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REVIEW ARTICLE

Role of autoantibody levels as biomarkers in the management of patients with myasthenia gravis: A systematic review and expert appraisal

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Abstract

Background and purpose: Although myasthenia gravis (MG) is recognized as an immunoglobulin G autoantibody-mediated disease, the relationship between autoantibody levels and disease activity in MG is unclear. We sought to evaluate this landscape through systematically assessing the evidence, testing the impact of predefined variables on any relationship, and augmenting with expert opinion.

Methods: In October 2020, a forum of leading clinicians and researchers in neurology from across Europe (Expert Forum for Rare Autoantibodies in Neurology in Myasthenia Gravis) participated in a series of virtual meetings that took place alongside the conduct of a systematic literature review (SLR).

Results: Forty-two studies were identified meeting inclusion criteria. Of these, 10 reported some correlation between a patient's autoantibody level and disease severity. Generally, decreased autoantibody levels (acetylcholine receptor, muscle-specific kinase, and titin) were positively and significantly correlated with improvements in disease severity (Quantitative Myasthenia Gravis score, Myasthenia Gravis Composite score,

Myasthenia Gravis Activities of Daily Living score, Myasthenia Gravis Foundation of America classification). Given the limited evidence, testing the impact of predefined variables was not feasible.

Conclusions: This first SLR to assess whether a correlation exists between autoantibody levels and disease activity in patients with MG has indicated a potential positive correlation, which could have clinical implications in guiding treatment decisions. However, in light of the limited and variable evidence, we cannot currently recommend routine clinical use of autoantibody level testing in this context. For now, patient's characteristics, clinical disease course, and laboratory data (e.g., autoantibody status, thymus histology) should inform management, alongside patient-reported outcomes. We highlight the need for future studies to reach more definitive conclusions on this relationship.

KEYWORDS
autoantibodies, biomarkers, myasthenia gravis

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction (NMJ), clinically characterized by muscle fatigable weakness [1]. With an incidence of 0.3–2.8 per 100,000, it affects ~700,000 people worldwide per year across ages and sexes [2]. The condition often presents with ocular symptoms (typically, double vision and/or droopy eyelids), and then frequently progresses to involve the facial, bulbar, neck, limb, and the respiratory muscles [1].

MG is mediated by immunoglobulin G (IgG) class autoantibodies directed toward selected molecules of the postsynaptic NMJ, leading to impaired neuromuscular transmission. In most patients (~85%), pathogenic autoantibodies are directed against nicotinic acetylcholine receptors (AChRs), with other autoantibodies targeting muscle-specific kinase (MuSK; ~6% of patients) and low-density lipoprotein receptor-related protein 4 (LRP4; ~2% of patients) [3–7]. Mechanisms involved in AChR autoantibody (AChR-ab; primarily of the IgG1 and IgG3 subclasses) pathogenesis include blocking of the ACh binding site, which impedes ACh-dependent signaling at the NMJ, followed by cross-linking, internalization, and subsequent degradation of AChR [8]; cross-linking and functional and structural depletion of AChR on the cell surface [9]; and activation of complement at the postsynaptic membrane that leads to disruption of AChR clusters, assembly of membrane attack complexes, and destruction of the postsynaptic membrane [10, 11]. MuSK autoantibodies (MuSK-abs; of IgG4 subclass) inhibit the interaction between MuSK and LRP4 and prevent agrin-stimulated MuSK phosphorylation, thus disrupting postsynaptic membrane structure and compromising NMJ transmission [12]. Potential mechanisms for the pathogenesis of LRP4 autoantibodies (primarily IgG1 subclass) include disruption of postsynaptic structure via recruitment of complement proteins or impaired signal transduction through a reduction in MuSK activation [5]. Other examples of autoantibodies of interest include the intracellular proteins ryanodine and titin; however, although their presence may indicate more severe disease [13], a causal relationship in MG is not yet clear.

With autoantibodies implicated in the pathogenesis of MG, there is significant clinical interest as to their clinical application in disease diagnosis and/or treatment. Italian, German, and British guidelines include autoantibody status (e.g., AChR-ab MG, MuSK-ab MG, LRP4-MG, seronegative MG) testing as a well-established tool in the diagnosis and serological classification of patients with MG [14–16]. However, beyond this role in diagnosis, the relationship between autoantibody levels and disease severity or specific clinical outcomes requires clarification, as findings are conflicting, and use in clinical practice is variable. In some studies, at the group level, AChR autoantibodies have shown utility as a marker for disease severity, with significant correlations between titers and Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Foundation of America (MGFA) clinical classification [17], whereas more recent studies suggest that no such correlation exists [18].

The objectives of the review are twofold: (i) to investigate the relationship between autoantibody levels (as reported by the study) and disease activity in patients with MG and (ii) to determine which other factors/variables impact how "AChR-ab and MuSK-ab level/disease activity" correlation data may influence individual patient management.

MATERIALS AND METHODS

Forum constitution

In October 2020, the Expert Forum for Rare Autoantibodies in Neurology in Myasthenia Gravis (EFRAN MG) was convened as a forum of 12 clinicians and researchers experienced in MG from across 12 centers in eight European countries (File S1). Participants were approached on the basis of their respective scientific and clinical expertise, with the group collectively providing a broad and representative understanding of the disease area. Funding for EFRAN MG and this project was provided by argenx.

The EFRAN MG met virtually over three meetings: (i) in October 2020, to agree on the systematic literature review (SLR) protocol (specifically, the objectives and research questions, and the process for conducting the review [including the selection criteria]); (ii) in June 2021, to review the SLR findings, discuss any potential implications for practice, and provide clinical insight; and (iii) in September 2021, to agree on an interpretation of the evidence in the context of current clinical practice and propose areas for future research.

Systematic review

The systematic review was conducted following the general principles published by the UK's National Health Service (NHS) Centre for Reviews and Dissemination [19]. A predefined protocol was developed following consultation with topic and methods experts. The review sought to address the question, "What is the correlation between autoantibody levels and 'disease activity' in people with myasthenia gravis?" (where disease activity is defined by the clinical outcome measure [e.g., QMG score, Besinger score] used to assess disease severity in each study retrieved by the SLR). Using the evidence gathered, secondarily, the review assessed the availability of evidence to determine, "Which other factors/variables should be accounted for when translating 'AChR-ab and MuSK-ab level/disease activity' correlation data to individual patient management?"

Medline and Embase (via OvidSP) were searched for articles published between 1 January 1980 and 1 February 2021 (considered an appropriate time frame to capture relevant evidence). The Medline search strategy is shown in File S2; no language limits were applied. Limited forward and backward citation chasing of included articles was performed, and studies cited within identified reviews were assessed for inclusion. Study selection criteria are summarized in Table 1. All studies were screened in Covidence (covidence.org), with eligibility criteria applied to unique titles/abstracts by two researchers independently. The full texts of articles initially considered as meeting the inclusion criteria were retrieved and the eligibility criteria applied in the same way. Discrepancies at both stages were discussed and resolved by another reviewer.

Data were collected using standardized, bespoke data extraction forms, piloted for use in this review. Data were extracted by one of three reviewers (L.C., J.V.C., M.C.), and checked by another (L.C., J.V.C., M.C.). Data were extracted on the study design, sample characteristics, autoantibody measured, assay type, outcome measures, and results. Subgroups considered during data extraction are shown in Table 1.

Quality assessment was conducted at the individual study level. The Cochrane Risk of Bias tool [20] was used to assess the risk of bias in randomized clinical trials (RCTs), and the Downs and Black tool [21] was used to assess the risk of bias in nonrandomized studies. These judgments were undertaken for each study at the same time as data extraction. Each item in the risk of bias assessment was considered separately, without an attempt to collate an overall score. The risk of bias tool was applied independently by up to two researchers and differences of opinion were resolved by discussion.

A meta-analysis of studies reporting a correlation coefficient between autoantibody and clinical outcome was planned. However, due to heterogeneity between included studies, pooling of data was not appropriate. Descriptive analysis was used to illustrate the characteristics of the included studies and explore the relationship and findings within and between included studies.

TABLE 1 Study selection criteria

	Parameter	Inclusion criteria	
Study selection criteria	Population	People with MG or LEMS	
	Autoantibodies agains	• AChR • MuSK • titin	• LRP4 • RyR • VGCC
	Outcomes	• QMG score • Besinger • MGFA classification • Osserman classification	• MG-ADL • MGC score • MGFA-PIS
	Studies	• RCTs • Longitudinal studies • Cross-sectional studies • Observational cohort studies	• Case series with >10 patients (where ≤10 patients, study included only if conducted in patients with rarer MG subtypes, e.g., LRP4 MG)
	Date limits	1980s onwards	
	Subgroups	• Early vs. late onset • Thymoma vs. nonthymoma • Sex • Pregnancy and neonatal • Juvenile vs. adult	• Ocular vs. generalized • Type of therapy • Disease severity • Remission

Abbreviations: AChR, acetylcholine receptor; LEMS, Lambert–Eaton myasthenic syndrome; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite (score); MGFA, Myasthenia Gravis Foundation of America; MGFA-PIS, MGFA Post-Intervention Status; MuSK, muscle-specific kinase; QMG, Quantitative Myasthenia Gravis (score); RCT, randomized clinical trial; RyR, ryanodine; VGCC, voltage-gated calcium channel.

RESULTS

The electronic searches retrieved a total of 6295 unique titles/abstracts. Screening of titles/abstracts against the inclusion and exclusion criteria resulted in the exclusion of 5579 and the retrieval of the full text of 716 articles. A total of 674 full texts were excluded (a list of studies excluded at full text together with reason is provided in File S3). Of the 42 studies that met the prespecified eligibility criteria, 10 studies reported a correlation coefficient, and 32 studies provided supporting data on autoantibody levels and clinical outcomes at one or more time points without reporting correlation statistics. The study selection process is summarized in Figure 1.

What is the correlation between autoantibody level and "disease activity" in people with MG?

A total of 10 included studies evaluated the correlation between autoantibodies (AChR, MuSK, and titin) and clinical outcomes (QMG score, Myasthenia Gravis Composite [MGC] score, Myasthenia Gravis Activities of Daily Living [MG-ADL] score, MGFA clinical classification), of which six were cross-sectional studies [17, 22–26] and four longitudinal studies [27–30]. No evidence was identified that evaluated LRP4, ryanodine, or voltage-gated calcium channel autoantibodies and Besinger score, Osserman clinical classification, or MGFA Post-Intervention Status scale outcome measures. A summary of evidence identified relative to the systematic review protocol is provided in Table 2. The majority of studies identified describe positive, significant correlations between autoantibody levels and improved clinical outcomes.

AChR autoantibodies

A total of eight studies, which were all assessed as having a moderate risk of bias, reported a correlation coefficient: five cross-sectional studies [17, 22–24, 26] and three longitudinal studies (maximum 24 weeks posttreatment) [27–29]. Study characteristics and baseline characteristics are provided in Tables 3 and 4, respectively. Within these studies, there were 15 comparisons between AChR-abs (including different antibody binding sites) and clinical outcomes (MG-ADL score, QMG score, MGFA clinical classification, MGC score), for which 11 positive, significant; two positive, nonsignificant; and two negative, nonsignificant correlation statistics (unclear/weak to strong) were reported[17,22–24,26–29](Table 5).

Summary baseline characteristics are reported in Table 4. They included a total of 572 patients (range = 28 [29] to 135 [23] patients), with the majority of studies having fewer than 100 [22, 26–29]. Patients were adults, and the majority were female (57%; 216/382 [17, 22–24, 27, 29]; male/female breakdown was not reported in two studies). MG disease subtype (i.e., ocular, generalized) varied across the studies (Table 4). Mean MG duration was reported in three of the eight studies [17, 24, 27], with this ranging from 6.95 (SD = 9.03) years [27] to 13.4 (SD = 13.1) years [17]. Background medication was variable across the studies.

Cross-sectional evidence

Aguirre et al. conducted a cross-sectional study in 60 adults with AChR-ab-positive generalised MG (gMG) [22]. The study reported positive, weak but significant correlations between AChR-ab titers and MGC and MG-ADL scores (Table 5) [22].

Barnett et al. used combined data from 135 patients previously enrolled into two RCTs that compared intravenous immunoglobulin (IVIg) with plasmapheresis, and IVIg with placebo. Patients had MG with worsening weakness that required a change in therapy [23]. A positive, weak, nonsignificant correlation between AChR-ab titers and QMG score was observed (Table 5) [23]. A subgroup analysis of AChR-ab status (AChR-ab-positive vs. AChR-ab-negative) identified a difference in QMG score; AChR-ab-positive patients (69%, 89/129) had a mean (SD) QMG score of 14.2 (4.5) compared with 12.0 (3.7) in AChR-ab-negative patients ($p = 0.008$) [23].

Chang et al. recruited 113 adults with MG; approximately 70% were positive for AChR-ab and, of them, approximately 71% had gMG [24]. The proportions of patients with AChR-ab in each MGFA class were not reported (data reported graphically only), although the majority of the total study population [85.8%] were MGFA classes I–IIIa [24]. AChR-ab titers appeared to parallel disease severity, that is, low AChR-ab titers more often in mild disease (MGFA classes I and II) and high titers more often in moderate to severe disease (MGFA classes III–V); however, the reported correlation was weak (Table 5) [24].

Masuda et al. conducted a retrospective cohort study designed to investigate the clinical relevance of an assay detecting autoantibodies against the major immunogenic region (MIR) of the AChR in MG [17]. The study was conducted in 102 AChR-ab-positive patients before treatment, with 77 patients being positive (defined as a titer > 16.8% of inhibition) for autoantibodies directed against the MIR. A positive, significant correlation between MIR autoantibody titer (%) levels was observed for QMG score (blinded data; $n = 30$), along with a moderate correlation for MGFA classification (at most acute presentation; Table 5) [17]. The study further investigated the correlation between binding autoantibody (i.e., autoantibodies binding any part of the AChR molecule) titers with QMG score, which yielded nonsignificant results. In this respect, however, the data showed a positive, significant correlation with MGFA clinical classification (only *p*-values reported; Table 5) [17].

Vemuri et al. conducted a prospective, observational study including 54 patients with MG (gMG, $n = 41$ [76%]; ocular MG, $n = 13$ [24%]). Of these, 26 patients (48%) were AChR-ab-positive (>0.40 nmol/L). Mean change in autoantibody level was not reported. There was a moderate, positive, and significant correlation between the change in AChR-ab titers and change in QMG score, MGC score, and MGFA classification at 24 weeks (Table 5) [26].

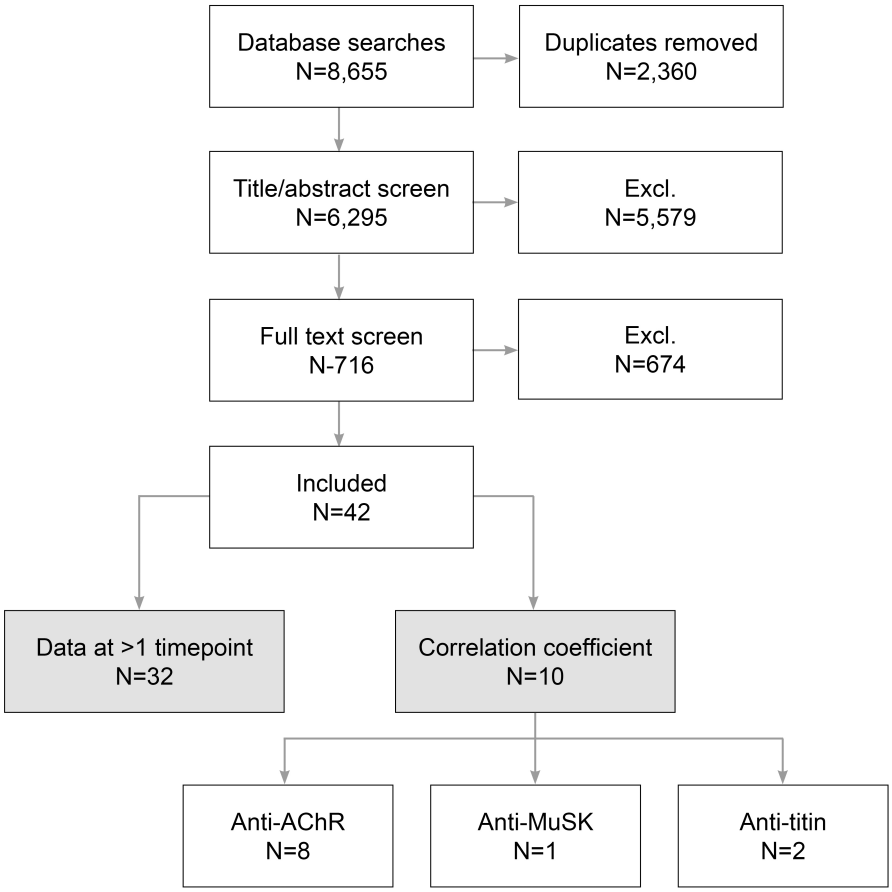

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses): study selection process. AChR, acetylcholine receptor; Excl., excluded; MuSK, muscle-specific kinase. Some included studies reported a correlation coefficient between more than one autoantibody clinical outcome pairing

TABLE 2 Evidence summary by autoantibody, study design, and outcome ($n = 10$)

	AChR-ab, $n = 8$[a]		MuSK-ab, $n = 2$[a]		Titin-ab, $n = 2$[a]		LRP4-ab, $n = 0$		Ryanodine-ab, $n = 0$		VGCC-ab, $n = 0$	
	XS	Long	XS	Long	XS	Long	XS	Long	XS	Long	XS	Long
MG-ADL	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
QMG	✓	✓	✗	✓	✓	✓	✗	✗	✗	✗	✗	✗
MGFA	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗
MGC	✓	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗
Besinger	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Osserman	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
MGFA-PIS	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

Note: ✓ = evidence identified; ✗ = no evidence identified.

Abbreviations: ab, autoantibody; AChR, acetylcholine receptor; Long, longitudinal; LRP4, low-density lipoprotein receptor-related protein 4; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite (score); MGFA, Myasthenia Gravis Foundation of America; MGFA-PIS, MGFA Post-Intervention Status; MuSK, muscle-specific kinase; QMG, Quantitative Myasthenia Gravis (score); VGCC, voltage-gated calcium channel; XS, cross-sectional.

[a]Some studies reported a correlation coefficient for more than one pairing of autoantibody with clinical outcome.

Longitudinal evidence

Hewett et al. conducted a phase 2, randomized, placebo-controlled, multicenter, double-blind study (ClinicalTrials.gov: NCT01480596) of 40 adult patients with gMG (MGFA classes II–IVa; QMG score ≥ 8, of which ≥ 4 points were derived from signs other than ocular). Patients were randomized 1:1 to receive belimumab 10 mg/kg or placebo in addition to standard of care over 36 weeks (24-week treatment period and 12-week follow-up period) [27]. Thirty-eight patients were AChR-ab-positive (belimumab, $n = 18$; placebo, $n = 20$); two (placebo) were MuSK-ab-positive [27]. During the treatment phase (to Week 24), a small decrease in AChR-ab titers occurred in both the belimumab and placebo groups; these returned to baseline levels during follow-up. Additionally, both belimumab and placebo had no statistical

TABLE 3 Evidence summary: Characteristics of studies reporting a correlation coefficient

First author and year, country	Study design	*N*	Ab	Assay	Interventional study	Clinical outcome	Risk of bias
Aguirre 2020, Argentina [22]	XS	60 (69 samples)	AChR	RIA	No	MGC score; MG-ADL score	Moderate
Barnett 2012, Canada [23]	XS	135	AChR	NR	IVIg vs. PLEX and IVIg vs. PBO[a]	QMG score	Moderate
Bartoccioni 2006, Italy [30]	Long	40 (83 samples)	MuSK	RIA	No	QMG score; MGFA clinical classification	Moderate
Chang 2014, Sri Lanka [24]	XS	113	AChR	RIA	No	MGFA clinical classification	Moderate
Chen 2004, China [25]	XS	154	Titin	ELISA	No	MGFA clinical classification	Moderate
Hewett 2018, Canada [27]	Long	40	AChR	NR	BLM vs. PBO	QMG score; MGC score	Moderate
Liu 2010, China [28]	Long	40	AChR Titin	AChR kit	DFPP vs. IA vs. IVIg	QMG score	Moderate
Masuda 2012, Japan [17]	XS	102	AChR	RIA	No	QMG score; MGFA clinical classification	Moderate
Vemuri 2020, India [26]	XS	54	AChR	RIA	No	QMG score; MGC score; MGFA grade	Moderate
Yokota 2015, Japan [29]	Long	28	AChR	NR	TAC	MGFA clinical classification	Moderate

Abbreviations: Ab, autoantibody; AChR, acetylcholine receptor; BLM, belimumab; DFPP, double-filtration plasmapheresis; ELISA, enzyme-linked immunosorbent assay; IA, immunoadsorption; IVIg, intravenous immunoglobulin; Long, longitudinal; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite score; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; NR, not reported; PBO, placebo; PLEX, plasmapheresis; QMG, Quantitative Myasthenia Gravis score; RIA, radioimmunoassay; TAC, tacrolimus; XS, cross-sectional.

[a]Data from patients enrolled in two previous, randomized controlled trials of IVIg versus PBO (double blind) and IVIg compared with PLEX (single blind, evaluator masked) were used.

TABLE 4 Evidence summary: Studies reporting a correlation coefficient, baseline characteristics

First author and year	Country	*N*	Age years, mean (SD)	Male/female, *n* (%)	Duration of MG, years, mean (SD)	Clinical subtype at recruitment, *n* (%)	QMG, mean (SD)	MGFA status, *n* (%)	Drug usage, *n* (%)
Aguirre 2020 [22]	Argentina	60 (69 samples)	Median 39, range = 20–88	15 (25)/45 (75)	Not reported	MGT, 14 (23); MGN, 42 (70); MGH, 4 (7); MG-thymectomy, 14 (23)	Not reported	Not reported	Symptomatic treatment, 14/69 (20); any immunosuppression, 55/69 (79); corticosteroid, 19 (35); azathioprine, 7 (13); corticosteroid + azathioprine, 25 (45); others, 4 (7)
Barnett 2012 [23]	Canada	135	Not reported	Not reported	Not reported	Not reported	13.6 (4.5)	I, 7 (5); II, 73 (54); III, 53 (39); IV, 1 (1); V, 1 (1)	Not reported
Bartoccioni 2006 [30]	Italy	40 (83 samples)	Mean age at onset = 36 years, range = 6–71	8 (20%)/32 (80%)	Not reported	Not reported	Not reported	PR-MM: 13/83 (16); class II, 39/83 (47); class III, 20/83 (24); class IV–V, 11/83 (13)	Under immunosuppression therapy, 53/83 (64%); thymectomy, 26/83 (31%)
Chang 2014 [24]	Sri Lanka	113	48.1 (14.8)	67 (59)/46 (41)	9.0 (9.8)	Ocular, 38 (33.6); generalized, 75 (66.4)	Not reported	I, 43 (38.1); II, 51 (45.1); III, 10 (8.8); IV, 7 (6.2); V 2 (1.8)	AChe inhibitors, 105 (92.9); prednisolone, 47 (41.6); azathioprine, 3 (2.7); prednisolone and azathioprine, 44 (38.9); none, 4 (3.53)
Chen 2004 [25]	China	154	40.2 (18.6)	78 (51)/76 (49)	1.67 (3.75)	MGT0, 45 (29); MGH, 56 (36); MGN, 53 (34)	Not reported	Not reported	Not reported
Hewett 2018 [27]	Canada	40	Belimumab, 52.7 (17.32); placebo, 59.0 (13.88)	Belimumab, 8 (44)/10 (56); placebo, 7 (33)/14(67)	Belimumab, 6.95 (9.03); placebo, 8.30 (8.06)	Not reported	Median score (range): belimumab, 12.0 (8.0–19.5); placebo, 12.50 (6.50, 23.0)	Belimumab: II, 16 (89); III, 2 (11); placebo: II, 15 (72); III, 6 (28)	Belimumab: cholinesterase inhibitor, 14 (78); steroid, 13 (72); immunosuppressant, 8 (44); other MG medication, 0; placebo: cholinesterase inhibitor, 21 (95); steroid, 19 (86); immunosuppressant, 11 (50); other MG medication, 1 (5 [PLEX])
Liu 2010 [28]	China	40	DFPP 55.2 (1.4); IA 57.2 (2.4); IVIg 53.2 (1.7)	DFPP 9 (60)/6 (40); IA 6 (60)/4 (40); IVIg 8 (53)/7 (47)	Not reported	With thymoma DFPP, 6 (40); IA, 4 (40); IVIg, 7 (47)	DFPP, 19.4 (2.2); IA, 16.3 (2.0); IVIg, 16.5 (1.7)	DFPP: II, 8 (53); III, 7 (47); IA: II, 7 (70); III, 3 (30); IVIg: II, 10 (67); III, 5 (33)	Not reported

TABLE 4 (Continued)

First author and year	Country	*N*	Age years, mean (SD)	Male/female, *n* (%)	Duration of MG, years, mean (SD)	Clinical subtype at recruitment, *n* (%)	QMG, mean (SD)	MGFA status, *n* (%)	Drug usage, *n* (%)
Masuda 2012 [17]	Japan	102	58.6 (17.1)	31 (30)/71 (70)	13.4 (13.1)	EOMG, 43 (42); LOMG, 36 (35); thymoma, 23 (23); ocular MG, 23 (23); bulbar symptoms, 45 (44)	Not reported	I, 23 (23); II, 55 (54); III, 11 (11); IV, 4 (4); V, 9 (9)	Prednisolone [mean ± SD dose = 6.4 ± 5.7 mg/day]
Vemuri 2020 [26]	India	54	Range = 8–54	Not reported	Onset of MG at <50 years, n 43 (79.6%)	Ocular, 40 (74.1); bulbar, 7 (13); general crisis, 1 (1.9); limb-girdle, 6 (11.1)	Not reported	Not reported	Intravenous methylprednisolone, 13 (24.1); intravenous immunoglobulin, 7 (13); oral steroids, 45 (83.3); azathioprine, 28 (51.9); MMF, 2 (3.7); thymectomy, 5 (9.25)
Yokota 2015 [29]	Japan	28	51.8 (15.1)	15 (54)/13 (46)	Not reported	Not reported	Not reported	Not reported	Steroid therapy during the observation period, 3 (11) [mean dose = 10.4 ± 4.9 mg/2 days]; steroid pulse therapy during the observation period, 3 (11)

Abbreviations: ACHe, acetylcholinesterase; DFPP, double-filtration plasmapheresis; EOMG, early onset myasthenia graivis; IA, immunoadsorption; IVIg, intravenous immunoglobulin; LOMG, late onset myasthenia gravis; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MGH, MG with thymus hyperplasia; MGN, MG with normal thymus; MGT, MG with thymoma; MMF, mycophenolate mofetil; PLEX, plasmapheresis; PR-MM, pharmacological remission or minimal manifestations; QMG, Quantitative Myasthenia Gravis score.

TABLE 5 Evidence summary: Studies reporting a correlation coefficient, Ab level, and clinical outcome results

First author and year, country	Interventions evaluated, study duration, *N*	Ab	Clinical outcome	*R* (*p*)	Summary
Cross-sectional					
Aguirre 2020, Argentina [22]	NA NA *N* = 60	AChR	MGC score	0.289 ($p = 0.001$)[a]	Weak significant correlation
Aguirre 2020, Argentina [22]	NA NA *N* = 60	AChR	MG-ADL	0.285 ($p = 0.001$)[a]	Weak significant correlation
Barnett 2012, Canada [23]	IVIg vs. PLEX & IVIg vs. PBO[b] NA *N* = 135	AChR	QMG score	0.11 ($p = 0.27$) (overall)[b,c]	Weak nonsignificant correlation
Chang 2014, Sri Lanka [24]	NA NA *N* = 113	AChR	MGFA clinical classification	0.34 ($p = 0.0002$)	Weak significant correlation
Masuda 2012, Japan [17]	NA NA *N* = 30[d]	AChR	QMG score	0.54 ($p = 0.001$)[e]	Moderate significant correlation (MIR Ab titer levels)
Masuda 2012, Japan [17]	NA NA *N* = 102	AChR	MGFA clinical classification	0.57 ($p < 0.0001$)[c]	Moderate significant correlation (MIR Ab titer levels)
Masuda 2012, Japan [17]	NA NA *N* = 30[d]	AChR	QMG score	NR ($p = 0.07$)[e]	Unclear nonsignificant correlation (binding Ab titer levels)
Masuda 2012, Japan [17]	NA NA *N* = 102	AChR	MGFA clinical classification	NR ($p < 0.0001$)[c]	Unclear significant correlation (binding Ab titer levels)
Chen 2004, China [25]	Cross-sectional NA NA *N* = 53 MGN	Titin	MGFA classification score	0.034 ($p = 0.420$)[c]	Weak nonsignificant correlation
Chen 2004, China [25]	Cross-sectional NA NA *N* = 56 MGH	Titin	MGFA classification score	0.351 ($p = 0.008$)[c]	Weak significant correlation
Chen 2004, China [25]	Cross-sectional NA NA *N* = 45 MGT	Titin	MGFA classification score	0.623 ($p = 0.003$)[c]	Positive moderate significant correlation
Chen 2004, China [25]	*N* = 19 EPT	Titin	MGFA classification score	0.582 ($p = 0.009$)[c]	Positive moderate significant correlation

TABLE 5 (Continued)

First author and year, country	Interventions evaluated, study duration, *N*	Ab	Clinical outcome	*R* (*p*)	Summary
Chen 2004, China [25]	*N* = 9 LPT	Titin	MGFA classification score	0.412 ($p = 0.271$)[c]	Positive moderate nonsignificant correlation
Chen 2004, China [25]	*N* = 4 S-cT	Titin	MGFA classification score	−0.775 ($p = 0.225$)[c]	Negative weak nonsignificant correlation
Chen 2004, China [25]	*N* = 13 MT	Titin	MGFA classification score	0.742 ($p = 0.004$)[c]	Positive strong significant correlation
Longitudinal					
Hewett 2018, Canada [27]	Longitudinal BLM vs. PBO 24 weeks *N* = 38	AChR (change from BL)	QMG (change from BL)	−0.025 (p = NR) (overall)[e]	Negative weak correlation
Hewett 2018, Canada [27]	Longitudinal BLM vs. PBO 24 weeks *N* = 38	AChR (change from BL)	MGC (change from BL)	−0.090 (p = NR) (overall)[e]	Negative weak correlation
Liu 2010, China [28]	Longitudinal DFPP vs. IA vs. IVIg 14 weeks *N* = 40	AChR (change from BL)	QMG (change from BL)	0.2821 ($p = 0.08$) (overall)[e]	Positive weak nonsignificant correlation
Vemuri 2020, India [26]	Longitudinal NA 12 & 24 weeks[f] *N* = 54	AChR (change from BL)	QMG (change from BL)	0.57 ($p = 0.01$)[c]	Positive moderate significant correlation
Vemuri 2020, India [26]	Longitudinal NA 12 & 24 weeks[f] *N* = 54	AChR (change from BL)	MGC (change from BL)	0.57 ($p = 0.01$)[c]	Positive moderate significant correlation
Vemuri 2020, India [26]	Longitudinal NA 12 & 24 weeks[f] *N* = 54	AChR (change from BL)	MGFA grade (change from BL)	0.43 ($p = 0.01$)[c]	Positive moderate significant correlation
Yokota 2015, Japan [29]	Longitudinal TAC Uncleari[i] *N* = 26[g]	AChR (change from BL)	MGFA clinical classification score (change from BL)	0.524 ($p = 0.009$)[c]	Positive moderate significant correlation
Bartoccioni 2006, Italy [30]	NA NR *N* = 40[h]	MuSK	QMG MGFA classification score	0.43 ($p < 0.0001$)[e]	Moderate significant correlation

(Continues)

TABLE 5 (Continued)

First author and year, country	Interventions evaluated, study duration, N	Ab	Clinical outcome	R (p)	Summary
Liu 2010, China [28]	Longitudinal DFPP vs. IA vs. IVIg 14 weeks N = 40	Titin (change from BL)	QMG (change from BL)	0.6107 ($p < 0.01$)[e]	Positive weak nonsignificant correlation

Abbreviations: Ab, autoantibody; AChR, acetylcholine receptor; BL, baseline; BLM, belimumab; DFPP, double-filtration plasmapheresis; EPT, epithelial predominant thymoma; IA, immunoadsorption; IVIg, intravenous immunoglobulin; LPT, lymphocytic predominant thymoma; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite (score); MGFA, Myasthenia Gravis Foundation of America; MGH, MG with thymus hyperplasia; MGN, MG with normal thymus; MIR, major immunogenic region; MT, mixed thymoma; MuSK, muscle-specific kinase; NA, not applicable; NR, not reported; PBO, placebo; PLEX, plasmapheresis; QMG, Quantitative Myasthenia Gravis (score); S-CT, spindle-call thymoma; TAC, tacrolimus.

[a]Tau.

[b]Data were used from patients enrolled in two previous, randomized, controlled trials studying IVIg versus PBO (double blind) and IVIg compared with PLEX (single blind, evaluator masked).

[c]Spearman rank correlation coefficient.

[d]Number of patients having the data of QMG score is 30 from a single study site.

[e]Pearson correlation coefficient.

[f]Study follow-up at 12 and 24 weeks, assumed that correlation assessed at 6 months.

[g]26 of 28 patients with AChR autoantibodies.

[h]40 patients with 83 serum samples.

[i]Time point unclear, start of tacrolimus administration to longest available follow-up.

impact on QMG scores. No correlations between change from baseline in AChR-ab levels and QMG or MGC scores were observed in the overall study population (Table 5).

Liu et al. conducted an RCT in which 40 patients with late onset (>50 years) MG were randomized to receive double-filtration plasmapheresis (DFPP; $n = 15$), immunoadsorption (IA; $n = 10$), or IVIg ($n = 15$) over 14 weeks [28]. AChR-ab levels decreased significantly in all groups ($p < 0.05$) after treatment. The QMG score improved in all three groups after treatment, along with symptoms. A weak, longitudinal nonsignificant correlation was observed between the change in AChR-ab level and the decrease of the QMG score (Table 5) [28].

Yokota et al. conducted a retrospective analysis in 28 patients who were treated with tacrolimus (3 mg/day usual starting dose) [29]. In the 26 AChR-ab-positive patients, the AChR-ab level decreased in 19 (73%) patients, with a reduction from a mean (±SD) of 153.4 (±278.2) nmol/L to 83.2 (±148.7) nmol/L ($p = 0.013$) [29]. The MGFA clinical classification score improved in 22 patients (22/28, 79%). There was a significant positive correlation between the change in the AChR-ab titers and the change in MGFA clinical classification (Table 5) [29].

MuSK autoantibodies

A total of one study, which was recorded as having a moderate risk of bias, reported a correlation coefficient. The study patients were adults, with 20% of patients being male (8/32) [30]. Clinical subtype of MG and duration of MG were not reported [30]. A total of 64% of patients were receiving immunosuppressive therapy, and 31% had undergone thymectomy [30]. Summary baseline characteristics are reported in Table 4.

Cross-sectional evidence

No cross-sectional evidence was identified.

Longitudinal evidence

Bartoccioni et al. [30] conducted a prospective study in 40 patients with AChR-ab-negative gMG who were scored positively on a non-quantitative immunoblot MuSK assay and retested for MuSK-ab by radioimmunoprecipitation. Data were not reported in the text for either mean antibody level or mean clinical outcome score (QMG score and MGFA clinical classification) [30]. In 14 patients, a significant, positive correlation between MuSK-ab levels and disease severity (QMG score and MGFA clinical classification) as measured before and after treatment was identified (Table 5).

Titin autoantibodies

A total of two studies reported a correlation coefficient between titin autoantibody level and clinical outcome: one cross-sectional study [25] and one longitudinal study (maximum 14 weeks posttreatment) [28], with both studies reporting positive correlations.

The studies included a total of 194 patients (40 [28] and 154 [25] patients). Study patients were adults, and 52% of patients were male (101/194) [25, 28]. MG disease subtype varied across the studies. The mean (±SD) duration of MG was reported in one (1.67 [±3.75] years) of the two studies [25]. Background medication varied between the studies. Summary baseline characteristics are reported in Table 4.

Cross-sectional evidence

Chen et al. conducted a retrospective analysis that included 154 patients with MG, grouped as MG with thymoma (MGT; $n = 45$), MG with thymus hyperplasia (MGH; $n = 56$), and MG with normal thymus ($n = 53$) [25]. Titin autoantibodies positively correlated with severity of MGH or MGT. For MGT, titin autoantibodies correlated closely with severity of disease in MG patients with epithelial predominant thymoma and mixed thymoma, as compared with MG patients with lymphocytic predominant thymoma and spindle-cell thymoma (Table 5) [25].

Longitudinal evidence

Liu et al. randomized 40 patients with late onset MG to receive DFPP ($n = 15$), IA ($n = 10$), and IVIg ($n = 15$) over 14 weeks [28]. Titin antibody levels decreased significantly in all study groups ($p < 0.05$) after treatment. The QMG score decreased in all three groups after treatment, along with symptom improvement. A strong longitudinal correlation was observed between titin antibody level and the decrease of the QMG score (Table 5) [28].

Descriptive studies not reporting a correlation coefficient

A total of 32 studies were included that reported an autoantibody level (either as mean/median or difference from baseline) and a clinical outcome (either as mean/median or difference from baseline) at more than one time point. Summary characteristics and results for included studies are provided in File S4. The majority of these studies assessed AChR-ab level and clinical outcome measures (QMG score, MGC score, MGFA clinical classification, Osserman classification [or modified Osserman classification]). One study assessed titin autoantibody levels and a modified Osserman classification. All studies noted a decrease in autoantibodies levels over time and a decrease (improvement) in clinical outcome (classification or score), although analysis of any statistical correlation was not performed.

Which other factors/variables should be accounted for when translating "AChR-ab and MuSK-ab level/disease activity" correlation data to individual patient management?

None of the identified evidence included data on adjusted or subgroup analyses to account for the impact of certain putative confounders (e.g., early vs. late onset, thymoma vs. nonthymoma, sex, clinical subtype, type of therapy, disease severity, assay type, remission status) on the correlation data. As such, this precluded our assessment of the impact of prespecified subgroups on the reported correlation coefficients (Table 6).

DISCUSSION

MG is an autoimmune disease mediated by autoantibodies of the IgG class that affect the postsynaptic membrane of the NMJ. Detection of these autoantibodies in patient serum is one of the main diagnostic tools for MG due to its high specificity and wide availability. However, beyond diagnosis, the use of autoantibody testing in clinical practice is variable, primarily driven by a lack of evidence demonstrating robust correlations with disease severity to support use in guiding patient management. As such, the utility of autoantibodies to those treating MG is currently limited to measuring autoantibody status (positive or negative) to help guide a particular therapeutic approach (e.g., MuSK-ab-positive MG may respond to rituximab; AChR-ab-positive patients may be offered thymectomy). Although autoantibody levels as a disease biomarker have been investigated in several studies (see Table 5 and File S4), a definitive correlation between the two has not been conclusively established in a large, confirmatory prospective study. Given this data gap, clinical guidelines do not provide recommendations around the use of autoantibodies to guide patient management.

In this review, we initially sought to identify studies that evaluated any correlation between autoantibody levels and disease severity (see Table 1). The majority of the studies reported a positive, significant relationship between decreased autoantibody levels and improved disease severity (see Table 5), despite limitations (discussed below). Based on this evidence, which is consistent with our clinical experience, we believe that potential exists for autoantibody levels to be used as a tool to help predict disease activity and clinical outcomes at an individual patient level or within disease subtypes. When considering this, it is acknowledged that there is an absence of predictive analyses within the dataset. These foundations lead us to agree that further evidence is required before clinical guidance on the use of autoantibody levels in patient management may be developed, which, for now, will remain an unmet need for both patients and clinicians.

Future studies should be designed to more formally assess the relationship between autoantibody levels and disease severity. We, therefore, recommend that longitudinal studies with larger datasets and subgroup analyses, which also investigate combinations of existing and potential biomarkers, be conducted to provide the high-quality evidence base from which such guidelines can be derived (see Box 1), thereby providing clarity to clinicians treating patients with MG, potentially improving outcomes.

In tandem, and from a practical perspective, enhancing the understanding of, and reducing variability in, autoantibody-level testing in MG between laboratories should be a priority for researchers

TABLE 6 Subgroup data available: Summary overview by study and stratification factor

Study	Assay type	Criteria	Age (e.g., adults vs. children)	Male vs. female	Background medication	Early onset vs. late onset (adults)	Generalized vs. ocular	Thymoma vs. no thymoma	Refractory vs. nonrefractory	Remission vs. no remission	Pregnant vs. not pregnant
AChR autoantibody											
Aguirre 2020 [22], noninterventional	RIA	BL characteristics	✓	✓	✓	✓	✗	✓	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Barnett 2012 [23], noninterventional	NR	BL characteristics	✓	✓	✓	✗	✗	✗	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Chang 2014 [24], noninterventional	RIA; CBA	BL characteristics	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Hewett 2018 [27], interventional (BEL vs. PBO)	NR	BL characteristics	✓	✓	✓	✗	✗	✓[a]	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Liu 2010 [28], interventional (DFPP vs. IVIg vs. IA)	AChR-ab kit	BL characteristics	✓	✓	✓	✓	✗	✓	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Masuda 2012 [17], noninterventional	RIA	BL characteristics	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Yokota 2015 [29], noninterventional	NR	BL characteristics	✓	✓	✓	✗	✗	✗	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
Vemuri 2020 [26], noninterventional	RIA	BL characteristics	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗
MuSK autoantibody											
Bartoccioni 2006 [30], noninterventional	RIA	BL characteristics	✓	✓	✓	✗	✗	✗	✗	✗	✗
		Correlation reported for subgroup	✗	✗	✗	✗	✗	✗	✗	✗	✗

Note: ✓ = yes; ✗ = no.

Abbreviations: ab, autoantibody; AChR, acetylcholine receptor; BEL, belimumab; BL, baseline; CBA, cell-based assay; DFPP, double-filtration plasmapheresis; IA, immunoadsorption; IVIg, intravenous immunoglobulin; MuSK, muscle-specific kinase; NR, not reported; PBO, placebo; RIA, radioimmunoassay.

[a]Information reported (e.g., age mean/median, proportion male/female) for full study population but no subgroup information reported in this respect.

BOX 1 Recommendation for the conduct of a large, prospective study designed to define the relationship between autoantibody levels and disease activity

Although current practice should center around clinical observations as the primary method for assessing disease activity, biomarkers—namely autoantibody levels—in MG could provide additional information not currently available. For example, if a patient has inactive clinical disease (minimal symptoms or in remission) on treatment, there are potentially two scenarios:

(i) MG is controlled by treatment; therefore, on weaning off therapy, the disease will become active and exacerbate.

(ii) MG is clinically and biologically inactive, and will remain in remission following weaning off treatment.

In this respect, key questions to be answered would be: Could the autoantibody level (e.g., change from baseline) while the patient is asymptomatic indicate or help to predict disease activity underlying an apparent remission and, therefore, assist in patient management (e.g., reducing immunosuppressive treatment)? Could autoantibody level be measured longitudinally while reducing medication, and thereafter, indicate or predict imminent disease exacerbation versus continued remission?

A potential hypothesis for this study would be that autoantibody levels, among other factors, may be a predictive marker for disease activity. These other factors may be, for example, concomitant diseases or alternative biomarkers (e.g., factor X, complement factor). The study should utilize:

- A multicenter approach;
- A well-defined cohort of patients (e.g., early ocular MG after diagnosis and before "causal" [e.g., thymectomy, immunosuppression] treatment);
- Adjustment for known confounders (e.g. thymoma, age, gender);
- Predictive power to validate clinical models (e.g., disease severity);
- Predefined sample size and endpoints;
- Defined threshold levels (e.g., continuous vs. dichotomous);
- Minimization of inter- and intrapatient random variation;
- Minimization of kit measurement performance variations (e.g., by central laboratory comparing measurements once all samples are stored vs. closed to sampling; decentralized testing in regional laboratories); and
- Validation in a separate cohort.

(see Box 2). By conducting this research, recommendations and standardized testing protocols that optimize the use of autoantibody levels for MG monitoring may help to advance patient outcomes. Our group provides an opportunity to develop such standards, bringing together clinicians and researchers with access to autoantibody testing laboratories for patients from across Europe.

In today's practice, given the paucity of robust, high-quality data to support the development of guidelines on autoantibody levels as biomarkers in MG, we agree that clinical observations of disease severity, above other assessments, should remain central to guiding patient management. These observations should include baseline and regular assessments of patient characteristics (e.g., comorbidities), clinical scores (e.g., MG-ADL, QMG), laboratory assessments (e.g., autoantibody status and thymus histology), and changes in treatments, along with a history of adverse events experienced.

The evolution of biomarkers, specifically autoantibodies, in MG to a point where they not only have robust prognostic value, but also allow for a correlation between fluctuations and the impact of interventions is the "holy grail" in the field. Given that depletion of autoantibodies through, for instance, plasmapheresis is often associated with an improvement in the severity of MG symptoms [31, 32], could autoantibodies fill this gap? We believe that, as this landscape evolves and more data become available, autoantibody level biomarkers, among others (e.g., cytokines, mRNA), may complement the existing armamentarium of clinical parameters in supporting the tailoring of care to the individuals' characteristics and needs.

We acknowledge that several treatments, such as plasma exchange, immunoadsorption, and now also anti-FcRn, reduce autoantibody levels and appear to lead to an improvement in clinical scores. However, such a relationship has not yet been confirmed in a large cohort of patients with MG on long-term treatment (or off treatment). However, at the individual level, there appears to be a tendency toward a parallel between a reduction in autoantibody levels and clinical outcome as a result of therapy.

To our knowledge, this is the first synthesis of existing evidence designed to test the relationship between autoantibody levels and clinical outcomes in MG. The review, which followed best practice guidelines, is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Extensive electronic searches were paired with forward and backward citation searching of included articles that reported a correlation coefficient. We are, therefore, confident that this review includes most if not all the available data within the confines of the methodology. Furthermore, the review's selection criteria (see Table 1) were sufficiently broad to cover the vast majority of patients with MG over an extended time period, along with outcomes that are relevant to current clinical practice. On this basis, however, we acknowledge that several articles of note including, for example, Drachman et al. [33] and Limburg et al. [34], were excluded. Nonetheless, the extent to which these data

BOX 2 Recommendation for the conduct of a study to reduce variability, investigate sensitivity/specificity, and define cutoffs (vs. baseline) to realize real-world use of autoantibody level testing

With different antibody testing methods being used nationally and internationally, this study would seek to more clearly define and standardize the monitoring of autoantibody levels across laboratories. Although we may want to reduce variability in autoantibody level testing, in practice, this may be difficult to achieve due to interindividual differences in levels between patients with MG, in which case, normalizations versus baseline are necessary. Therefore, such a study could focus on how high the levels are versus cutoff when tested at baseline, with variations always compared to the baseline. Furthermore, drawing comparisons between the tests used by different laboratories (all testing the same blinded samples) will be useful to assess sensitivity and specificity.

The study should investigate:

- Issues surrounding the variation;
- Minimization of inter- and intrapatient random variation; and
- Minimization of kit measurement performance variations (e.g., by central laboratory comparing all samples versus closed to sampling, decentralized testing in regional laboratories).

The study should utilize:

- A multicenter approach;
- A well-defined cohort of patients;
- Adjustment for known cofounders (if any) for interference with test assays; and
- A predefined sample size.

remain relevant to today's practice after 4 decades of evolution in the field is uncertain. The body of literature identified spans an extended time period (2006–2020) during which research and reporting methods have improved considerably. Lastly, there have been several studies published since our data were collected, including the study by Marcuse et al., which describes an inverse correlation between change in AChR-ab levels and the odds of an improvement in scoring by MGFA classification [35]. However, again, this study was conducted in a relatively small patient population ($N = 90$), and the authors conclude that further research is required before recommendations can be made, supporting our findings to date [35].

Conversely, the lack of a consistent clinical outcome measure(s) used uniformly by clinicians to assess severity of MG has hindered interpretation of the data. Most identified studies were of small sample size and cross-sectional in design, with limited data available from longitudinal studies (the majority of which did not report statistical significance). These studies often assessed the correlation as exploratory objectives, with limited scope to test the impact of influential factors (e.g., background treatments, type of MG, comorbidities, age, assay type). Furthermore, data reporting was inconsistent between studies (e.g., a correlation coefficient with or without a *p*-value or *p*-value with no correlation coefficient). The data heterogeneity (e.g., variability in study population [type of MG], assay type, outcome measures) abrogated the pooling of data through methods such as a meta-analysis (the methods by Hedges–Olkin method and Hunter–Schmidt were considered). Specifically, with reference to the radioimmunoassay, it should be acknowledged the assay could distort any comparison we might make, especially with respect to the use of differing cutoff values and further serial dilution when titers are high. Ultimately, standardized, internationally accepted measurement methods would be needed, as we allude to in Box 2. We had hoped to explore the impact of specific attributes or characteristics (e.g., MG type, age); however, the absence of any reference throughout the dataset to these potentially confounding variables, along with relatively small number of robust studies, meant this was not possible.

Additionally, and importantly, the individual studies retrieved by this review are not without their own limitations. For example, in the phase 2 study by Hewett et al. [27], the interventional (belimumab 10 mg/kg) and comparator (placebo) arms both induced only small reductions of AChR-ab levels, which were accompanied by nonsignificant changes in disease severity (QMG or MGC scores) between arms. Given this, overall, there was no potential for a relationship to be identified, thus compromising the correlation calculation.

The results of this review provide an overarching framework for the conduct of future research to definitively understand the relationship between autoantibody levels and disease severity in MG. Given the tentative evidence of a positive correlation between decreases in both measures, this research should build on the work to date and address the identified limitations, allowing a more definitive conclusion to be drawn. This could lead to the development of guidelines covering the use of autoantibody levels in the clinical management (i.e., both prognostic and treatment-related decision-making) of patients with MG. Until such time, however, clinical observations of disease severity should remain paramount to guiding MG management.

AUTHOR CONTRIBUTIONS

Maria-Isabel Leite and Andreas Meisel provided clinical insight and direction throughout the project and cochaired the three EFRAN-MG meetings. All authors contributed to the design of the study. Louise Crathorne designed the search strategy. Louise Crathorne in conjunction with three additional researchers screened and data-extracted the literature. Louise Crathorne and Kris Holmes carried out the data syntheses. Louise Crathorne and Kris Holmes drafted the manuscript, and all authors commented on subsequent drafts, contributed to the discussion and clinical implications, and approved the final version.

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CONFLICT OF INTEREST

A.M. has received speaker honoraria from Alexion Pharmaceuticals, argenx, Grifols, and Hormosan Pharma; honoraria from Alexion Pharmaceuticals, argenx, Janssen, and UCB for consulting services; and financial research support from Octapharma and Alexion Pharmaceuticals. He is chairman of the medical advisory board of the German Myasthenia Gravis Society. M.-I.L. is funded by the NHS England (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from the UK association for patients with myasthenia (the Myaware) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen Idec, Novartis, UCB, and the Guthy-Jackson Charitable Foundation. M.-I.L. serves on scientific or educational advisory boards for UCB, argenx, and Viela/Horizon. M.S. has received speaker honoraria from Alexion Pharmaceuticals, argenx, Bayer, Biogen, CSL Behring, Genzyme, Grifols, Merck, Miltenyi Biotec, Novartis, Roche, Teva, and Hormosan Pharma. He is vice chairman of the medical advisory board of the German Myasthenia Gravis Society. A.B. has participated on advisory boards and/or in educational programs for argenx, Sanofi Genzyme, UCB, and Ultragenyx pharmaceutical. He has received financial support to participate in meetings from the Association Institut de Myologie (AIM), Sanofi Genzyme, and Ultragenyx Pharmaceutical. R.M. has received funding for travel, meeting attendance, or advisory Board participation from Alexion, argenx, BioMarin, Catalyst, Sanofi, Regeneron, and UCB. A.E. is a scientific award jury member for Grifols and a safety data monitor for UCB, and has received speaker honoraria from Alexion Pharmaceuticals and consultancy fees from argenx, through EFRAN MG. R.J.M. has received speaker honoraria from Sanofi, Pfizer, Sobi, Alnylam, and Biogen. J.V. receives grant support from Health Holland/TKI for the Target to B consortium and from the Prinses Beatrix Spierfonds (W.OR 20–05). He has been involved in consultancies for argenx and NMD Pharma, and in trials for argenx and Alexion. He is coinventor on patent applications based on MuSK-related research. The Leiden University Medical Center has received royalties from TECAN/IBL, along with support from argenx for research in MG. J.V. is also a member of the European Reference Network for Rare Neuromuscular Diseases. F.B. has received honoraria from argenx. A.K.-P. has received speaker honoraria or travel grants from argenx, Kedrion, Takeda, and CSL Behring, and honoraria from argenx for consulting services. A.R.P. serves as a scientific consultant for argenx. K.H. and L.C. are employees of Prescript Communications. S.S. has no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study. Data were extracted from identified publications.

ETHICS STATEMENT

Given that this report did not involve human participants, ethics approval was not applicable.

DATA AVAILABILITY STATEMENT

All information presented within was sourced from published articles.

DISCLAIMERS

The views expressed in this article are those of the authors and not necessarily those of their associated institutions, nor of argenx.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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