigkeit vom histopathologischen Befund **sollte** adjuvant eine postoperative Radiotherapie (PORT) vorgenommen werden. b) Bei fehlender OP-Fähigkeit und Thymomverdacht **sollen** eine Biopsie und ggf. eine konservative Therapie (in der Regel Strahlentherapie) durchgeführt werden. c) In Abhängigkeit vom präoperativen Staging und der Erfahrung des Operateurs **können** minimal-invasive neben transsternalen Operationstechniken **erwogen werden.** d) Auch bei Kindern und Jugendlichen **soll** ein Thymom – trotz der Seltenheit – bildmorphologisch ausgeschlossen werden.	
Konsensstärke: starker Konsens	

Narayanaswami P et al., 2020 [3]
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 10 of 12, October 2023) am 19.10.2023

#	Suchfrage
1	[mh "myasthenia gravis"]
2	myastheni*:ti,ab,kw
3	(((musk OR achr* OR anti acetylcholine receptor OR (muscle specific AND kinase)) AND (mg OR ab OR antibod*)) OR gmg OR achrab*):ti,ab,kw
4	[mh ^"neuromuscular diseases"]
5	((neuromuscular OR neuro-muscular) AND (disease* OR disorder*)):ti
6	#1 OR #2 OR #3 OR #4 OR #5
7	#6 with Cochrane Library publication date from Oct 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 19.10.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"myasthenia gravis"[mh]
2	Myastheni*[tiab]
3	((musk*[tiab] OR achr*[tiab] OR anti acetylcholine receptor[tiab] OR (muscle specific[tiab] AND kinase[tiab])) AND (mg[tiab] OR ab[tiab] OR antibod*[tiab])) OR gmg[tiab] OR achrab*[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND

#	Suchfrage
	(survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	(#5) AND ("2018/10/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 19.10.2023

verwendete Suchfilter:
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]
3	((musk*[tiab] OR achr*[tiab] OR anti acetylcholine receptor[tiab] OR (muscle specific[tiab] AND kinase[tiab])) AND (mg[tiab] OR ab[tiab] OR antibod*[tiab])) OR gmg[tiab] OR achrab*[tiab]
4	"neuromuscular diseases"[mh:noexp]
5	(neuromuscular[ti] OR neuro-muscular[ti]) AND (disease*[ti] OR disorder*[ti])
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2018/10/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 19.10.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-268

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) Bundesärztekammer, Dezernat 1 – Ärztliche Versorgung und Arzneimittel, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Datum der Erstellung	6. November 2023

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Zusätzlich zur Standardtherapie zur Behandlung von erwachsenen Patienten mit generalisierter Myasthenia gravis (gMG) angewendet, die Anti-Acetylcholin-Rezeptor (AChR)-Antikörper positiv sind
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Man unterscheidet einen symptomatischen und einen verlaufsmodifizierenden, immuntherapeutischen Behandlungsansatz, meistens werden beide verzahnt verfolgt. Pharmakologische Behandlung bei generalisierter Myasthenia gravis und positiven Anti-Acetylcholin-Rezeptor-AK, wobei die Grenze zwischen Standardtherapie und Ansätzen jenseits der Standardtherapie im klinischen Alltag nicht scharf definiert ist: Standardtherapie: Acetylcholinesterase-Inhibitoren (AChE-I), das Mittel der Wahl ist Pyridostigmin (1). Mehr als 80 % der Patienten sind im Krankheitsverlauf mit der ausschließlichen Gabe von AChE-I aber unzureichend behandelt (2), hier kommen Glukokortikosteroide und/oder eine Immunmedikation (Mittel der 1. Wahl ist Azathioprin) zum Einsatz. Jenseits der Standardtherapie: Immuntherapeutika der 2. Wahl sind Ciclosporin A, Methotrexat, Mycophenolatmofetil und Tacrolimus (1). Bei therapierefraktären, schwersten Verläufen können Komplementinhibitoren (Eculizumab, Ravulizumab) oder FcRn-Modulatoren (Efgartigimod) zum Einsatz kommen (1). Eine aktuelle Metaanalyse konnte keinen Unterschied in der Wirksamkeit von Komplementinhibitoren und FcRn-Modulatoren feststellen (3). Nachgeordnet sind die Gabe von intravenösen Immunglobulinen und die Plasmapherese/Immunadsorption. Die Behandlung schwerster Verläufe ist oft individualisiert und Zentren vorbehalten, die auf die Behandlung von Menschen mit Myasthenie spezialisiert sind.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Bei Unverträglichkeit von oder Kontraindikationen gegenüber Azathioprin kommen die Immuntherapeutika der 2. Wahl (Ciclosporin A, Methotrexat, Mycophenolatmofetil und Tacrolimus) frühzeitiger als oben dargestellt zum Einsatz.

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1. Wiendl H., Meisel A. et al.: Diagnostik und Therapie myasthener Syndrome, S2k-Leitlinie. In: Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie; 2022. Verfügbar unter: www.dgn.org/leitlinien.
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