学　位　論　文

Reduction rate of anti-acetylcholine receptor antibody titer levels is an early prognostic indicator for myasthenia gravis

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ORIGINAL ARTICLE

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Reduction rate of anti-acetylcholine receptor antibody titer levels is an early prognostic indicator for myasthenia gravis

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Abstract

Background: A realistic treatment goal for myasthenia gravis (MG) is achieving minimal manifestations or better status with prednisolone at ≤5 mg/day (MM-or-better-5 mg), considering a patient's health-related quality of life. Prognosis prediction during the early phases of immunotherapies might be critical for determining subsequent treatment strategies; however, the appropriate biomarkers remain unknown.

Aim: This study aimed to clarify whether the reduction rate of anti-acetylcholine receptor antibody (RR-AChR Ab) titer levels is a useful biomarker for predicting MM-or-better-5 mg achievement.

Methods: We retrospectively investigated patients with MG and AChR Abs who received immunotherapy for the first time. The RR-AChR Ab titer levels were calculated in the early (within 30 days), middle (31–60 days), and late (61–100 days) periods after starting immunotherapies. A receiver operating characteristic (ROC) curve was generated to determine an appropriate cutoff value for RR-AChR Abs to achieve an MM-or-better-5 mg.

Results: Of 53 patients, 24 (45%) achieved MM-or-better-5 mg after 1 year. For the early period, the RR-AChR Ab cutoff value to predict MM-or-better-5 mg was 1.68%/day with an area under the curve (AUC) of 0.75 (sensitivity, 85%; specificity, 70%). However, the middle and late posttreatment AUC values did not predict MM-or-better-5 mg achievement.

Conclusion: The RR-AChR Ab might be an appropriate prognostic biomarker during the early period of MM-or-better-5 mg achievement. In the era of early fast-acting treatment strategies, the RR-AChR Ab trend after starting immunotherapies may guide the subsequent treatment choices.

KEYWORDS
anti-acetylcholine receptor antibodies, fast-acting treatment, minimal manifestations, myasthenia gravis, prognostic prediction

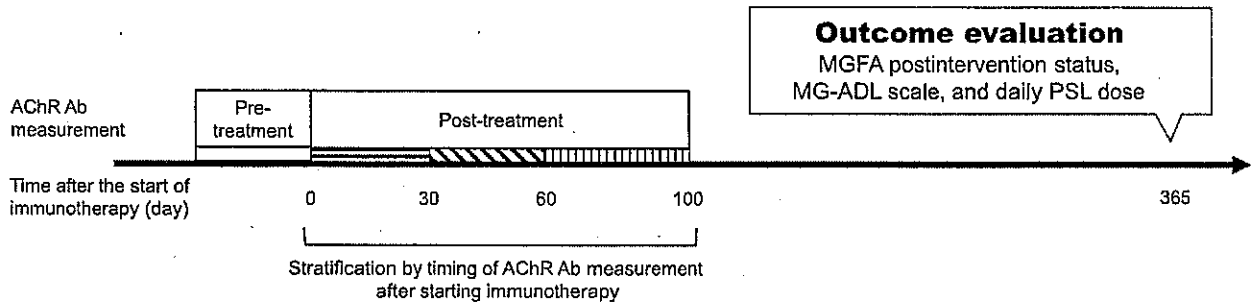

FIGURE 1 Evaluation time of anti-acetylcholine receptor antibody (AChR Ab) titer levels and clinical status. AChR Ab titer levels were measured in the early (within 30 days; $n=33$), middle (31–60 days; $n=34$), and late periods (61–100 days; $n=38$), and the reduction rate of anti-acetylcholine receptor antibody (RR-AChR Ab) was calculated in each period. Clinical status was assessed 1 year after starting immunotherapies. MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; PSL, prednisolone.

1 | INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction characterized by easy fatigability showing diurnal variation. Eighty-five percent of patients with MG have anti-acetylcholine receptor antibodies (AChR Abs).[1,2] While it is established that AChR Abs are strongly involved in MG pathogenesis, AChR Ab titer levels themselves do not reflect inter-patient disease severity. Thus, whether changes in AChR Ab titer levels are markers of disease activity remains unclear.[3–5]

Few patients achieve complete stable remission (CSR) or pharmacologic remission (PR) with conventional MG therapy, as assessed by the Myasthenia Gravis Foundation of America (MGFA) postintervention status.[6] Therefore, the goal of MG treatment is to achieve minimal manifestations or better (MM-or-better) status and to maintain medication side effects as asymptomatic or mild symptoms without requiring intervention.[7,8] Japanese practical guidelines for MG recommend the early MM-or-better status achievement with prednisolone (PSL) at ≤5 mg/day (MM-or-better-5 mg), which is achievable for more patients than CSR or PR and can provide patients a high health-related quality of life.[9,10] Oral PSL ≤5 mg/day status is a key treatment for MG and is described as level 1 low-dose oral monotherapy in the Myasthenia Gravis Status and Treatment Intensity score.[11] Under these circumstances, evaluating the reduction rate of AChR Ab titer levels (RR-AChR Ab) after 71 days (median) of immunosuppressive treatment was suggested to predict MM-or-better status after 1 year of immunosuppressive therapy.[12] However, whether the RR-AChR Ab can be used to predict MM-or-better-5 mg remains unclear. Recently, early fast-acting treatment (EFT) strategies that aggressively use fast-acting treatments (FTs), consisting of intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIg), plasma exchange (PE), and/or their combinations, have been widely used to quickly improve symptoms and reduce oral steroid dosage.[10,13,14] Predicting the treatment effect immediately after starting FTs to develop a subsequent treatment strategy would be useful when implementing FT.

This study aimed (1) to determine the utility of RR-AChR Ab in predicting MM-or-better-5 mg, with a particular emphasis on the health-related quality of life of patients and (2) to determine whether RR-AChR Ab assessment immediately after starting immunotherapies is appropriate for predicting MM-or-better or MM-or-better-5 mg achievement. Furthermore, as EFT strategies have been recommended for MG treatment,[10,14] we also evaluated the association between RR-AChR Ab and early immunotherapies.

2 | METHODS

2.1 | Patients

This retrospective observational study included 83 patients with AChR Ab-positive MG treated at our hospital between 2005 and 2022. The patients' profiles, including the age of onset, sex, presence or absence of a thymoma, MGFA classification,[6] and ELT (early-onset, late-onset, thymoma-associated MG) classification[15] were extracted from their medical records. Changes in the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale scores,[16] MGFA postintervention status, AChR Ab titer levels, and daily dose of oral PSL were additionally investigated. AChR Ab titer levels were measured using radioimmunoassay.

2.2 | Evaluating RR-AChR Ab

The RR-AChR Ab was calculated using a previously reported formula[12] as follows: RR-AChR Ab (%/day) = (pretreatment AChR Ab titer level − posttreatment AChR Ab titer level)/pretreatment AChR Ab titer level/days between starting immunotherapies and measurement of AChR Ab titer levels × 100. AChR Ab measurement was classified into three time periods to determine the optimal timing of RR-AChR Ab evaluation for prognostic prediction: within 30 days after starting immunotherapies (early period), 31–60 days (middle period), and 61–100 days (late period) (Figure 1). If AChR

Ab titer levels were measured multiple times after starting immunotherapies, each result was included in the corresponding period. If multiple measurements were performed during the same period, the highest RR-AChR Ab titer level was used for evaluation.

2.3 | Statistical analyses

Receiver operating characteristic (ROC) analyses of RR-AChR Abs for achieving MM-or-better and MM-or-better-5 mg status 1 year after starting immunotherapies were performed at each evaluation period. If the number of patients who either achieved or failed to achieve this status was <10, the ROC analysis was not performed.[17] Cutoff value was determined using the corresponding Youden index when the area under the curve (AUC) was >0.70 (moderate accuracy). Fisher's exact and Mann–Whitney *U* tests were performed for categorical and continuous variables, respectively, to evaluate differences. The significance level was set at $p < 0.05$. All statistical analyses were performed using EZR[18] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

2.4 | Ethics

The Research Ethics Committee of Kagawa University Faculty of Medicine approved this study (approval number: 2022-018). The contents of this study were published on the website of Kagawa University Hospital, and the patients were free to opt out of participating in the study.

3 | RESULTS

3.1 | Patient profile

Of the 83 patients with MG, we excluded 14 who did not receive immunotherapy (IVMP, IVIg, PE, oral PSL, tacrolimus [TAC], or cyclosporin A [CSA]), 13 who did not undergo AChR Ab measurement during the follow-up period, and three who were not followed up after 1 year of immunotherapy. Therefore, a total of 53 patients were included in the analysis. Patient profiles are shown in Table 1.

3.2 | Relationship between patient profile and outcomes

3.2.1 | MM-or-better status achievement

The MG-ADL scale score was significantly lower in the achieving group than in the nonachieving group before ($p = 0.021$) and after ($p = 0.001$) immunotherapy. In the nonachieving and achieving groups, thymoma was present in 4/6 (67%) and 12/47 patients

TABLE 1 Demographic data of patients.

Characteristics	*n* = 53
Age of onset (years)	63.1 (19.9–84.7)
Sex (male:female) (*n*)	20:33
MGFA classification before immunotherapy (I:II:III:IV:V) (*n*)	16:27:5:2:3
ELT classification (early-onset:late-onset:thymoma-associated) (*n*)	7:30:16
MG-ADL scale	
Before immunotherapy	6 (0–21)
One year after starting immunotherapies	0 (0–16)
AChR Ab titer level	
Before immunotherapy (nmol/L)	48.9 (0.5–1400)
One year after starting immunotherapies (nmol/L)	7.5 (0.3–775)
MM or better status	
One year after starting immunotherapies (*n*)	47 (89%)
At daily PSL dose of ≤5 mg 1 year after starting immunotherapies (*n*)	24 (45%)
Fast-acting treatment (*n*)	35 (66%)
IVMP:IVIg:PE (*n*)	26:19:2
Oral immunosuppressive treatment (only PSL:PSL + TAC:only TAC:PSL + CSA:PSL + TAC + CSA) (*n*)	24:24:1:1:1
Daily oral PSL dose 1 year after starting immunotherapies (mg/day)	6 (0–30)

Note: Data are presented as medians (full range) or numbers (percentages).

Abbreviations: AChR Ab, anti-acetylcholine receptor antibody; CSA, cyclosporin A; ELT, early-onset, late-onset, thymoma-associated myasthenia gravis; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; PE, plasma exchange; PSL, prednisolone; TAC, tacrolimus.

TABLE 2 Comparison of patient background and treatment between the achieving (MM-or-better or MM-or-better-5 mg) and nonachieving groups 1 year after starting immunotherapies.

Characteristics	MM-or-better			MM-or-better-5 mg		
	Achieving ($n=47$)	Nonachieving ($n=6$)	p-Value	Achieving ($n=24$)	Nonachieving ($n=29$)	p-Value
Age of onset (years)	65.3 (19.9–84.7)	61.2 (33.6–81.9)	0.933[a]	67.45 (19.9–84.7)	60.9 (29.4–81.9)	0.205[a]
Sex (male:female) (n)	19:28	1:5	0.390[b]	12:12	8:21	0.154[b]
MGFA classification before immunotherapy (I:II:III:IV:V) (n)	16:22:4:2:3	0:5:1:0:0	0.274[b]	9:10:2:1:2	7:17:3:1:1	0.709[b]
ELT classification (early-onset:late-onset:thymoma-associated) (n)	7:28:12	0:2:4	0.151[b]	2:17:5	5:13:11	0.164[b]
MG-ADL scale						
Before immunotherapy	6 (0–21)	10 (7–13)	0.021[a]	6 (0–21)	8 (4–15)	0.090[a]
One year after starting immunotherapies	0 (0–4)	13 (2–16)	0.001[a]	0 (0–4)	0 (0–16)	0.056[a]
AChR Ab titer level						
Before immunotherapy (nmol/L)	47.9 (0.5–1400)	66.55 (21.2–135.0)	0.299[a]	25.6 (0.5–958.5)	68.4 (1.1–1400)	0.008[a]
One year after starting immunotherapies (nmol/L)	6.5 (0.3–775)	35.95 (10.9–91.1)	0.014[a]	2.3 (0.3–430)	16.85 (0.6–775)	0.001[a]
Fast-acting treatment (n)	31 (66%)	4 (67%)	1.0[b]	19 (79%)	16 (55%)	0.085[b]
IVMP (n)	24 (51%)	2 (33%)	0.669[b]	16 (67%)	10 (34%)	0.028[b]
IVIg (n)	15 (32%)	4 (67%)	0.172[b]	8 (33%)	11 (38%)	0.780[b]
PE (n)	1 (2%)	1 (17%)	0.216[b]	1 (4%)	1 (3%)	1.0[b]
Oral immunosuppressive treatment						
PSL only (n)	24 (51%)	0 (0%)	0.027[b]	7 (29%)	17 (59%)	0.052[b]
PSL + TAC (n)	19 (40%)	5 (83%)	0.080[b]	14 (58%)	10 (34%)	0.102[b]
Daily oral PSL dose 1 year after starting immunotherapies (mg/day)	5 (0–30)	13.75 (5–22.5)	0.058[a]	5 (0–5)	10 (5–30)	<0.001[a]

Note: Data are presented as medians (full range) or numbers (percentages). a: Mann–Whitney U-test; b: Fisher's exact test. The significance level was set at $p<0.05$.

Abbreviations: AChR Ab, anti-acetylcholine receptor antibody; ELT, early-onset, late-onset, thymoma-associated myasthenia gravis; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MM-or-better, minimal manifestations or better status; MM-or-better-5 mg, minimal manifestations or better status at daily prednisolone doses of ≤5 mg; PE, plasma exchange; PSL, prednisolone; TAC, tacrolimus.

(26%), respectively. AChR Ab titer levels were not significantly different between the achieving and nonachieving groups before immunotherapy but were significantly lower in the achieving group than in the nonachieving group 1 year after starting immunotherapies ($p=0.014$). The difference in the FT rate between the two groups was insignificant; however, all patients in the nonachieving group received not only PSL but also TAC or CSA.

3.2.2 | MM-or-better-5 mg achievement

The difference in the MG-ADL scale scores between the achieving and nonachieving groups before or after starting immunotherapies was insignificant. Contrastingly, AChR Ab titer levels were significantly lower in the achieving group than in the nonachieving group before ($p=0.008$) and after ($p=0.001$) starting immunotherapies. IVMP as an FT was used significantly more frequently in the achieving group than in the nonachieving group ($p=0.028$; Table 2).

3.3 | Evaluating RR-AChR Ab

RR-AChR Ab titer levels were calculated in 33, 34, and 38 patients during the early, middle, and late periods, respectively. Because only six patients failed to achieve MM-or-better status, ROC analysis was not performed for the same. The AUC of the ROC curves for predicting MM-or-better-5 mg after 1 year were 0.75, 0.64, and 0.69 for the early, middle, and late periods, respectively. Only the AUC for the early period showed moderate accuracy in predicting MM-or-better-5 mg achievement. The median time from starting immunotherapies to measuring of AChR Ab titer levels in the early period was 21 days (range: 7–30). The cutoff value of the RR-AChR Ab

titer levels determined using the corresponding Youden index was 1.68%/day (sensitivity, 85%; specificity, 70%) (Figure 2).

3.4 | Characteristics of patients with high RR-AChR Ab titer levels in the early period

Patients with high RR-AChR Ab titer levels (>1.68%/day; $n=17$) were compared with those with low RR-AChR Ab titer levels (≤1.68%/day; $n=16$) in the early period (Table 3). Differences in the patient background (age of onset, sex, and MGFA and ELT classifications) between the high and low RR-AChR Ab groups were insignificant. Differences in the MG-ADL scale scores and AChR Ab titer levels between the high and low RR-AChR Ab groups before and after starting immunotherapies were insignificant. During the early period, FTs ($p<0.001$), particularly IVMP ($p<0.001$), were used significantly more frequently in the high RR-AChR Ab group than in the low RR-AChR Ab group. Oral immunosuppressive treatment by only PSL was significantly more common in the low RR-AChR Ab group than in the high RR-AChR Ab group ($p=0.037$).

4 | DISCUSSION

This retrospective observational study suggested that assessing the RR-AChR Ab titer levels successfully predicted MM-or-better-5 mg after 1 year of immunotherapy, with the early period (median: 21 days) being the optimal time of assessment after starting immunotherapies. Furthermore, IVMP as an early immunotherapy might have been highly involved in achieving MM-or-better-5 mg 1 year after starting immunotherapies.

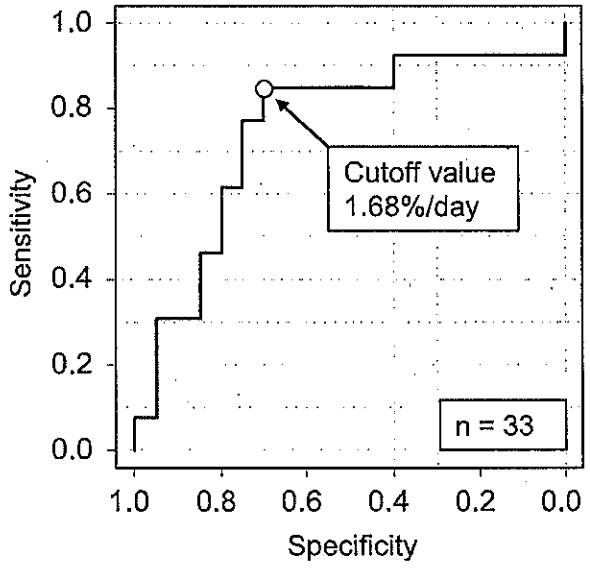

FIGURE 2 An ROC curve for predicting MM-or-better-5 mg 1 year after starting immunotherapies. The reduction rate of anti-acetylcholine receptor antibody (RR-AChR Ab) titer levels in the early period (within 30 days of starting immunotherapies). A cutoff value of 1.68%/day for RR-AChR Ab was able to predict MM-or-better-5 mg achievement (sensitivity, 85%; specificity, 70%). MM-or-better-5 mg, minimal manifestations or better status with daily oral prednisolone ≤5 mg; ROC, receiver operating characteristic; RR-AChR Ab, reduction rate of anti-acetylcholine receptor antibody.

. MM-or-better, a conventional treatment goal,[7,8] was predictable, with a cutoff value of 0.64%/day for RR-AChR Ab (sensitivity, 69%; specificity, 73%).[12] In our study, MM-or-better was achieved in 89% of patients after 1 year of immunotherapy. Therefore, a sufficient sample size for the ROC curve analysis could not be obtained. The higher achievement rate of MM-or-better in our study than that previously reported[12] (79%) might be related to the difference in the severity of patients, as the percentage of MGFA class I patients in our study was 30% compared with 19% in the previous report.[12]

The treatment goal in the international consensus guidance for the management of MG is to achieve MM-or-better status and to maintain medication side effects as asymptomatic or mild symptoms without requiring intervention.[7,8] Meanwhile, MM-or-better-5 mg is a practical and concrete treatment goal that provides patients with a good health-related quality of life as CSR or PR.[9,10,19] This study showed that the 1.68%/day cutoff value for RR-AChR Ab assessed in the early period successfully predicted MM-or-better-5 mg achievement. Recently, EFT significance has been emphasized in achieving early MG improvement and oral PSL dosage reduction, with intermittent FT addition as needed.[10,13,14] Under these circumstances, evaluating RR-AChR Ab titer levels immediately after early immunotherapies might be a useful indicator to determine the treatment strategy (FT repetition or maintenance therapy with a small dose of PSL and nonsteroidal immunosuppressants). In Japan, national health insurance regulations limit nonsteroidal immunosuppressants (calcineurin inhibitors; TAC, and CSA) to low doses such that they do not affect patients' health-related quality of life.[9,19] The 45% rate of MM-or-better-5 mg achievement in this study was comparable to the achievement rates reported in a previous report: 49.4% and 42.1% in the groups with and without EFT,[14] respectively. Based on these results, the cutoff value for RR-AChR Ab titer levels immediately after starting immunotherapies might apply to other cohorts.

Herein, the achievement rate of MM-or-better-5 mg was 65% in the high RR-AChR Ab group and as low as 12% in the low RR-AChR Ab group. Since the illness severity (MG-ADL scale score) between the two groups was similar, the higher frequency of IVMP use in the high-RR-AChR Ab group may have accounted for this difference. This result is consistent with that of previous reports,[20,21] which found that using IVMP, IVIg, and PE within the first 6 months of treatment determined MM-or-better-5 mg after 2 years,[20] and using EFT including IVMP could achieve MM-or-better-5 mg earlier and more frequently.[21] Thus, prompt therapy intensification, such as additional IVMP, may be desirable when the RR-AChR Ab titer level is <1.68%/day in the early period (within 30 days of starting immunotherapies).

This study had a few limitations. First, this was a single-center, retrospective, observational study with a small number of patients. To evaluate the validity of the RR-AChR Ab titer levels to predict

TABLE 3 Comparison of patient characteristics between the high and low RR-AChR Ab groups for the cutoff value of 1.68%/day in the cases where AChR Ab titer levels were evaluated within 30 day of starting immunotherapies.

Characteristics	High ($n = 17$)	Low ($n = 16$)	p-Value
Age of onset (years)	68.1 (19.9–84.7)	50.7 (29.4–79.9)	0.078[a]
Sex (male:female) (*n*)	7:10	4:12	0.465[b]
MGFA classification at the initial visit (I:II:III:IV:V) (*n*)	2:9:2:2:2	4:9:3:0:0	0.434[b]
ELT classification (early-onset:late-onset:thymoma-associated) (*n*)	2:10:5	4:6:6	0.427[b]
MG-ADL scale			
Before immunotherapy	8 (3–21)	7 (4–13)	0.620[a]
One year after starting immunotherapies	0 (0–2)	0 (0–13)	0.219[a]
AChR Ab titer level			
Before immunotherapy (nmol/L)	50.8 (12.8–958.5)	68.9 (1.1–1400)	0.801[a]
One year after starting immunotherapies (nmol/L)	3.1 (0.3–430)	16.85 (0.6–775)	0.095[a]
Time from start of immunotherapy to measurement of AChR Ab (day)	21 (11–30)	23.5 (7–30)	0.415[a]
MM or better status at daily PSL dose of ≤5 mg 1 year after starting immunotherapies (*n*)	11 (65%)	2 (12%)	0.004[b]
Fast-acting treatment during the early period (*n*)	16 (94%)	4 (25%)	<0.001[b]
IVMP (*n*)	11 (65%)	0 (0%)	<0.001[b]
IVIg (*n*)	9 (53%)	4 (25%)	0.157[b]
PE (*n*)	1 (6%)	0 (0%)	1.0[b]
Oral immunosuppressive treatment during the early period			
PSL only (*n*)	6 (35%)	12 (75%)	0.037[b]
PSL + TAC (*n*)	8 (47%)	3 (19%)	0.141[b]

Note: Data are presented as medians (full range) or numbers (percentages). a: Mann–Whitney *U*-test; b: Fisher's exact test. The significance level was set at $p < 0.05$.

Abbreviations: AChR Ab, anti-acetylcholine receptor antibody; ELT, early-onset, late-onset, thymoma-associated myasthenia gravis; IVIg, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; PE, plasma exchange; PSL, prednisolone; RR-AChR Ab, reduction rate of anti-acetylcholine receptor antibody; TAC, tacrolimus.

MM-or-better-5 mg, a multicenter prospective study of a large number of patients with a standardized initial treatment regimen and RR-AChR Ab assessment timing is needed. Second, the clinical significance of RR-AChR Ab was not validated as an indicator for developing a treatment strategy after the early immunotherapies to achieve early treatment goals. Achieving an early MM-or-better-5 mg through additional FT in patients with low RR-AChR Ab should be further investigated.

In conclusion, RR-AChR Ab calculated within 30 days of starting immunotherapies was useful in predicting MM-or-better-5 mg achievement after 1 year in patients with AChR Ab-positive MG. A high RR-AChR Ab predicted MM-or-better-5 mg achievement and was obtained in patients receiving EFT, especially IVMP. In patients with low RR-AChR Ab titer levels, FT addition could potentially accelerate MM-or-better-5 mg achievement. Large prospective multicenter studies are required to evaluate the clinical significance of RR-AChR Ab in treating MG.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest for this article.

DATA AVAILABILITY STATEMENT

Data are available upon request owing to privacy/ethical constraints.

PATIENT CONSENT STATEMENT

The contents of this study were published on the website of Kagawa University Hospital, and the patients were free to opt out of participating in this study.

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