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Efficacy and safety of rituximab in anti-MuSK myasthenia Gravis: a systematic review and meta-analysis

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This systematic review and meta-analysis evaluated the effectiveness and safety of rituximab in patients with myasthenia gravis harboring antibodies to muscle-specific kinase (anti-MuSK). Four databases were searched from inception to December 23, 2023. We included adult patients (aged ≥ 18 years) who were diagnosed with anti-MuSK myasthenia gravis and who received rituximab. The outcomes assessed were the proportions of patients who achieved minimal manifestations or better and those who achieved complete stable remission or pharmacologic remission, according to the Myasthenia Gravis Foundation of America Postintervention Status (MGFA-PIS) scale at the last follow-up. Additional outcomes were mean glucocorticoid dose reduction and severe adverse events. Twelve studies with 111 participants were included. Overall, 82% (95% CI, 71–91%; $I^2 = 30.12\%$, $P = 0.15$) of patients achieved MGFA-PIS minimal manifestations or better, and 56% (95% CI, 45–67%; $I^2 = 0.00\%$, $P = 0.60$) achieved MGFA-PIS complete stable remission or pharmacologic remission. The mean reduction in the glucocorticoid dose was 17.15 mg (95% CI, 11.77–22.53; $I^2 = 32.40\%$, $P = 0.19$). Only one patient developed osteomyelitis during rituximab treatment. This study demonstrated that rituximab is a safe and effective treatment for anti-MuSK myasthenia gravis, helping patients achieve minimal manifestations, complete stable remission, or pharmacologic remission with minimal serious adverse events.

Keywords Anti-MuSK, Myasthenia gravis, Rituximab

Myasthenia gravis (MG) is an autoimmune disorder first documented in the 17th century by Thomas Willis (Oxford, 1621–1675)[1]. The main pathology involves antibodies disrupting acetylcholine receptor clustering at the neuromuscular junction[2], leading to decreased efficiency of neurotransmission. Consequently, the primary symptoms are muscle weakness and fatigability, without affecting sensory function, bowel or bladder function, cognition, or reflexes[3,4]. There are several subtypes of MG, the most common of which involve anti-acetylcholine receptor antibodies. Other subtypes include antibodies to muscle-specific kinase (anti-MuSK), which are found in approximately 7–10% of all MG patients. In anti-MuSK MG, about 40% of patients present with bulbar weakness. Limb weakness is less common initially but can develop as the disease progresses[2].

Medical treatments for MG include acetylcholinesterase inhibitors and immunomodulating agents such as corticosteroids, azathioprine, tacrolimus, mycophenolate mofetil, cyclosporine, methotrexate, and cyclophosphamide. However, in anti-MuSK MG, conventional treatments are often less effective. Numerous studies have explored the application of monoclonal antibodies, including rituximab, in the management of MG patients, particularly those who have not responded adequately to conventional therapies[5,6]. While observational studies have suggested that rituximab is effective in MG patients with autoantibodies against the acetylcholine receptor, demonstrating significant clinical improvements and reduced immunosuppressant dependency[7], a randomized controlled trial has also confirmed its efficacy in generalized MG, further supporting its role as a viable therapeutic option[8].

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Despite emerging evidence, comprehensive data regarding rituximab dosage, efficacy, and safety in anti-MuSK MG patients are still lacking. Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety of rituximab in anti-MuSK MG patients.

Methods

Protocol registration

The study protocol was registered with PROSPERO (registration number: CRD42024495993).

Search strategy

Two independent reviewers (S.C. and P.B.) systematically searched four electronic databases (Scopus, Embase, PubMed, and the Cochrane Library), covering the period from inception until December 23, 2023. The search terms included keywords such as "anti-MuSK," "myasthenia gravis," and "rituximab." A detailed list of all the search terms employed is provided in the **Supplementary Material**. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[9].

Inclusion and exclusion criteria

We included published, full-text articles that evaluated the clinical response to rituximab treatment in adult participants (aged ≥ 18 years) diagnosed with anti-MuSK MG. The studies needed to report at least one of the following: baseline Myasthenia Gravis Foundation of America (MGFA) clinical classification, Myasthenia Gravis Foundation of America postintervention status (MGFA-PIS)[10], steroid dose reduction, and adverse events. Eligible studies were randomized controlled trials, observational studies, case-control studies, and case series with a minimum of five participants.

Studies were excluded if they were deemed irrelevant; were news, articles, letters, books, documentation, meta-analysis, reviews, or non–peer-reviewed publications; were published in languages other than English; or did not provide comprehensive reports on rituximab treatment outcomes.

Study selection

The identified references were imported into Covidence software for duplicate removal and initial screening. Two reviewers (S.C. and P.B.) independently screened titles and abstracts, with their decisions blinded to each other until both had completed their assessments. Discrepancies were resolved through consensus with two additional researchers (V.V. and J.J.). S.C. and P.B. then independently reviewed the full-text articles, with disagreements resolved through discussion involving V.V. and J.J.

Data extraction

Two reviewers (S.C. and P.B.) systematically extracted the data via a standardized form. The extracted information comprised the following:

- **Study design and characteristics**: Study type, total number of participants, sex distribution, age at disease onset, age at initiation of rituximab treatment, history of thymoma, and thymectomy status.
- **Treatment details**: Number of participants receiving rituximab, dosage administered, concurrent immunosuppressive therapies, and steroid dosage.
- **Treatment outcomes**: MGFA-PIS at 3, 6, and 12 months and at the last follow-up visit; average reduction in steroid dosage; and adverse events observed during rituximab treatment.

Additional information was requested from study authors when the data required clarification or were insufficient for analysis.

Quality assessment

The quality of the included cohort studies was assessed via the modified Newcastle–Ottawa Quality Assessment Scale[11], focusing on participant selection and outcome ascertainment. The comparability domain was not applicable because of the single-arm nature of the studies. Investigators V.V. or J.J. resolved discrepancies in quality assessments. A funnel plot was used to evaluate the potential for publication bias among the included studies.

Outcomes

The primary outcomes were the proportions of anti-MuSK MG patients who achieved minimal manifestations (MM) or better and those who achieved complete stable remission (CSR) or pharmacologic remission (PR), according to the MGFA-PIS at the last follow-up. The secondary outcomes were the mean reduction in glucocorticoid dosage at the last visit and the occurrence of serious adverse events. A subgroup analysis was conducted to evaluate the proportion of patients who achieved MGFA-PIS MM or better, classified by pretreatment severity on the basis of the MGFA clinical classification[10]: mild to moderate (MGFA class asymptomatic–III) and severe (MGFA classes IV and V).

Statistical analysis

All the statistical analyses were performed with Stata MP, release 18 (StataCorp LLC, College Station, TX, USA). Random-effects meta-analyses using the DerSimonian–Laird method were performed to determine the pooled prevalence of MGFA-PIS outcomes (CSR, PR, and MM), along with their 95% confidence intervals (CIs), on the basis of effect sizes from single-arm studies. The mean difference in the glucocorticoid doses before rituximab treatment and at the last follow-up was calculated. Subgroup analyses of the pooled prevalence of MGFA-PIS

MM or better were performed based on MGFA clinical classification severity. Heterogeneity was assessed via the I^2 statistic and Cochrane's Q test, with I^2 values categorized as insignificant (less than 25%), low (26–50%), moderate (51–75%), or high (greater than 75%). Publication bias was evaluated using funnel plots to assess outcome symmetry. A P value of <0.05 was considered statistically significant.

Results

Study selection

The search strategy yielded 1150 publications. The Covidence software removed 398 duplicates, leaving 752 studies for title and abstract screening. After this screening, 38 studies were assessed for eligibility through full-text review. Of these, 26 studies were excluded for the following reasons: study outcomes did not meet our criteria ($n=13$), the sample size was less than five participants ($n=10$), interventions involved treatments other than rituximab ($n=1$), and study designs did not satisfy our inclusion criteria ($n=2$; Fig. 1). Ultimately, 12 studies were included for data extraction.

Study characteristics

Table 1 summarizes the baseline characteristics of the included studies. Ten studies were retrospective, and two were prospective. The age of the participants at the initiation of rituximab ranged from 38 to 54 years. Sample sizes varied from 5 to 16 patients, with a predominance of female participants. A total of 111 participants were included. None of the patients had thymomas, and 12 had undergone thymectomy. Most participants (72 out of 111; 65%) had moderate to severe MG, classified as MGFA classes III to V, before receiving rituximab. The distribution of patients by MGFA classification was as follows: asymptomatic ($n=1$), class I ($n=5$), class II ($n=36$), class III ($n=39$), class IV ($n=23$), and class V ($n=10$). Nine of the 12 studies employed low-dose rituximab regimens (100–600 mg per dose), with mean prednisolone doses before rituximab treatment ranging from 7.6 to 60 mg.

The proportion of participants who achieved MM or better

All 12 studies, encompassing 111 participants, reported the proportion of patients who achieved MGFA-PIS MM or better at the last follow-up visit. Overall, 82% (95% CI, 71–91%; $I^2=30.12\%$, $P=0.15$) of the participants achieved MGFA-PIS MM or better, indicating low heterogeneity among the studies (Fig. 2).

The proportion of participants who achieved CSR or PR

Eleven studies with 95 participants reported the proportion of patients who achieved MGFA-PIS CSR or PR at the last follow-up. The pooled proportion was 56% (95% CI, 45–67%; $I^2=0.00\%$, $P=0.60$), with no heterogeneity detected among these studies (Fig. 3).

Baseline MG severity and rituximab response

A subgroup analysis was conducted to assess rituximab response based on baseline MG severity. Seven studies reported outcomes for patients with mild to moderate MG (MGFA class asymptomatic–III), with 88.0% (95% CI, 71–99%; $I^2=37.41\%$, $P=0.14$) achieving MGFA-PIS MM or better, indicating low heterogeneity. Eight studies reported outcomes for patients with severe MG (MGFA classes IV and V), with 87% (95% CI, 58–100%; $I^2=41.17\%$, $P=0.10$) achieving MGFA-PIS MM or better, also showing low heterogeneity. There was no statistically significant difference in the rate of achieving MGFA-PIS MM or better between the two groups ($P=0.70$; Fig. 4).

Reduction in the glucocorticoid dose

Six studies involving 68 participants reported the mean difference in glucocorticoid dosage at the last follow-up. The mean reduction was 17.15 mg (95% CI, 11.77–22.53; $I^2=32.40\%$, $P=0.19$; Fig. 5).

Safety

Only one serious adverse event was reported: a patient developed osteomyelitis during rituximab treatment[22]. Most studies did not report any mild adverse events either due to lack of investigation or because they were not reported separately for anti-MuSK MG patients. The reported mild events were mild malaise[15], facial flushing, and generalized skin rash[23].

Risk of bias

The modified Newcastle–Ottawa Scale was used to assess the quality of the 12 studies. Five studies achieved a perfect score of six stars, whereas seven studies received five stars. The comparability criterion was not applicable because of the observational nature of the studies (**Supplementary Table S1**).

To evaluate potential publication bias, funnel plots were constructed to display standard errors and effect sizes from the included studies. The plots demonstrated a symmetrical distribution, indicating no discernible publication bias (**Supplementary Material**).

Discussion

Our meta-analysis demonstrated that patients with anti-MuSK MG who received rituximab achieved MGFA-PIS MM or better. Approximately half of these patients also attained CSR or PR, and rituximab therapy led to decreased steroid doses.

The pathogenesis of anti-MuSK MG involves antibodies of the IgG4 subclass, which exert pathogenic effects on synaptic transmission, as shown in in vivo experiments[24,25]. Rituximab is a B-cell depletion therapy that

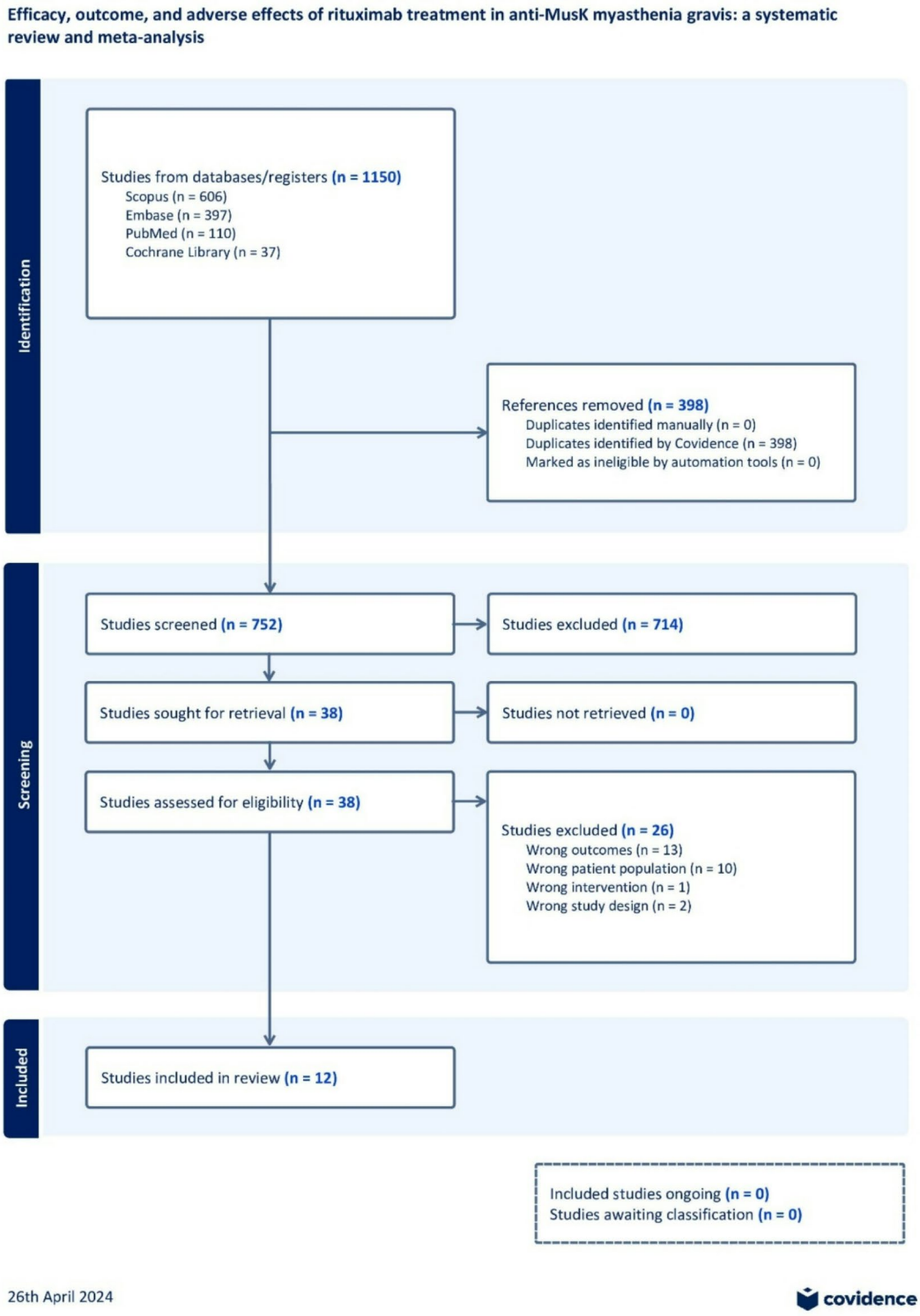

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

targets CD20-positive cells, including pre-B cells, immature B cells, and plasmablasts. Since short-lived plasma cells produce MuSK-IgG4 antibodies[26], rituximab reduces the B-cell population, thereby decreasing MuSK antibody titers.

Over the past decade, rituximab has been increasingly used as a second-line treatment for MG, with recent studies highlighting its benefits. Achieving MGFA-PIS MM or better signifies a near-complete resolution of symptoms—the primary goal of treatment. Our meta-analysis revealed that 82% of anti-MuSK MG patients achieved MGFA-PIS MM or better following rituximab treatment. This finding aligns with a previous meta-

Study	Year	Country	Sample size, n	Female, n (%)	Age at rituximab initiation, mean (SD)	Thymectomy, *n* (%)	Mean prednisolone dose at rituximab, mg/day (SD)	Rituximab regimen	Follow-up duration, months
Yang et al.[12]	2024	China	9	8 (88.89)	53.57 (14.28)	NA	50.00 (9.27)	Induction (over 3 consecutive days: 100, 200, and 200 mg). Retreatments (500 mg) every 6 months or 1 year.	Median 13.0 (IQR 9.0–20.0)
Heckmann et al.[13]	2022	South Africa	5	5 (100.00)	45.77 (9.32)	1 (20.00)	23.00 (13.04)	375 mg/m^2 single infusion.	Median 48.0 (IQR 29.0–60.0)
Castiglione et al.[14]	2022	Argentina	8	8 (100.00)	39.50 (16.39)	1 (12.50)	24.75 (17.98)	Regimen 1: two doses of 500 mg within 2 weeks (n = 2, 25%). Regimen 2: two doses of 1000 mg within 2 weeks (n = 4, 50%). Regimen 3: three doses of 500 mg within 3 weeks (n = 2, 25%).	Median 18.5 (IQR 12.5–24.5)
Meng et al.[15]	2022	China	8	8 (100.00)	52.77 (15.93)	0 (0)	60 (NA)	Protocol A: two infusions of 375 mg/m^2 within 2 weeks (n = 5, 62.5%). Protocol B: single infusion of 375 mg/m^2 (n = 3, 37.5%).	Median 25.5 (IQR 19.5–28.0)
Zhao et al.[16]	2021	China	9	7 (77.78)	38.09 (14.18)	NA	NA	Induction: 100 mg/week x 3 weeks. Maintenance: 100 mg every 6 months if B cells repopulated.	Median 21.0 (IQR 7.25–29.75)
Zhou et al.[17]	2021	China	12	11 (91.67)	40.00 (13.85)	0 (0)	27.29 (20.71)	600 mg (day 1 = 100 mg and day 2 = 500 mg).	Mean 6.0 (SD 0)
Santos et al.[18]	2020	France	5	4 (80.00)	53 (16.1)	0 (0)	7.6 (10.5)	Regimen 1: 1 g x 2 doses with a 2 weeks interval; then, 1 g with 6 months interval (n = NA). Regimen 2: two doses of 1 g within 2 weeks, at 6 months, and relapse (n = NA). Regimen 3: 375 mg/m^2/week x 4 weeks and relapse (n = NA). Regimen 4: 1 g every 2 months in the first year and every 6 months (n = NA).	NA
Litchman et al.[19]	2020	United States	16	14 (87.50)	40.35 (–)	5 (31.25)	30.9 (24.9)	375 mg/m^2/week x 4 weeks (1 cycle) and then 1 cycle every 6 months.	Mean 57.29 (SD 38.10)
Choi et al.[20]	2019	South Korea	6	4 (66.67)	51.33 (15.40)	0 (0)	NA	Two infusions of 375 mg/m^2 with an interval of 2 weeks. Retreatment with 375 mg/m^2 after clinical relapse or circulating B lymphocytes > 1% of total lymphocyte counts.	Median 25.5 (IQR 15.25–32.5)
Topakian et al.[21]	2019	Austria	14	13 (92.86)	45.43 17.91)	3 (21.43)	14.79 (11.34)	Regimen 1: Two 375 mg/m^2 infusions within 1–2 weeks (n = NA). Regimen 2: Two 500 mg infusions within 2 weeks (n = NA). Regimen 3: Two 1 g infusions within 2 weeks (n = NA). Other regimens (n = NA).	Median 16.5 (range 8.25–64.5)
Roda et al.[22]	2019	United States	13	NA	NA	2 (15.38)	20.47 (14.69)	Regimen 1: 375 mg/m^2/week x 4 weeks (n = NA). Regimen 2: 1000 mg at week 1 and 3 (n = NA).	NA
Manera et al.[23]	2012	Spain	6	6 (100.00)	44.83 (9.85)	NA	49 (NA)	375 mg/m^2/week x 4 weeks; monthly for the subsequent two months.	Median 43.5 (range 32.5–54.5)

Table 1. Overview of the key features of the studies included in the meta-analysis. *IQR* interquartile range, *NA* not available.

analysis on rituximab for refractory MG of all antibody types[27], which reported that 79% of participants with anti-MuSK antibodies achieved MGFA-PIS MM or better. We also found that two-thirds of anti-MuSK MG patients achieved MGFA-PIS CSR or PR. The mean prednisolone dose was significantly reduced to 17 mg/day after rituximab therapy. This number is astonishing as it diminishes the corticosteroid needed by more than 50% from the baseline, while recent evidence on rituximab in AChR-positive MG showed a considerably smaller figure[7]. The major side effects of rituximab that we need to be aware of are infusion-related reactions and serious infections, particularly progressive multifocal leukoencephalopathy as it may cause fatality[28,29]. Only one of the 111 participants experienced a serious adverse event: osteomyelitis[22]. Considering its high effectiveness and low incidence of serious adverse events, rituximab is a valuable treatment option for anti-MuSK MG.

We conducted a subgroup analysis to determine whether rituximab efficacy varied with disease severity. The analysis indicated that the proportion of patients who achieved MGFA-PIS MM or better was similar among those with mild to moderate anti-MuSK MG and those with severe disease, with no statistically significant difference. This finding is consistent with a previous meta-analysis in refractory MG that included all antibody types[27]. These results suggest that rituximab offers similar benefits across different severities and can be initiated at any stage of the disease.

A strength of our study is the selective inclusion of anti-MuSK MG patients from studies published between 2012 and 2023, which differs from previous meta-analysis that included MG patients with various antibody types. We observed no heterogeneity between studies in terms of the proportion of participants who achieved MGFA-PIS MM or better.

One notable limitation of our analysis is the absence of randomized controlled trials (RCTs) investigating rituximab in patients with anti-MuSK MG. All included studies were observational and single-arm, lacking the rigor of RCTs and direct comparison groups. While several studies have shown promising results, the lack of RCTs, particularly in anti-MuSK MG, limits the ability to draw definitive conclusions regarding the efficacy and safety of rituximab in this subgroup of patients. Current RCTs involving biological therapies in MG have

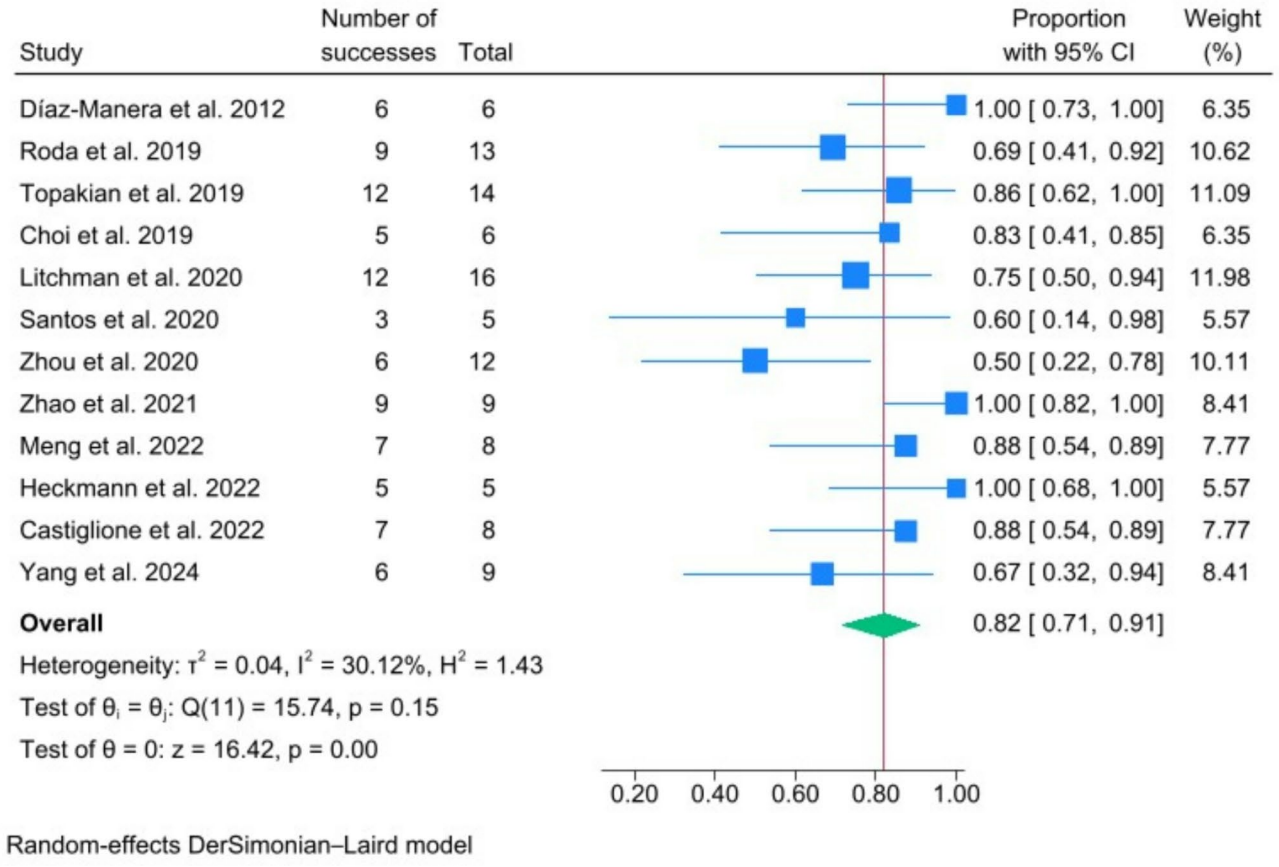

Fig. 2. Forest plot illustrating the mean effect size and 95% CI of participants who achieved MGFA-PIS MM or better at the last visit.

primarily focused on complement inhibitors, such as eculizumab, and FcRn inhibitors, such as efgartigimod and rozanolixizumab, which have shown efficacy in anti-AChR MG[30–33]. These trials reported that 47–72% of participants achieved a ≥ 2-point improvement in MG-ADL scores, while 59–63% achieved a ≥ 3-point improvement in QMG scores. However, rituximab remains unexplored in these trials, leaving the evidence for its use in anti-MuSK MG reliant on observational studies. Moreover, most studies had small sample sizes, leading to broad confidence intervals in the statistical analyses. The diversity of rituximab regimens and varying follow-up durations among the included studies could affect the clinical responses, indicating a possible dose-response relationship.

Although rituximab has demonstrated high efficacy in achieving MGFA-PIS MM or better and reducing glucocorticoid dependency, the potential long-term risks of anti-CD20 therapy warrant careful consideration. Evidence from other conditions treated with rituximab indicates an association with hypogammaglobulinemia and increased susceptibility to serious infections[28,34–37]. However, most studies included in this analysis were observational, with relatively short follow-up durations, which may have limited the ability to capture these long-term adverse effects comprehensively. Additionally, the focus on effectiveness outcomes in observational studies may introduce bias, potentially underestimating the risks associated with long-term use of rituximab. Future studies with extended observation periods and standardized monitoring of immunoglobulin levels and infection rates are essential to fully assess the long-term benefit-risk profile of rituximab in anti-MuSK MG.

Future studies should incorporate quantitative measures such as the Quantitative Myasthenia Gravis Score and the Myasthenia Gravis Activities of Daily Living scale. While MGFA-PIS provides an objective assessment of broad clinical outcomes, it does not capture the extent of muscle weakness or functional limitations in daily activities. Both objective and subjective measures are essential for a comprehensive evaluation of patient outcomes. Additionally, assessing outcomes at fixed intervals—such as 3, 6, and 12 months—and employing more robust study designs will help establish treatment effects more conclusively. Strict adherence to standardized protocols is encouraged to ensure consistency and reliability in variable assessments.

In conclusion, rituximab has demonstrated effectiveness and safety as a treatment for anti-MuSK MG. It has the potential to help patients with any baseline severity, especially those with mild to moderate disease, achieve MGFA-PIS MM or better. Additionally, rituximab reduces the required maintenance dose of prednisolone.

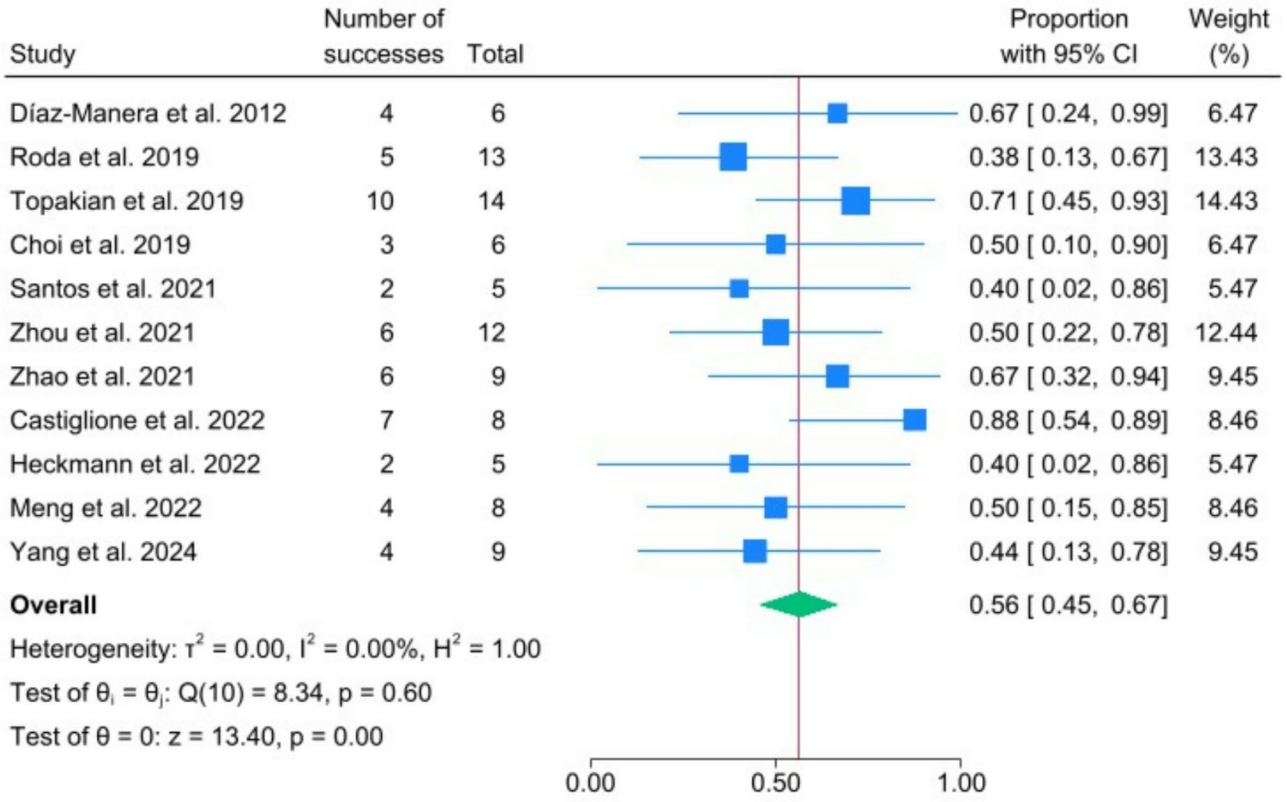

Fig. 3. Forest plot showing the mean effect size and 95% CI of the proportion of participants who achieved MGFA-PIS CSR or PR at the last visit.

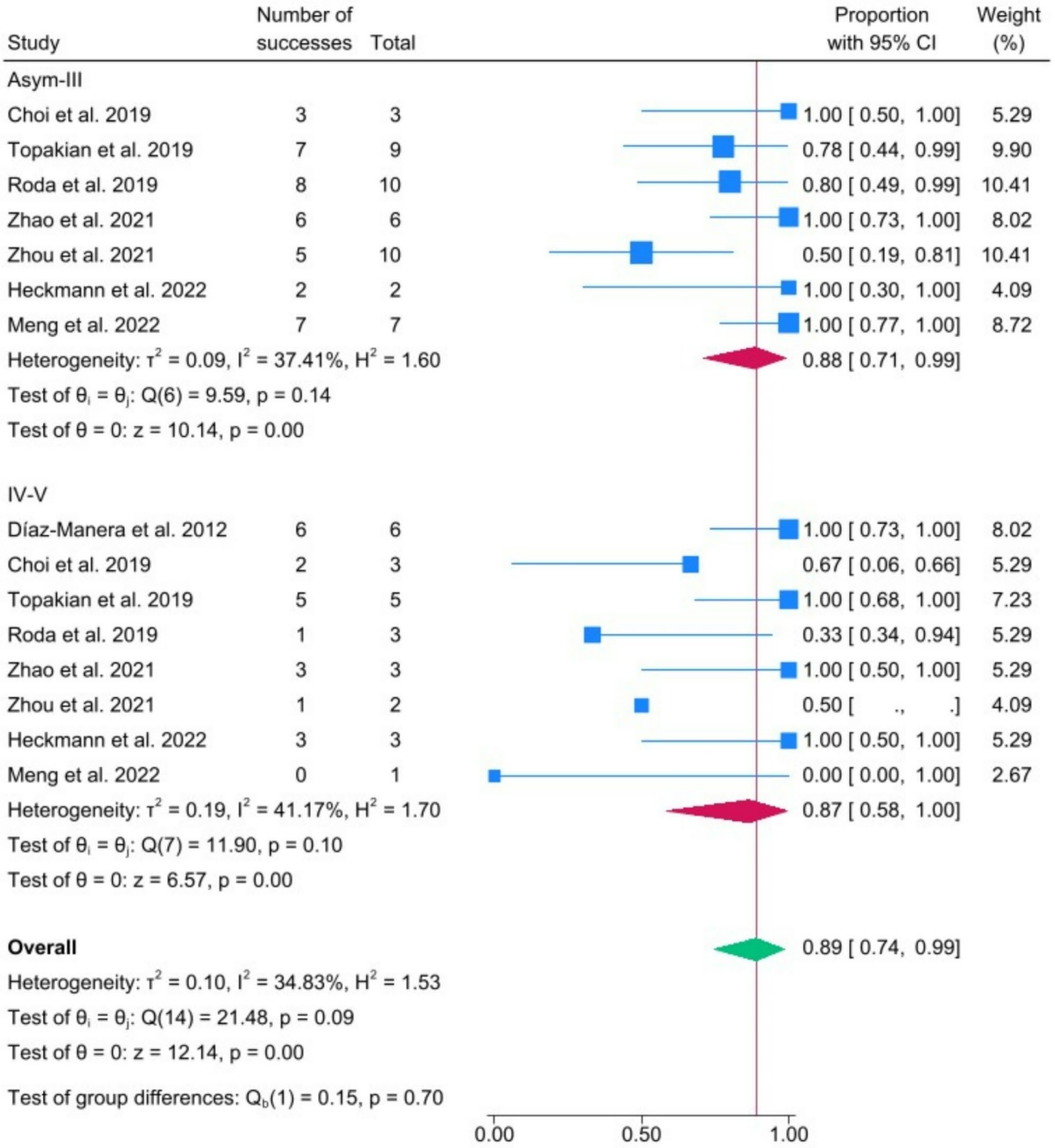

Fig. 4. Forest plot showing the subgroup analysis for the proportion of participants who achieved MGFA-PIS MM or better in the mild-to-moderate and severe groups. *Asym*, asymptomatic.

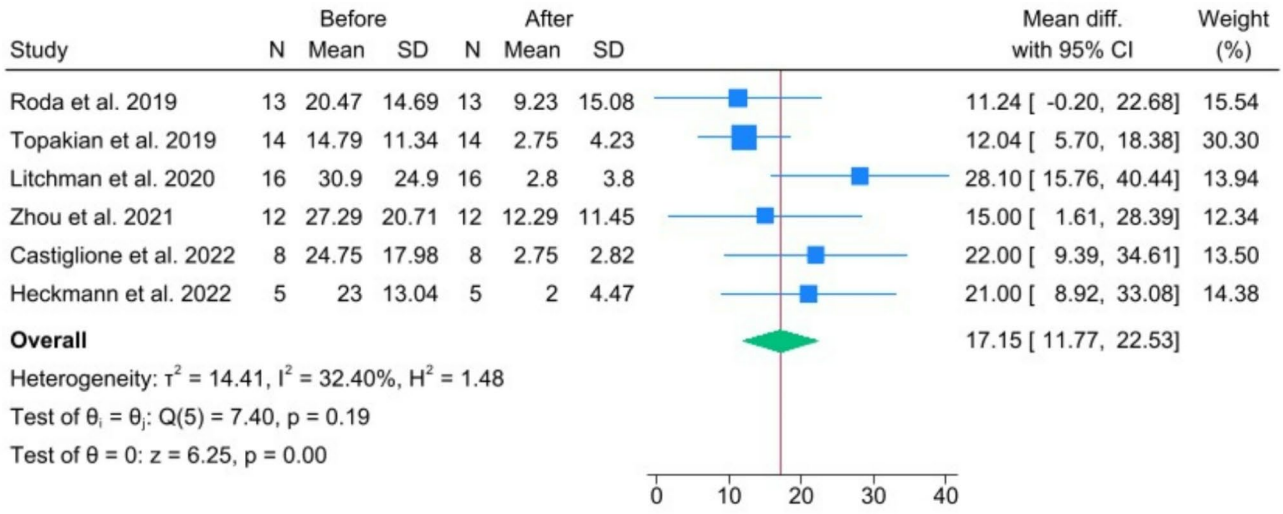

Fig. 5. Forest plot showing the mean difference and 95% CI of the glucocorticoid dose at the last visit.

Data availability

Additional data from this study are available upon request from the corresponding author.

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Conceptualization and design: S.C., P.B., J.J., E.U., N.A., and V.V. Methodology: V.V. and J.J. Data collection: S.C. and P.B. Analysis and interpretation of data: S.C., P.B., J.J., E.U., N.A., and V.V. Discussion of the results: S.C., P.B., J.J., E.U., N.A., and V.V. Supervision: J.J., E.U., and V.V. Validation: J.J., E.U., N.A., and V.V. Drafting of the manuscript: S.C., P.B., J.J., E.U., N.A., and V.V. Revision of the manuscript: S.C., P.B., J.J., E.U., and V.V. All the authors read and approved the final version of the manuscript for submission.

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Declarations

Competing interests

The authors declare no competing interests.

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