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SCIENTIFIC ARTICLE - SYSTEMATIC REVIEW

TREATMENT OF MYASTHENIA GRAVIS WITH RITUXIMAB: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives: Myasthenia Gravis (MG) is an autoimmune neuromuscular disease that is cha-racterized by muscle weakness and fatigue. Despite the availability of several therapeutic op-tions, some patients show inadequate response or intolerance to conventional treatments. In this context, rituximab emerges as a promising alternative. This study aims to analyse the effi-cacy and role of rituximab in the treatment of myasthenia gravis.

Methodology: A systematic review and meta-analysis were conducted, involving searches in the databases PubMed, EMBASE, LILACS, Cochrane Library, and Web of Science until January 2024. Studies evaluating rituximab in any dosage and infusion regimen in patients with a clinical diagnosis of myasthenia gravis were included.

Results: Of the 3188 articles initially identified, 34 studies met the inclusion criteria, totaling 725 participants. The results demonstrated that 65.7% of the patients achieved a status of mi-nimal manifestation or better on the Myasthenia Gravis Foundation of America Post-intervention Status (MGFA-PIS) scale. Additionally, the analysis revealed a significant re-duction in the dose of corticosteroids and improvements in the scores of the Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Activities of Daily Living (MG-ADL), and Myasthenia Gravis Quality of Life (MG-QoL15) scales, indicating improvement in symp-toms and quality of life.

Conclusion: Rituximab proved to be an effective alternative for controlling Myasthenia Gra-vis, significantly improving symptoms and reducing the need for corticosteroids. However, further randomized and controlled studies are needed to definitively establish its safety and efficacy in the long term.

Keywords: Meta-analysis, Myasthenia gravis, Neuromuscular junction diseases, Rituximab, Systematic review.

INTRODUCTION

The Myasthenia Gravis (MG) is an autoimmune neuromuscular disease characterized by muscle weakness and fatigability[1], resulting from antibodies against the acetylcholine receptor (anti-AChR), antibodies against muscle-specific kinase (anti-MuSK), or antibodies against low-density lipoprotein receptor-related protein 4 (anti-LRP4).[2]

Although several treatment options are available to manage this chronic condition—such as

acetylcholinesterase inhibitors, corticosteroids, and other immunosuppressive therapies[2]—some patients may show an inadequate response or intolerance to conventional treatments.

In this context, rituximab has emerged as a therapeutic option for patients with myasthenia gravis.[3]. Rituximab is a monoclonal antibody directed against CD20, a transmembrane protein found on the surface of B lymphocytes.[4]

Clinical studies and case reports have shown promising results with the use of rituximab in the treatment of myasthenia gravis.[4] B-cell depletion by rituximab[4] can reduce the production of pathogenic antibodies and modulate the immune response, leading to symptom improvement and a reduced need for corticosteroids.

However, despite these encouraging results, the use of rituximab in myasthenia gravis is still considered off-label, and further studies are needed to assess its efficacy, safety, and the best administration protocol, including dosage, frequency, and duration of treatment.

Therefore, the objective of this systematic review and meta-analysis is to review and analyze the available evidence on the use of rituximab in the treatment of myasthenia gravis, with the aim of providing a comprehensive overview of the efficacy and safety of this medication in the management of myasthenia gravis.

METHODS

This single-arm systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Search Strategy

Two researchers independently conducted a systematic search in the PubMed, EMBASE, LILACS, Cochrane Library, and Web of Science databases. The search was performed without date restriction, in January 2024, and included only studies in English. The search strategy was adapted for each database.

2.2 Eligibility Criteria

2.2.1 Study Type

We restricted our analysis to studies that met the following inclusion criteria: (1) published randomized and non-randomized studies; (2) studies evaluating the treatment of Myasthenia Gravis with rituximab, at any dose and infusion regimen; and (3) studies reporting outcomes of interest. Small case series with fewer than five participants and studies not published in English were excluded.

2.2.2 Participants

This study included participants who met the following eligibility criteria: clinical diagnosis of myasthenia gravis, supported by positive serology and/or electrophysiological findings; any severity grade, according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification; and all disease subtypes, based on serological classification, thymic status, and clinical phenotype. Participants under the age of 18 were excluded.

2.2.3 Outcomes of Interest

The primary outcomes evaluated were: (1) the proportion of patients who achieved minimal

manifestation (MM) status or better, according to the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) scale; and (2) the corticosteroid-sparing effect. Secondary outcomes included: (1) change in the Myasthenia Gravis Quantitative Score (QMG); (2) change in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score; (3) change in the Myasthenia Gravis Quality of Life 15-Item (MG-QoL15) score; and (4) the incidence of adverse events.

2.3 Study Selection and Data Extraction

Study selection and data extraction were performed independently by two authors, following predefined search criteria and quality assessment methods. Disagreements were resolved by consensus between the two authors.

2.4 Statistical Analysis

The results for binary variables were obtained through the proportion of events, and for continuous variables, the mean difference was calculated. The analysis results were presented with a 95% confidence interval. We used the I^2 statistical test to assess heterogeneity. For outcomes with high heterogeneity ($I^2 \geq 25\%$), pooled estimates were calculated using the DerSimonian–Laird random-effects model. P-values < 0.05 were considered statistically significant. Statistical analyses were performed using the OpenMeta-analyst software.

RESULT

3.1 Study and Population Characteristics

A total of 3,188 publications were identified through the database search strategy. After removing duplicates and excluding studies based on title/abstract screening, 76 publications remained and were reviewed according to the inclusion and exclusion criteria. Thirty-four studies[5–38] were included (FIGURE 1), of which two were randomized controlled trials.[6,32]

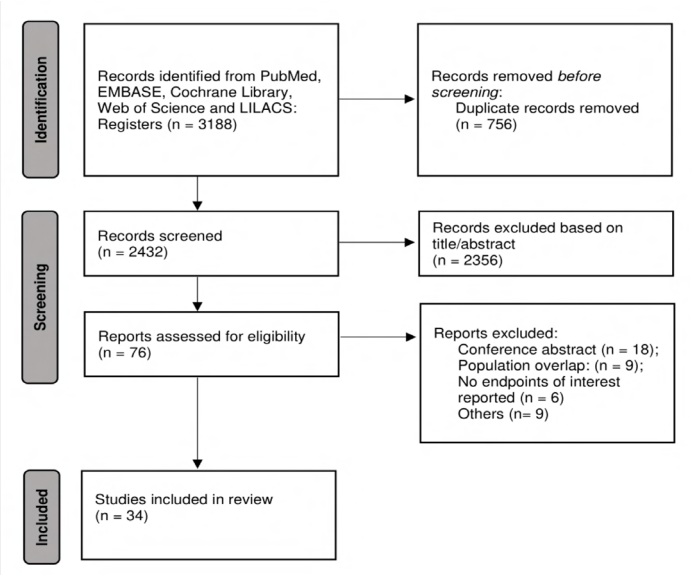

Figure 1 – PRIMSA flowchart detailing the study screening and selection process.

In total, 725 participants were included: 287 (40%) male and 438 (60%) female. Of these, 458 (63%) were anti-AChR positive, 201 (28%) anti-MuSK positive, 60 (8%) were double seronegative for anti-AChR and anti-MuSK, and 4 patients were double seropositive for anti-AChR and anti-MuSK. Thymoma was detected in 97 participants (13%) (not reported in 11 studies) (TABLE 1). The mean age at diagnosis of myasthenia gravis was 32.57 years (not reported in 11 studies), and the mean age at initiation of rituximab therapy was 38.21 years (also not reported in 11 studies). Table 2 summarizes the basic characteristics of the studies included in the systematic review.

The dose and rituximab administration regimen varied considerably among studies. The most commonly used induction protocols were: (1) 375 mg/m² weekly for 4 weeks and (2) two doses of 1000 mg administered 15 days apart.

Table 1 – General characteristics of the population

Characteristic	Total (%)
Sex	
Female	438 (60%)
Male	287 (40%)
Serology	
Anti-AChR	458 (63%)
Anti-MuSK	201 (28%)
Double seronegative	60 (8%)
Double soropositive	4 (1%)
Thymic Abnormalities	
Thymoma	97 (13%)
Total population	**725**

3.2 Efficacy Assessment

3.2.1 Proportion of Patients Who Achieved Minimal Manifestation Status or Better

Post-intervention status assessed using the MGFA-PIS scale was reported in 24 studies. We observed that 65.7% (95% CI: 0.553 – 0.761) of participants achieved minimal manifestation status or better. Heterogeneity was high (I^2 = 91.09%) (FIGURE 2).

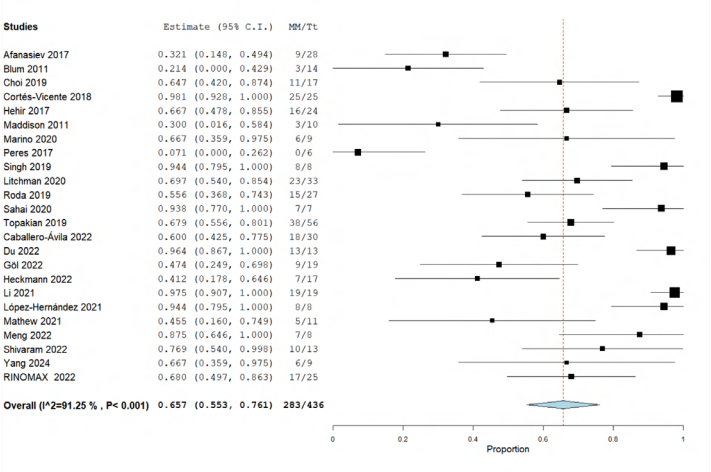

Figura 2 – Forest plot da proporção de pacientes que alcançaram um MGFA-PIS de MM ou melhor. Abreviações: CI: intervalo de confiança; MM: número de participantes que alcançaram o status de Manifestações Mínimas ou melhor; Tt: número total de participantes.

3.2.2 Corticosteroid-Sparing Effect

Corticosteroid doses were reported in thirteen studies. The average reduction in corticosteroid dose following rituximab treatment was 21.6 mg of prednisone (95% CI: 26.610 – 16.591). However, heterogeneity was high (I^2 = 80.13%) (FIGURE 3).

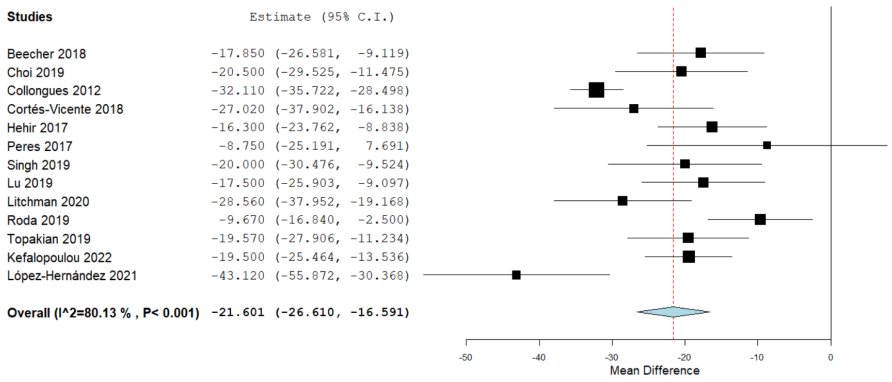

Figure 3 – Forest plot of the mean effect of rituximab therapy on corticosteroid dose reduction. Abbreviations: CI: confidence interval.

3.2.3 QMG

Six studies reported the QMG (Quantitative Myasthenia Gravis) scale. The analysis revealed a mean reduction of 8.31 points (95% CI: 10.772 – 5.863). However, heterogeneity was high (I^2 = 72.18%) (FIGURE 4).

3.2.4 MG-ADL

The MG-ADL (Myasthenia Gravis – Activities of Daily Living) scale was evaluated in four studies, which reported a reduction of 5.08 points (95% CI: 8.412 – 1.756). However, heterogeneity was high (I^2 = 91.73%) (FIGURE 4).

3.2.5 MG-QoL15

Four studies reported the MG-QoL15 (Myasthenia Gravis – Quality of Life 15-item) scale. Our analysis showed a reduction of 16.245 points (95% CI: 26.101 – 6.930). However, heterogeneity was high (I^2 = 87.04%) (FIGURE 4).

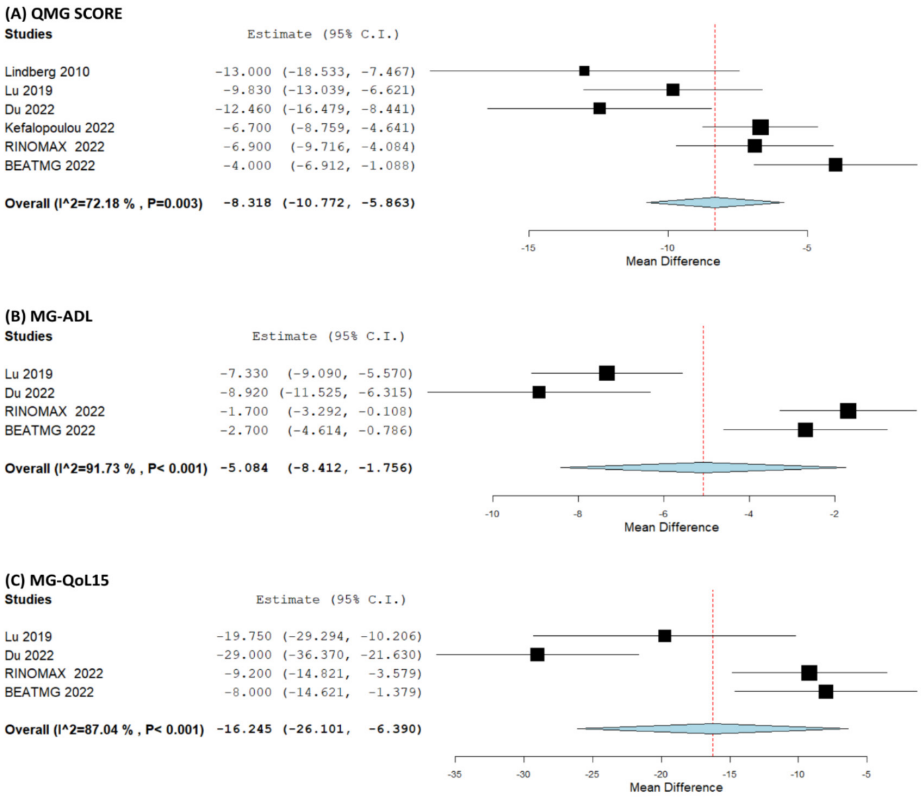

Figure 4 – (A) Forest plot of the mean difference on the Quantitative Myasthenia Gravis (QMG) scale; (B) Forest plot of the mean difference on the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale; (C) Forest plot of the mean difference on the Myasthenia Gravis-Quality of Life 15 (MG-QoL15) scale. Abbreviations: CI: confidence interval.

3.3 Safety

A total of 257 adverse events were reported, 57 of which were classified as serious adverse events. Among the serious adverse events, one case of progressive multifocal leukoencephalopathy (PML) was documented.

DISCUSSION

Several studies have already reported the use of rituximab in the treatment of Myasthenia Gravis; however, most of these are observational. Two randomized studies—RINOMAX[32] and BEAT-MG Phase II[6]—were published in 2022 and provided more robust data regarding the use of rituximab in MG treatment. Current guidelines support rituximab as a therapeutic option for refractory MG.[3] Moreover, recent evidence suggests the possibility of its use as a first-line therapy in anti-MuSK-positive patients.[3]

In this systematic review, 34 studies[5–38] were included, of which two were randomized[6,32] and 94.12% were non-randomized[5,7–31,33–38]. These studies included participants with refractory MG, non-refractory MG, and individuals considered naïve to corticosteroid-sparing immunotherapy. Additionally,

participants with different MG subtypes were included, based on serological profile, age of disease onset, and thymic status.

In our meta-analysis, we found that 65.7% of patients achieved minimal manifestation (MM) status or better on the MGFA-PIS scale. A previous meta-analysis reported similar data, with 64%[39] of patients reaching minimal manifestation status or better.

The efficacy of rituximab therapy in MG patients was also evaluated using the QMG and MG-ADL scales, showing a mean reduction of 8.31 and 5.08 points, respectively, after the intervention—demonstrating improvement in both symptoms and disease severity. A previous meta-analysis also reported a reduction in QMG score post-intervention, with a standardized mean difference of -1.55[39].

The impact of rituximab treatment on the quality of life of individuals with myasthenia gravis was assessed using the MG-QoL15 scale, with a mean reduction of 16.245 points, indicating an improvement in quality of life.

Another very important goal in treating patients with myasthenia gravis is reducing the need for corticosteroids. The results of this meta-analysis showed a mean reduction of 21.6 mg of prednisone with rituximab treatment. A previous meta-analysis also showed a reduction in corticosteroid doses, with a standardized mean difference of -1.46.[39]

However, in contrast to the results of this meta-analysis, the randomized, double-blind, placebo-controlled study BEAT-MG[6], conducted in anti-AChR-positive MG patients, did not demonstrate a statistically significant corticosteroid-sparing effect of rituximab compared to placebo. Moreover, the study did not show a statistically significant clinical improvement.

RINOMAX[32] is another randomized, double-blind, placebo-controlled study—composed predominantly of anti-AChR-positive patients (92%)—and was published in 2022. In this study, the group treated with rituximab showed a higher percentage of patients achieving minimal manifestation status (71%) compared to the placebo group (29%), thus meeting the primary endpoint. Additionally, the rituximab group required fewer hospitalizations and rescue therapies, as well as lower corticosteroid doses. Despite these benefits, the study did not demonstrate a significant reduction in QMG and MG-ADL scores.

This discrepancy between results may be attributed to the significant heterogeneity in study populations and methodologies, further reinforcing the need for new randomized clinical trials.

The studies included in this systematic review and meta-analysis employed a variety of therapeutic protocols, as there is no established protocol for the use of rituximab in MG. Among the induction regimens, the most frequently used were 375 mg/m² weekly for 4 weeks and two doses of 1000 mg administered 15 days apart, which are regimens already used in other conditions.[40,41] The frequency and criteria used to indicate maintenance/reinfusion doses also varied, with doses given at fixed intervals or based on clinical and/or laboratory criteria. The lack of an optimized protocol for MG may affect the outcomes of this therapy; therefore, new evidence is needed to determine the most effective dosing regimen.

Overall, rituximab was well tolerated by participants. However, there was one case of PML (progressive multifocal leukoencephalopathy), a severe condition caused by reactivation of the JC virus, which has a high mortality rate. The patient diagnosed with PML died. There is substantial evidence supporting the safety of rituximab in immune-mediated and hematologic diseases.[40,41,42] This medication is considered safe, with only a small percentage of patients experiencing serious adverse effects[9,40,42]. The results from the BEAT-MG study further support the safety of rituximab in MG.[6]

Despite the observed impact on standardized scales—MGFA-PIS, QMG, MG-ADL, MG-QoL15—and the corticosteroid-sparing effect, the results of this study presented considerable heterogeneity. This heterogeneity may be associated with the wide diversity of the study population, which included patients with

varying serological profiles, age of disease onset, thymic alteration status, and refractoriness to conventional immunotherapy, as well as different pre-intervention clinical statuses, various infusion protocols, and different follow-up durations.

Another limitation of this study is the inability to clearly identify which subgroups respond best to rituximab, although current data already suggest greater benefit in anti-MuSK-positive patients[3]. The single-arm nature of this meta-analysis is also a limitation, but this characteristic reflects the design of most of the included studies.

Therefore, it is essential to conduct large randomized clinical trials to evaluate the efficacy and safety of rituximab in the context of myasthenia gravis.

In conclusion, there is a growing body of literature indicating the benefit of rituximab therapy in MG, which, in this meta-analysis, is evidenced by improvements in standardized scales—MGFA-PIS, QMG, MG-ADL, MG-QoL15—as well as by its corticosteroid-sparing effect.

Table 2 – Characteristics of included studies. Abbreviations: H: male; F: female; DSN: double seronegative; SD: standard deviation; MGFA-PIS: Myasthenia Gravis Foundation of America Post-intervention Status; MM: minimal manifestation status; NR: not randomized; R: randomized; ND: not available; DSP: double seropositive.

STUDY	TYPE OF STUDY	SAMPLE SIZE	Sex M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	Antibodies AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; > MM
AFANASIEV, 2017[5]	NR	28	13 (46%) / 15 (54%)	50.6 (12.0)	21 / 3 / 4	**Induction:** 1000 mg on Day 1 and Day 15 or 375 mg/m² weekly for 4 weeks. **Maintenance:** 1000 mg or 375 mg/m² every 6 months..	9
[illegible]	R	58	14 (39%) / 11 (44%)	53.2 (17.3)	35 / 0 / 0	**Induction:** 375 mg/m² weekly for 4 weeks. **Maintenance:** 375 mg/m² weekly for 4 weeks in the sixth month.	ND
BEECHER, 2018[7]	NR	22	12 (55%) / 10 (45%)	49.4 (13.4)	10 / 9 / 3	**Induction:** 375 mg/m² weekly for 4 weeks, followed by 2 infusions every 4 weeks, or 750 mg on Day 1 and Day 15. **Maintenance:** 2 doses of 750 mg/m² (up to a maximum of 1 g per dose) with a 2-week interval, depending on clinical status.	ND
BLUM, 2011[8]	NR	14	6 (39%) / 9 (64%)	51.14 (16.42)	11 / 3 / 0	**Induction:** 500 mg on Day 1 and Day 15. **Maintenance:** if B-cell count exceeds 1% in two measurements associated with clinical signs of worsening.	3
BRAUNER, 2020[9]	NR	72	41 (57%) / 31 (43%)	60 (18)	60 / 0 / 12	**Induction:** single infusion of 500 mg (n = 57), 100 mg (n = 12), or 1000 mg (n = 3). **Maintenance:** 500 mg every 6 months or 100 mg (n = 3).	ND
[illegible]	NR	30	3 (10%) / 27 (90%)	46.9 (18.3)	18 / 12 / 0	**Induction:** 375 mg/m² weekly for 4 weeks, followed by 1 monthly dose for 3 months. **Maintenance:** according to clinical status.	18
CHOI, 2019[11]	NR	17	11 (65%) / 6 (35%)	50.52 (15.55)	9 / 6 / 2	**Induction:** 375 mg/m² on Day 1 and Day 15. **Maintenance:** single infusion of 375 mg/m², based on B-cell frequency and clinical status.	11
[illegible]	NR	20	9 (45%) / 11 (55%)	ND	12 / 4 / 3 *(1 DSP)	**Induction:** 375 mg/m² weekly for 4 weeks or 1000 mg on Day 1 and Day 15. **Maintenance:** 375 mg/m² every 3 months or 1000 mg depending on clinical status.	ND
CORTÉS-VICENTE, 2018[13]	NR	25	1 (4%) / 24 (96%)	51.34 (15.82)	0 / 25 / 0	**Induction:** 375 mg/m² weekly for 4 weeks, followed by 375 mg/m² monthly for 2 months, or 1000 mg on Day 1 and Day 15, or 375 mg/m² weekly for 4 weeks. **Maintenance:** according to clinical status.	25

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥ MM
DOS SANTOS, 2020[14]	NR	29	12 (41%) / 17 (59%)	49.6 (16.3)	20 / 5 / 4	**Protocol A:** two infusions of 1 g spaced 2 weeks apart, followed by 1 g every 6 months (N = 22). **Protocol B:** two infusions of 1 g spaced 2 weeks apart and one infusion at 6 months. Reinfusions according to clinical status (N = 3). **Protocol C:** 375 mg/m^2 weekly for 4 weeks. Reinfusions according to clinical status (N = 1). **Protocol D:** 1 g infusion every 2 months for 1 year, then 1 g every 6 months (N = 3).	ND
DOUGHTY, 2021[15]	NR	40	22 (55%) / 18 (45%)	55.5 (18.1)	28 / 9 / 3	**Induction:** 1000 mg × 2 or 375 mg/m^2 × 4. **Maintenance:** reinfusion in 31 patients.	ND
DU, 2022[16]	NR	13	6 (46%) / 7 (54%)	ND	13 / 0 / 0	**Induction:** 100 mg weekly for a maximum of 3 weeks. **Maintenance:** 100 mg according to clinical status and CD19+ lymphocyte population.	13
FATEHI, 2021[17]	NR	34	12 (35%) / 22 (65%)	47.9 (15.2)	17 / 9 / 8	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** 1000 mg every 6 months.	ND
GÖL, 2022[18]	NR	19	10 (53%) / 9 (47%)	48.6 (12.3)	10 / 6 / 1 (*2 DSP)	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** 1000 mg every 6 months, depending on clinical status.	9
HECKMANN, 2022[19]	NR	17	1 (6%) / 16 (94%)	36.38 (15.17)	10 / 5 / 2	**Induction:** Single infusion of 375 mg/m^2.	7
HEHIR, 2017[20]	NR	24	3 (13%) / 21 (88%)	ND	0 / 24 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks. **Maintenance:** 375 mg/m^2 weekly for 4 weeks or 2 doses of 1000 mg with a two-week interval.	16
KEFALOPOULOU,2022[21]	NR	30	10 (33%) / 20 (67%)	ND	16 / 6 / 8	**Induction:** 375 mg/m^2 weekly for 4 weeks. **Maintenance:** 375 mg/m^2 weekly for 2 weeks every 6–8 months (AChR+) or 375 mg/m^2 weekly for 2 weeks based on clinical status (MuSK+).	ND
LI, 2021[22]	NR	19	7 (37%) / 12 (63%)	ND	19 / 0 / 0	The mean dose per Rituximab cycle was 183 mg (range: 100–400 mg). Reinfusion depends on the CD19+ lymphocyte population, with a mean interval of 6.9 months.	19
LINDBERG, 2010[23]	NR	5	2 (40%) / 3 (60%)	ND	5 / 0 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks. **Maintenance:** 2 doses of 1000 mg with a two-week interval (in some patients).	ND

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥ MM
LITCHMAN, 2020[24]	NR	33	9 (27%) / 24 (73%)	ND	17 / 16 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks. **Maintenance:** 375 mg/m^2 weekly for 4 weeks every 6 months.	23
LÓPEZ-HERNÁNDEZ, 2021[25]	NR	8	2 (25%) / 6 (75%)	ND	8 / 0 / 0	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** 1000 mg every 6 months, depending on clinical response.	8
LU, 2019[26]	NR	12	2 (17%) / 10 (83%)	30.6 (29.6)	12 / 0 / 0	**Induction:** 600 mg as a single infusion. **Maintenance:** 600 mg every 6 months (at 6 and 12 months).	ND
MADDISON, 2011[27]	NR	10	0 (0%) / 10 (100%)	32.7 (12.21)	7 / 3 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks. **Maintenance:** monthly infusion in three patients.	3
MARINO, 2020[28]	NR	9	1 (11%) / 8 (89%)	50.4 (12.8)	0 / 9 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks, followed by one dose of 375 mg/m^2 after 3 months.	6
MATHEW, 2021[29]	NR	11	9 (82%) / 2 (18%)	50.54 (18.71)	11 / 0 / 0	**Induction:** 500 mg on Day 1 and Day 15; three patients received an additional 500 mg dose two weeks later due to clinical worsening. **Maintenance:** 500 mg every 6–12 months, depending on clinical status.	5
MENG, 2022[30]	NR	8	8 (100%) / 0 (0%)	ND	0 / 8 / 0	**Induction:** 375 mg/m^2 on Day 1 and Day 15 or a single infusion of 375 mg/m^2. **Maintenance:** according to clinical status.	7
PERES, 2017[31]	NR	6	1 (17%) / 5 (83%)	62.0 (16)	4 / 0 / 2	**Induction:** 1000 mg on Day 1 and Day 15. **Maintenance:** according to clinical status, CD19+ lymphocyte population, and immunoglobulin levels, with a minimum interval of 4 months.	0
RINOMAX, 2022[32]	R	25	18 (72%) / 7 (28%)	67.4 (13.4)	23 / 0 / 0	**Induction:** single infusion of 500 mg.	17
RODA, 2019[33]	NR	27	5 (19%) / 22 (81%)	41.85	10 / 13 / 4	**Induction:** 375 mg/m^2 weekly for 4 weeks or 1000 mg in weeks 1 and 3. **Maintenance:** according to clinical status.	15
SAHAI, 2020[34]	NR	7	2 (29%) / 5 (71%)	ND	7 / 0 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks, or 1000 mg on Day 1 and Day 15, or a single infusion of 1000 mg. **Maintenance:** every 6–12 months in three patients.	7
SHIVARAM, 2022[35]	NR	13	6 (46%) / 7 (54%)	44.84 (15.73)	10 / 1 / 1 (*1 DSP)	**Induction:** 375 mg weekly for 1–4 weeks or 1000 mg on Day 1 and Day 15. **Maintenance:** 500–600 mg depending on the	10

STUDY	TYPE OF STUDY	SAMPLE SIZE	SEX M(%)/F(%)	Mean age at initiation of Rituximab Mean (SD) in years	ANTIBODIES AChR / MuSK / DSN	RITUXIMAB PROTOCOL	MGFA-PIS; ≥ MM
						CD19+/CD20+ lymphocyte population, with a minimum interval of 3 months.	
SINGH, 2019[36]	NR	8	7 (88%) / 1 (13%)	38.12 (11.94)	6 / 2 / 0	**Induction:** 375 mg/m^2 weekly for 4 weeks. **Maintenance:** 375 mg/m^2 weekly for 4 weeks every 6 months.	8
TOPAKIAN, 2019[37]	NR	56	22 (39%) / 34 (61%)	51.01 (20.13)	39 / 14 / 3	**Induction:** 375 mg/m^2 on Day 1 and Day 15, or 500 mg on Day 1 and Day 15, or 1000 mg on Day 1 and Day 15; other protocols used in 9 patients. **Maintenance:** based on B-cell population or clinical status.	38
YANG, 2024[38]	NR	9	1 (11%) / 8 (89%)	ND	0 / 9 / 0	**Induction:** 500 mg divided over three consecutive days (100 mg on Day 1, 200 mg on Days 2 and 3). **Maintenance:** 500 mg every 6–12 months.	6

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