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A retrospective study of the safety and efficacy of rituximab in Iranian patients with myasthenia gravis: A single-center experience

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Keywords
Rituximab; Myasthenia Gravis; Activities of Daily Living; Outcome Measures; Acetylcholine Receptor; Autoantibodies; Muscle-Specific Tyrosine Kinase

Abstract

Background: This retrospective cohort study was conducted to evaluate the efficacy and tolerance of rituximab (RTX) for the management of myasthenia gravis (MG).

Methods: This retrospective cross-sectional study was conducted on 61 patients with refractory and non-refractory MG who received RTX. The Myasthenia Gravis Activities of Daily Living (MG-ADL) profile was used to assess MG symptoms and their effects on daily activities at the start of RTX and in the last follow-up. The Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) scale has been used as an outcome measure after treatment with RTX in the 12th month and the last follow-up.

Results: The mean age of the patients was 40.31 ± 13.53 years (range: 15-78 years). Of 61 patients, eight (13.1%) were double seronegative, 29 (47.5%) had anti-acetylcholine receptor (AChR+) antibody, and 24 (39.3%) had anti-muscle-specific tyrosine kinase antibody (MuSK+). According to the mean rank table, the results of this study showed that the drug was more effective in improving the symptoms of MuSK+ patients compared to the other two groups (P = 0.006). The mean MG-ADL was 4.86 ± 1.83 before treatment and 1.51 ± 2.02 in the last follow-up visit.

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Paired t-test showed a significant association between MG-ADL before and after treatment in the last visit [t(55): 11.30, 95% confidence interval (CI): 2.79-3.99, P = 0.001)].

Conclusion: This retrospective study showed a considerable effect of RTX as induction therapy in patients with MG, especially those with MuSk+ MG.

Introduction

Acquired autoimmune myasthenia gravis (MG) is an antibody-mediated disorder of the neuromuscular junction, which results in a cholinergic transmission defect.[1,2] Its incidence ranges between 0.3 and 2.8 in 100000, and it is estimated to affect more than 700000 people worldwide.[3,4] Autoantibodies against the muscle-specific tyrosine kinase (MuSK), acetylcholine receptor (AChR), and lipoprotein-related protein 4 (LRP4) are involved in the pathogenesis of MG.[5,6] Most patients with MG present with fluctuating, generalized weakness, and need long-term immunosuppressive medication to achieve the treatment goal of minimal manifestations (MM).[7-9] However, steroids and conventional steroid-sparing oral immunosuppressive agents such as azathioprine and cyclosporine may have intolerable side effects, take a long time to take effect, or even fail to achieve and maintain enough control of symptoms.[10] In recent years, rituximab (RTX), a monoclonal antibody that depletes B cells and B-cell precursors by binding to the CD20 surface antigen, has evolved as a likely off-label treatment option for both AChR+ and MuSK+ MG.[8-11]

The efficacy of RTX in the treatment of MG is not supported by high quality evidence-based data. All previous studies had a retrospective design with relatively small sample sizes.[1,5,7,10,12-22]

Most of the previous studies assessed the effect of RTX on MuSK+ and AChR+ MG, and few small studies assessed the effect of RTX on double seronegative MG.[23-26]

The main objective of the present study was to evaluate the efficacy and the tolerability of RTX in the management of MG (AChR+, MuSK+, and double seronegative) in a retrospective cohort.

Materials and Methods

Study design: This retrospective cross-sectional study was conducted in Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, from 2012 to 2020. The Ethics Committee of Tehran University of Medical Sciences approved this study.

Participants: The patients with MG were identified based on clinical history, neurological examination, laboratory evaluation, and electrophysiological documentation of a neuromuscular transmission defect. The AChR+ and double seronegative MG patients who were refractory to treatment and MuSK+ patients were included in the study. The patients were divided to three groups according to antibody status (AChR+, MuSK+, or double seronegative). All alternative clinical diagnoses were ruled out by proper investigations. All patients who received RTX as part of their treatment protocol were followed in the Neuromuscular Center of Shariati Hospital from 2012 to 2020. The patients were followed up 12 months after treatment.

Data source and measurement: The Myasthenia Gravis Activities of Daily Living (MG-ADL) profile was used to assess MG symptoms and their effects on daily activities at the start of RTX and in the last follow-up. For outcome measurement, Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) was applied in the last follow-up.

MGFA-PIS estimates the patient's status [complete stable remission (CSR), pharmacological remission (PR), MM] and the change of status since the initiation of treatment [improved (I), unchanged (U), worse (W), exacerbated (E)]. Patients were defined as refractory when there was no clinical response or if the clinical picture became worse after a combination of prednisolone and at least one RTX protocol.

RTX treatment included the use of either 1000 mg on day 1 and day 15. The induction treatment was followed by maintenance treatment, including 500 or 1000 mg infusion with 6 months or more periodicity.

The blood CD19+ and CD20+ B-cell counts were routinely checked during the follow-up of the patients, and RTX reinfusion was considered based on the clinical exacerbation or rise of CD19 counts above 0.1%, whichever occurred first.

The data were analyzed using the SPSS software (version 24, IBM Corporation, Armonk, NY, USA). Qualitative variables were described as frequency (percentage) and compared between groups using the chi-square test as appropriate. The one-sample Kolmogorov-Smirnov test was used to test the normal distribution of quantitative data. Paired t-test was used to examine the intragroup difference, one-way analysis of variance (ANOVA) was used for intergroup comparison, and Dunnett T3 post-hoc test was used to determine the

difference. The Kruskal-Wallis H test was used to evaluate statistically significant differences between groups of an independent variable against a continuous or ordinal dependent variable. The level of significance was set at 0.05.

Results

Sixty-one patients with MG were treated with RTX between 2012 and 2020. Two female anti-AChR+ patients were excluded due to the side effects of the first dose [one due to shortness of breath and the other due to erythema multiforme (EM)] (Figure 1).

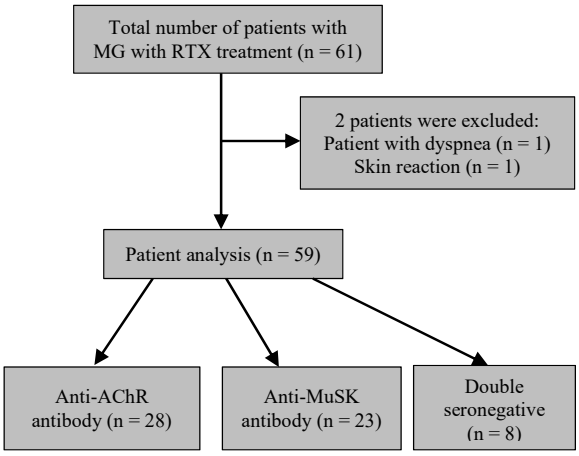

Figure 1. Recruitment of patients with generalized myasthenia gravis (MG)
AChR: Acetylcholine receptor; RTX: Rituximab; MG: Myasthenia gravis; MuSK: Muscle-specific tyrosine kinase

A total of 59 patients with MG (41 women and 18 men) with a mean age of 40.31 ± 13.53 years (range: 15-78 years) were studied. The mean age of patients at disease onset was 29.20 ± 4.69 years (range: 4-69 years). Of 59 patients, 28 (47.5%) were anti-AChR positive, 23 (39.3%) were anti-MuSK positive, and eight (13.1%) were double seronegative. There was no significant difference in age, gender, and age of disease onset between AChR+, MuSK+, and double seronegative groups (Table 1). Fifty-four patients (93.2%) received corticosteroids and 47 patients (79.7%) received other immunosuppressive therapies [azathioprine: 19 (31.1%), mycophenolate mofetil: 4 (6.5%), cyclosporine: 23 (37.7%), cyclophosphamide: 1 (1.6%)]. Ten (16.4%) received RTX as the first line of immunosuppressive treatment, who were all MuSK+. Thirty-eight (64.4%) patients had a history of thymectomy and pathology evaluation was compatible with a diagnosis of thymoma in nine (23.7%) patients.

The mean duration of disease before the initiation of RTX therapy was 6.83 ± 5.37 years (Table 1). There was no significant difference in duration of disease before treatment with RTX between the three groups (P = 0.180).

The MG-ADL score was investigated in all patients before receiving RTX and in the last follow-up visit. The average MG-ADL was 4.86 ± 1.83 before treatment and 1.51 ± 2.02 in the last visit. Paired t-test showed a significant difference between MG-ADL before and after treatment in the last visit [t(55): 11.30, 95% confidence interval (CI): 2.79-3.99, P = 0.001]. One-way ANOVA showed a significant difference in the scores of MG-ADL after receiving RTX (Figure 2). The mean MG-ADL after RTX was lower in the anti-MuSK positive group compared to other groups (before treatment: 4.38 ± 1.52, after treatment: 0.29 ± 0.85, P = 0.001).

Paired t-test showed a significant difference in the mean pyridostigmine intake before (178.36 ± 90.99 mg) and after RTX treatment (91.42 ± 94.95 mg) [t(54): 6.92, 95% CI: 60.56-109.97, P = 0.001].

Table 1. Demographic and treatment characteristics of patients

Characteristic	All patients	AChR+	MuSK+	Seronegative	P
Gender [n (%)]					0.870
Men	20 (32.8)	10 (50.0)	7 (35.0)	3 (15.0)	
Women	41 (67.2)	19 (46.3)	17 (1.5)	5 (12.5)	
Age (year) (mean ± SD)	40.31 ± 13.50	39.72 ± 13.30	37.92 ± 12.40	49.63 ± 15.10	0.100
Age of disease onset (year) (mean ± SD)	29.20 ± 14.60	28.00 ± 13.70	27.38 ± 13.50	39.00 ± 18.90	0.120
Duration of disease before treatment (year) (mean ± SD)	6.83 ± 5.27	7.20 ± 5.12	6.76 ± 5.82	5.15 ± 5.37	0.760
Dose of pyridostigmine (mg) (mean ± SD)					
Before RTX	178.36 ± 90.90	206.50 ± 74.10	140.00 ± 101.10	216.00 ± 52.60	0.019
After RTX	91.42 ± 94.50	128.88±108.74	47.50 ± 58.62	100.00 ± 78.70	0.007

RTX: Rituximab; SD: Standard deviation; AChR: Acetylcholine receptor; MuSK: Muscle-specific tyrosine kinase

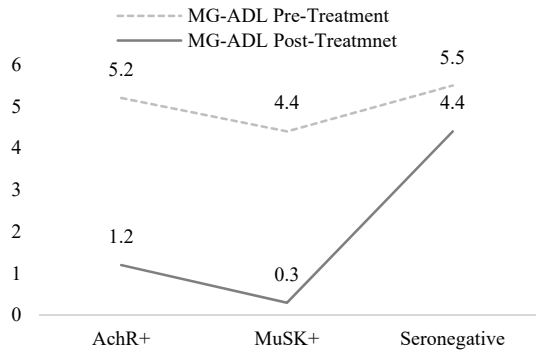

Figure 2. Myasthenia Gravis Activities of Daily Living (MG-ADL) score before and after treatment with rituximab (RTX) in three groups of patients with myasthenia gravis (MG)
AChR: Acetylcholine receptor; MuSK: Muscle-specific tyrosine kinase; MG-ADL: Myasthenia Gravis Activities of Daily Living

According to one-way ANOVA, there was a significant difference in the pyridostigmine dosage in three groups (AChR+, MuSK+, and double seronegative) before (P = 0.019) and after RTX therapy (P = 0.007) (Table 1). The pyridostigmine dose was lower in the anti-MuSK+ group compared to other groups before and after RTX treatment (P = 0.034 and P = 0.005, respectively). The mean dose of prednisolone was 23.90 ± 14.41 mg before treatment, which decreased to 11.00 ± 5.85 mg in the first year after treatment [t(55): 7.71, 95% CI: 9.15-15.57, P = 0.001]. Figure 3 shows the dosage of prednisolone in the three groups before and after treatment.

According to the MGFA-PIS, the outcome of patients in the last follow-up showed that one patient was in CSR and 11 patients (18.64%) were in PR. Forty patients (67.8%) had MMs. Overall, 53 patients (89.8%) had good outcomes (MM or better) in the last follow-up, whereas four patients (6.8%) became worse and two patients (3.4%) remained unchanged. There was no mortality after treatment. There was no evidence that age, sex, age of disease onset, thymectomy, and previous immunosuppressive therapies had an effect on the MGFA-PIS outcome (Table 2).

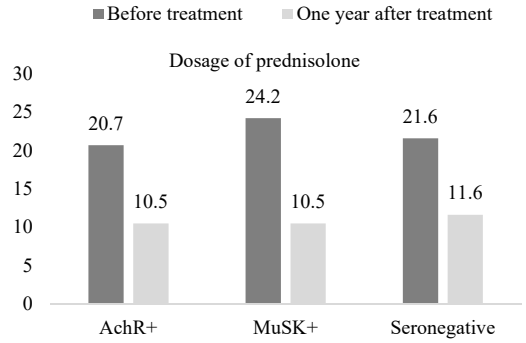

Figure 3. Prednisolone dosage before and after rituximab (RTX) treatment in patients with myasthenia gravis (MG)
AChR: Acetylcholine receptor; MuSK: Muscle-specific tyrosine kinase

Figure 4 shows after RTX treatment results of MGFA-PIS in three groups of patients with MG. Based on the Kruskal-Wallis H test, with 95% CI, we can say that the impact of RTX varies in different groups. According to the mean rank table, the results showed that the drug was more effective in MuSK+ patients compared to the other two groups (P = 0.006). No serious side effects were detected in the participants.

Table 2. Demographic characteristics of patients with myasthenia gravis (MG) and clinical outcome based on Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS)

Variables	Good outcome (CSR, PR, MM)	Poor outcome (unchanged/worse)	P
Age (year) (mean ± SD)	39.8 ± 13.8	44.0 ± 14.7	0.490
Age of onset (year) (mean ± SD)	29.1 ± 14.5	29.0 ± 20.2	0.190
Female sex [n (%)]	33 (63.5)	5 (83.3)	0.310
Thymectomy [n (%)]	32 (61.5)	5 (83.3)	0.410
AChR+ [n (%)]	25 (48.1)	4 (77.7)	0.330
MuSK+ [n (%)]	24 (46.2)	0 (0)	0.030
Double seronegative [n (%)]	4 (71.7)	3 (50.0)	0.120
MG-ADL pretreatment (mean ± SD)	4.9 ± 1.8	4.4 ± 1.5	0.120
Azathioprine [n (%)]	39 (81.3)	4 (100)	0.450
MMF [n (%)]	25 (52.1)	4 (100)	0.080
Cyclosporine [n (%)]	16 (32.7)	3 (75.0)	0.120
Pyridostigmine (mg) (mean ± SD)	174.7 ± 91.7	225.0 ± 75.4	0.290
Prednisolone (mg) (mean ± SD)	24.2 ± 14.4	15.5 ± 6.8	0.190

P-value < 0.05 is significant
MG-ADL: Myasthenia Gravis Activities of Daily Living; AChR: Acetylcholine receptor; MuSK: Muscle-specific tyrosine kinase; MM: Minimal manifestations; CSR: Complete stable remission; PR: Pharmacological remission; SD: Standard deviation; MMF: Mycophenolate mofetil

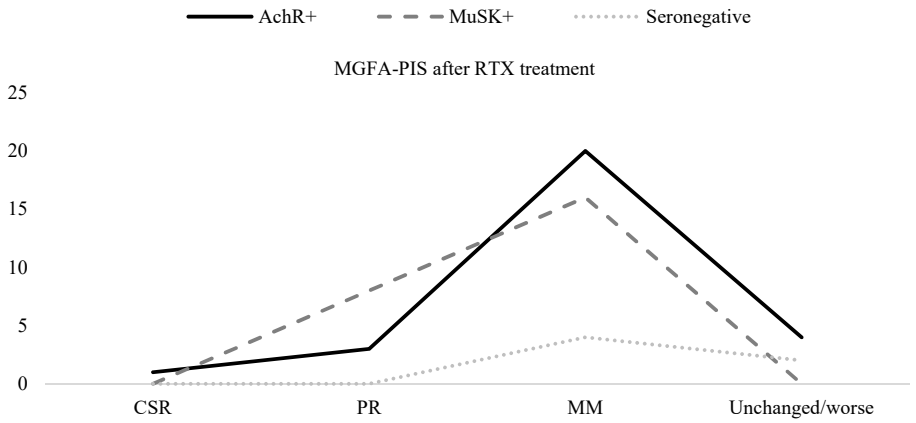

Figure 4. Rituximab (RTX) treatment results of Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) in patients with myasthenia gravis (MG)
CSR: Complete stable remission; PR: Pharmacological remission; MM: Minimal manifestations; AChR: Acetylcholine receptor; MuSK: Muscle-specific tyrosine kinase; MGFA-PIS: Myasthenia Gravis Foundation of America Post-Intervention Status; RTX: Rituximab

Discussion

This study was conducted to demonstrate the effectiveness of RTX in subsets of seropositive and seronegative MG patients. The results showed the marked efficacy of RTX in patients with MG according to MG-ADL, MGFA-PIS, and prednisolone dose reduction.

We report a retrospective study of 59 patients with MG without optimal response to prednisolone or other immunosuppressive agents which showed a good clinical outcome after RTX therapy in 88.1% of patients according to MGFA-PIS (CSR, PR, or MM) and only 10.2% of patients had a poor clinical outcome with a mean follow-up duration of 36 months. The MG-ADL score reduced markedly after receiving RTX, particularly in patients with MuSK+ MG. In addition, the dose of prednisolone reduced significantly in all three groups, especially in the second year of RTX therapy. Previous studies showed good clinical outcome after RTX therapy based on the MGFA-PIS in patients with MG, which is consistent with our results. In a large cohort study, Grob et al. found that 70.0% of patients with MG experienced general improvement or remission after receiving RTX.[27] Lee et al. studied 123 patients with generalized MG and found that 78.0% of the patients had good long-term clinical outcome.[28]

Tandan et al. recently reviewed the efficacy and safety of RTX in 169 patients with MG. The results showed a significant reduction in the proportion of relapses in anti-AChR+ (93% before vs. 26% after) and anti-MuSK+ patients (100% before vs. 14% after). MuSK+ patients experienced a larger reduction in the number of relapses. MM and better post-intervention status (PIS) were achieved in 72.0% of MuSK+ MG and 30.0% of AChR+ MG patients. Only one out of seven seronegative MG patients responded to RTX. Response predictors were MuSK+ MG, less severe disease, and younger age at treatment.[29]

Another systematic review of 165 patients with AChR-MG receiving RTX treatment showed significant clinical improvement in 68% of the patients (113/165). A full remission of MG was reported in 36% of the patients and MM status ranged between 27% and 64% (mean: 54%). The purpose of this systematic review was to describe the best evidence for RTX in the AChR subtype.[30]

Singh and Vinayak reported that eight patients with refractory MG (six AChR+ and two MuSK+) showed a dose reduction after four cycles of RTX, of whom seven were completely tapered off prednisolone and there was a 53.8% dose reduction in azathioprine.[13]

There is no generally accepted protocol for the use of RTX in MG. In the present study, patients were treated with an induction dose of RTX (one or two doses of RTX 1 g repeated two weeks apart or 4 doses of RTX 500 mg repeated one week apart). They subsequently received a maintenance dose of 500-1000 mg every 6 months according to the CD19 count. Recently, 15 more patients with refractory MG were treated with a low dose of 600 mg RTX and evaluated by serial clinical scales, flow cytometry of peripheral blood T and B cells, and

antibody titer before and six months after RTX treatment. The Quantitative Myasthenia Gravis Score (QMGS), Manual Muscle Testing (MMT), MG-ADL, and MG-specific quality of life (MG-QOL) improved significantly, and a mean steroid-dosage reduction of 40% was achieved in patients with refractory MG six months after RTX infusion.[11]

Topakian et al. studied 56 patients with antibodies against AChR, MuSK, and double seronegative present in 69.6%, 25.0%, and 5.4% of them, respectively. Three months after RTX, 14 of 53 (26.4%) patients were in remission. In the last follow-up after a median of 20 months, 42.9% of the patients were in remission and 25.0% had MM. Remission was more frequent in patients with MuSK antibodies versus those with AChR antibodies (71.4% vs. 35.9%), and the presence of MuSK antibodies independently predicted remission after RTX. In this study, it was found that RTX was well tolerated, safe, and efficacious in older patients, even in patients aged 80-89 years.[10] The present study showed no significant difference between response to RTX and age or age at disease onset. Brauner et al. conducted a very large case series on 72 patients. Twenty-four patients received RTX within 12 months of disease onset and 48 received RTX later; 34 of whom had therapy-refractory disease. The median time to remission was shorter for new-onset versus refractory disease [7 vs. 16 months: hazard ratio (HR): 2.53, 95% CI: 1.26-5.07 after adjustment for age, sex, and disease severity] and for RTX versus conventional immunosuppressant therapies (7 vs. 11 months: HR: 2.97, 95% CI: 1.43-6.18 after adjustment). This study described the clinical outcomes of different treatment modalities of MG. RTX proved to be more favorable in the treatment of new-onset generalized MG, with even better performance compared to conventional immunosuppressant therapy.[30]

To date, only a few small studies have been published on the use of RTX in MG, but all have reported the efficacy of RTX in patients with refractory MG. In our study, RTX was well tolerated, safe, and efficacious in older patients, which is similar to the findings of a study by Topakian et al.[10] Our findings lend support to RTX as a treatment option in elderly and patients with double seronegative MG.

RTX was well tolerated in our patients; only one patient developed severe hypogammaglobulinemia after nine doses and two patients developed dyspnea and EM after RTX injection.

The limitations of this case series are its single-center and retrospective nature.

Conclusion

This retrospective study on RTX for MG, one of the largest to date, showed the considerable effect of RTX as induction therapy in patients with MG, especially those with MuSK-antibody-positive disease. Older patients as well as those with seronegative antibody responded to this treatment, which suggests that further investigation of RTX in these groups is warranted.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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