Title: Factors Affecting Outcome in Myasthenia Gravis

Author information:

Jintana B. Andersen, MD, PhD[1], Nils Erik Gilhus, MD, PhD[1,2], Donald B. Sanders, MD[3]

1. Department of Clinical Medicine, University of Bergen, Bergen, Norway

2. Department of Neurology, Haukeland University Hospital, Bergen, Norway

3. Department of Neurology, Duke University Medical Center, Durham, North Carolina, USA

Corresponding author:

Dr. Jintana B. Andersen, University of Bergen, Department of Clinical Medicine, Jonas Lies vei 87, 5021 Bergen, Norway

Email address: Jintana.Andersen@k1.uib.no

Telephone and fax: +47 99 03 28 18/+47 55 97 51 65

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NE Gilhus: Drafted and revised manuscript.

DB Sanders: Clinical assessment of patients, study design, statistical analysis, drafted and revised manuscript.

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ABSTRACT

Methods & Aims: Information from myasthenia gravis (MG) patients treated and evaluated for at least 2 years between 1980 and 2014 was reviewed to assess the effect of demographics, antibody status and titer, thymus histology, and clinical severity on outcome after 2, 5, and 10 years of treatment.

Results: Among 268 patients, 74% had acetylcholine receptor-antibodies, 5% had muscle specific tyrosine kinase-antibodies, and 22% had neither. Optimal outcome was achieved by 64% of patients at 2 years of follow-up, 73% at 5 years, and 75% after 10 years. Optimal outcome was achieved more often in patients with late onset, in those who had thymectomy, and in those with ocular-only disease at maximum severity. The only consistent independent predictor of Optimal outcome was onset after age 50 years after multivariate analysis.

Conclusions: Prognosis is favorable for the majority of MG patients, regardless of age, maximum disease severity, or antibody status.

Introduction

Acquired myasthenia gravis (MG) is a rare neuromuscular junction (NMJ) disorder, with autoantibodies that target mainly the acetylcholine receptor (AChR) (1-2) or muscle-specific tyrosine kinase (MuSK) (3). Autoantibodies against other important NMJ proteins such as lipoprotein receptor-related protein 4 (LRP4) and agrin (4-5), striated muscle antibodies, and a range of other autoantibodies found in thymomatous MG (6), indicate that MG is a heterogeneous disease (7). The prevalence of MG is rising, principally due to decreased mortality and partly due to increasing incidence in older age groups (8-9), improved care, and better case ascertainment. Established management provides symptomatic relief that can induce stable remission, and promising new treatments are emerging (10-11). Nevertheless, the clinical course of MG in most patients is still characterized by exacerbations and remissions (7).

Prognostic markers could help predict the clinical response to different treatments and guide treatment decisions in MG. Studies to determine such markers have used heterogeneous designs and various measurements of clinical severity and outcome (12). With the goal of identifying factors that influence outcome, we describe and evaluate the clinical course and outcome of MG patients followed for over 3 decades, using a consistent treatment approach and standardized outcome measures.

Patients and Methods

This project was approved by the Duke University Medical Center Institutional Review Board, and informed consent for this study was waived. Data were obtained from the Duke MG Patient Database for patients seen in the Duke MG Clinic between July 1, 1980 and December 31, 2014. This physician-derived database contains comprehensive demographic

and clinical information on all in- and out-patients seen in the MG clinic at Duke University Medical Center since 1980. The database is updated after each visit following a standardized evaluation of the patient's clinical status. Acquired MG was defined by the following 3 criteria, all of which should be fulfilled:

1. Patients were normal at birth and later developed weakness.
2. Abnormal neuromuscular transmission was demonstrated by 1 or more of the following, and there was no other neuromuscular disease present to produce these findings: a decrementing response to repetitive nerve stimulation, increased jitter on single-fiber EMG, or positive edrophonium test.
3. AChR antibodies or MuSK antibodies were elevated, or there was unequivocal improvement after thymectomy and/or immunomodulatory therapy.

Only patients who had been treated by the same neurologist (DBS) with follow-up data for at least 2 years were included. Treatment was individualized for each patient according to the general treatment algorithm in figure 1, with the primary goal of achieving a Myasthenia Gravis Foundation of America (MGFA) Post-Intervention Status (PIS) of Minimal Manifestations or better (13), with no more than mild side-effects. Secondary treatment goals were to reduce the number of treatment modalities and the dose of all medications to the minimum necessary to maintain the optimum clinical response. For example, once clinical benefit was seen, the cholinesterase inhibitor dose was reduced to the minimal amount that produced demonstrable clinical benefit, or discontinued, if tolerated.

Thymectomy was recommended in all patients with generalized MG and onset before 50 years, regardless of serology, including those with MuSK antibodies. Thymectomy was also performed in some patients with onset after age 50 if treatment goals had not been achieved with other treatments. Thymectomy was performed by a sternal-splitting approach in most

patients, and all thymic tissue was examined histologically. Prednisone was usually begun at a high daily dose, typically 60 mg/day, and tapered on an alternate day dose schedule once clinical benefit had been present for at least 3 days. In recent years, plasma exchange (PLEX) was performed prior to beginning high-dose prednisone to prevent or minimize exacerbations. In some patients with purely ocular MG, prednisone was begun at a lower dose, typically 20mg/day, and adjusted up or down, depending on the clinical response. Azathioprine, mycophenolate, or cyclosporine were added as steroid-sparing agents and as initial immunosuppression if steroids were contraindicated or produced unacceptable side-effects.

The following variables were examined: Age of onset (defined as first symptoms attributed to MG), gender, race, presence and concentration of autoantibody, thymus histology, treatment modalities, the MGFA clinical classification (13) at maximum severity, and the MGFA PIS at 2, 5, and 10 years of follow-up and at the last visit. Patients were grouped according to their antibody status: AChR-antibody positive, MuSK-antibody positive, or double negative, i.e., AChR-antibody negative and MuSK-antibody negative. Thymus histology was categorized as either normal (including fatty, cystic, and atrophic thymuses), hyperplastic, or thymoma. MG onset before age 50 was defined as early onset. Information missing from the registry was, if possible, completed by reviewing the medical records.

Disease distribution and severity was categorized as ocular (MGFA class 1), or mild (MGFA class 2A and 2B), moderate (MGFA class 3A and 3B), or severe (MGFA class 4A, 4B and 5) generalized MG. In patients who had received PLEX or intravenous immunoglobulin, clinical assessments were performed at least 4 weeks after the last treatment. Outcome categories were defined as:

"Optimal" - MGFA PIS of Minimal Manifestations (MM), Pharmacological Remission (PR), or Complete Stable Remission (CSR)

"Intermediate" - MGFA PIS category Improved (IMP)

"Poor" – MGFA PIS categories Unchanged (UNC) and Worse (W).

Therapy was categorized as:

"no treatment"

"acetylcholinesterase inhibitor only"

"thymectomy only"

"immunosuppressive drugs only"

"combination therapy" - 2 or more of the above therapy modalities.

Statistical analyses

Differences in baseline characteristics among the antibody groups were assessed by the Fisher exact test for categorical variables and non-parametric tests for continuous variables. The Wilcoxon signed-rank test was used to compare the rate of Optimal outcome at 2 and 5 years, and at 5 and 10 years. The cumulative chance of achieving Optimal outcome in different groups was assessed by Kaplan-Meier analysis. Differences between the survival curves were evaluated by the log-rank test. Variables with significant differences in survival curves were evaluated by the Cox proportional hazards regression analysis. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Two-sided *P*-values < 0.05 were considered statistically significant. Statistical significance in the regression model was calculated using the Wald Chi-Square test. All statistical analyses were performed using JMP®, 11.2 (SAS Institute Inc. Cary, NC, USA).

Results

Follow-up information of at least 2 years was available for 268 patients. One hundred ninety-seven patients had elevated AChR-antibodies (74%), 13 had MuSK-antibodies (5%), and 58 were double negative (22%). The main clinical and demographic characteristics of the study population are given in table 1. The study population consisted of more males (57%) than females. AChR-positives were more often Late Onset (56%), male (62%), and white (82%) compared to MuSK-positives, who were predominantly Early Onset (92%), female (92%), and African-American (62%). Patients without AChR- or MuSK-antibodies were more often Early Onset (52%), male (52%), and white (78%).

Thymectomy was performed in 110 patients (40%), and at different rates among the antibody groups (P=0.02). Over 50% of MuSK-positives underwent thymectomy compared to 26% of the double negatives and 45% of AChR-positives. Of those undergoing thymectomy, 42% had normal thymus histology, 38% had hyperplastic thymus, and 20% had thymoma, with no differences among the antibody groups. All 22 patients with thymoma were AChR-positive; they constituted 25% of all AChR-positives who underwent thymectomy. For the remaining AChR-positive thymectomy patients, 38% had normal thymus histology, and 37% had a hyperplastic thymus. Among the 7 MuSK-positive thymectomy patients, thymus histology was normal in 4 and hyperplastic in 3. Of the 15 double negative thymectomy patients, thymus histology was normal in 9 and hyperplastic in 6.

The distribution of maximum weakness differed among the antibody groups (P<0.001) (figure 2). Patients with moderate or severe weakness at maximum represented 56% of the study population; only 13% had purely ocular manifestations at least 2 years after onset. Among the AChR-positives, 8% had purely ocular weakness, with a similar frequency of mild (30%), moderate (33%), and severe (29%) weakness. Among the MuSK-positive patients, none had purely ocular weakness at maximum, only 15% had mild disease at maximum, and the majority had either moderate (35%) or severe weakness (46%). Among the double negative

patients, the maximum weakness was either ocular (36%) or mild (38%) in most; only 12% and 14% had moderate or severe weakness at maximum, respectively.

Among the AChR-positive patients, the mean antibody level ranged from 5.4 to 21.1 nM/L among the different MGFA classes (P=0.01), being lowest in the ocular patients (5.4 nM/L, ± 7.8) and highest in patients with moderate weakness (21.1 nM/L, ± 48.1). AChR-antibody levels were similar in patients with mild (14.4 ± 23.8 nM/L) and severe generalized weakness (15.2 ± 23.2 nM/L). Mean AChR-antibody levels were not significantly different among the different thymic histology groups (P=0.1); the highest mean concentration (37.9 nM/L) was in the hyperplastic group (table 2).

Clinical severity was different among the antibody groups at 2 (P=0.02) and 5 years of follow-up (P=0.02) and at the last visit (P=0.005), but not at 10 years follow-up (figure 3 and supplementary table S1, available online), probably because too few patients were followed that long. At 2 years, 30% of the AChR-positive, 26% of the double negative, and 15% of the MuSK-positive patients were in PR or CSR. MuSK-positive patients had more severe weakness at initial presentation, but the majority had mild weakness throughout the subsequent follow-up periods. The proportion of patients in PR or CSR was similar throughout the follow-up periods for the AChR-positive and double negative patients.

The treatment at different time points is shown in tables 3 and 4, and there was no difference among the antibody groups (data not shown). Four patients (1%) received no treatment and were in CSR at their last clinic visit, i.e. in spontaneous remission. Of these, 2 were AChR-positives, and 2 were double negative. Twelve percent of all thymectomized patients were in CSR at the last visit; 10 were AChR-positive, 1 was MuSK-positive, and 2 were double negative. The proportion of thymectomized patients in CSR at their last visit did not differ among the antibody groups (table 1).

Outcome was not different among the different antibody groups at any time point (figure 4 and supplementary table S2, available online). Clinical information was complete for 262 patients (98%) at 2 years of follow-up, at which time 65% had achieved an Optimal and 27% an Intermediate outcome. Optimal outcome was achieved in 68% of AChR-positives, 57% of double negatives, but only 38% of the MuSK-positives at 2 years. Overall, 4% of all patients were in CSR at this time point, including 5% of the AChR-positive and 4% of the double negative patients. No MuSK-positive patients were in CSR at 2 years. The majority of MuSK-positive patients (54%) had an Intermediate outcome at 2 years, compared to 23% and 36% of the AChR-positive and double negative patients, respectively. At 2 years of follow-up, 8% of all patients had a Poor outcome: 9% of the AChR-positive, 8% of the MuSK-positive, and 7% of the double negative patients.

Clinical information was complete for 213 patients (80%) at 5 years of follow-up, at which time 73% had achieved an Optimal outcome: 76% of the AChR-positive, 40% of the MuSK-positive, and 72% of the double negative patients. The rate of Optimal outcome did not differ at 5 years compared to 2 years of treatment (P=0.3). At 5 years of follow-up 7% of patients were in CSR, and 6% had a Poor outcome.

At 10 years of follow-up, clinical information was complete for 44% of the patients, of whom 75% had an Optimal outcome: 79% of the AChR-positive, 50% of the MuSK-positive, and 68% of the double negative patients. Only 3% had a Poor outcome at that time point. Eight patients (7%) were in CSR, none of whom were MuSK-positive. The Optimal outcome rate did not differ at 5 and 10 years (P=0.5).

The mean follow-up time was 10.6 years (±6.7, interquartile range 5.8, 14.2), with no difference among the antibody groups. At their last visit, 67% of all patients had achieved an Optimal outcome: 70% of the AChR-positive, 46% of the MuSK-positives, and 62% of the

double negative patients. Only 8% had a Poor outcome at their last visit: 7% of the AChR-positive, 8% of the MuSK-positive, and 12% of the double negative patients. Eight percent were in CSR at their last clinic visit, with similar frequencies among the groups.

The probability of achieving an Optimal outcome did not differ among the antibody groups at any time point (table 5). At 2 and 5 years of follow-up, the probability of achieving an Optimal outcome differed according to age (P=0.001 at both time points), race (P<0.001 at both time points), thymectomy (P=0.003 and P=0.01, respectively), and maximum disease severity (P=0.006 and $P=0$.02, respectively). After adjusting for these variables in the Cox model (table 6), independent predictors of Optimal outcome were: onset after age 50 years (HR: 1.7, 95% CI 1.1, 2.6, P=0.01), Other race, i.e. not White or African-American (HR: 10.2, 95% CI 2.9, 35.7, P<0.001, and HR: 32.8, 95% CI 6.5, 165.4, <0.001, respectively), and ocular class at maximum severity (HR: 2.3, 95% CI 1.3, 4.1, P=0.004 and HR: 2.2, 95% CI 1.2, 3.9, P=0.01, respectively). Thymectomy was not an independent predictive factor for Optimal outcome. Also, at 10 years of follow-up, the probability of achieving Optimal outcome differed according to onset age (P<0.001), thymectomy (P=0.001), and disease distribution at maximum severity (P=0.02). Race was not a significant predictive factor of Optimal outcome. After adjusting in the Cox model, only onset after age 50 years (HR: 3.9, 95% CI 2.0, 7.4, P<0.001) independently predicted Optimal outcome. At their last clinic visit, Optimal outcome differed according to onset age (P=0.006), thymectomy (p=0.045) and disease distribution at maximum severity (P=0.01). Only onset after age 50 (HR: 1.5, 95% CI 1.0, 2.2, P=0.03), and ocular class at maximum disease severity (HR: 2.1, 95% CI 1.3, 3.6, P=0.005) remained as independent predictors of Optimal outcome at the last clinic visit.

Discussion

In this review of MG patients treated and evaluated in a consistent fashion over 3 decades, we demonstrate that age at onset was the most consistent independent predictor of both short- and long-term outcome. In addition, disease distribution at maximum severity independently predicts the short-term outcome, but not the long-term outcome. We found distinct clinical differences among the 3 antibody groups, with differences in clinical severity early in the course of the disease. Nevertheless, the chance of achieving an Optimal outcome did not differ among the 3 antibody groups. The rate of spontaneous remission was only 1%, with no differences in the rate among the antibody groups. However, this comparison was based on very small numbers.

This study has several strengths. The data are longitudinal and comprehensive. The patients studied were followed by the same neurologist over 34 years, minimizing evaluation bias, and using the same overall treatment approach.

Our findings show that MG onset after age 50 years increased the chances for an Optimal outcome. This is in contrast to previous similar studies where Late onset is associated with a poorer prognosis (7-14). There is a potential referral bias to our clinic towards patients with more severe disease, but this bias is expected to be the same for all age groups. It is probable that older patients are more aggressively treated in our clinic: 87% of patients over age 50 were treated with an immunosuppressive agent, either alone, or in combination with another treatment modality. In a nationwide Norwegian population with no selection bias, only 56% of patients over age 50 were treated with immunosuppressive medications (15). In a hospital-based Israeli population, 65% of patients over 69 years were treated with prednisone (16), of whom 90% improved, with no difference in therapeutic response for Early and Late onset. In our study, outcome was not related to treatment modality.

The clinical distribution at maximum weakness differed among the 3 antibody groups. However, the chance of achieving Optimal outcome did not differ for Mild or Moderate compared to Severe disease, which is in line with previous reports (17-19). Ocular patients were more likely to achieve an early Optimal outcome, but the later outcome did not differ from those with generalized disease. The MuSK-positive patients had more severe disease than AChR-positive and double negative patients, as demonstrated by the higher proportion with moderate and severe maximum weakness. None of our MuSK-positive patients had purely ocular symptoms at maximum disease severity. Nevertheless, the majority of these patients achieved an Optimal or Intermediate outcome, a similar long-term prognosis as AChR-positive patients, in accordance with previous studies (20-22). A higher proportion of MuSK-positives had Severe disease at maximum weakness. More distinct MG subgroup-specific treatment strategies in the future would most likely reduce the gap in severity between MuSK and AChR-antibody positive disease (23).

Thymectomy was performed in both double negative and MuSK-positive patients. The role of thymectomy in these 2 groups is still unclear (24-25). Univariate analysis at all time-points clearly indicates that thymectomy is associated with a favorable outcome overall. The majority of the thymectomized patients in our study were AChR-positives. Nevertheless, thymectomy represents a selection bias towards more severe disease (18), in that this group includes all patients with thymoma, all but 1 of whom had generalized weakness. This may explain why thymectomy does not independently predict outcome after adjusting for age at onset and disease severity. Also, loss to follow-up is a potential problem when interpreting the long-term outcome in thymoma patients due to the small numbers. Comprehensive information on deaths was not available in our database, but our findings are in line with previously reported outcomes for thymoma patients (26).

All thymoma patients were AChR-positive, but otherwise we found no difference in AChR-antibody level according to thymus histology. The chance of achieving Optimal outcome was also the same for the different thymus histology. There was a difference in AChR-antibody concentration according to the clinical distribution at maximum disease severity. However, a low AChR-antibody level was not associated with a higher chance of achieving Optimal outcome. This is in line with previous reports that antibody level does not correlate with clinical severity (27-29).

In conclusion, prompt interventions and aggressive treatment strategies early in the course of MG enhance the ultimate outcome. Both short- and long-term prognosis is favorable for the majority of patients, regardless of age, maximum disease severity and antibody findings.

Abbreviations

AChR; acetylcholine receptor

CSR; complete stable remission

DBS; Donald B. Sanders

DN; double negative

HR; hazard ratio

IMP; improved

LRP4; lipoprotein receptor-related protein 4

MG; myasthenia gravis

MGFA; Myasthenia Gravis Foundation of America

MuSK; muscle-specific tyrosine kinase

MM; minimal manifestations

PIS; Post-Intervention Status

PLEX; plasma exchange

PR; pharmacologic remission

UNC; unchanged

W; worse

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Captions/legends

Figure 1. Treatment algorithm.

Figure 2. Maximum severity.

Figure 3. Clinical severity at 2, 5, and 10 years of follow-up and at last clinic visit according to the different antibody status.

Figure 4. Outcome at 2, 5, and 10 years of follow-up and at last clinic visit according to antibody status.

Table 1. Clinical characteristics of 268 MG patients, 1980-2014.

	All	AChR-positive	MuSK-positive	Double Negative	
	n=268	n=197 (74%)	n=13 (5%)	n=58 (22%)	*P-value**
Age at onset, years, mean (SD)	48 (19.7)	49 (20.2)	31 (14.1)	45 (17.5)	0.002
Age groups					0.002
Early onset (< 50 years)	128 (48)	86 (44)	12 (92)	30 (52)	
Late onset (≥ 50 years)	140 (52)	111 (56)	1 (8)	28 (48)	
Gender					<0.001
Female	114 (43)	74 (38)	12 (92)	28 (48)	
Male	154 (57)	123 (62)	1 (8)	30 (52)	
Race†					0.006
White	211 (79)	161 (82)	5 (38)	45 (78)	
African-American	51 (19)	33 (17)	8 (62)	10 (17)	
Other	5 (2)	3 (2)	0	2 (3)	
Thymectomy	110 (40)	88 (45)	7 (54)	15 (26)	0.02
Thymus histology‡					0.1
Normal/fatty/cystic/atrophic	46 (42)	34 (38)	4 (57)	9 (60)	
Hyperplastic	42 (38)	33 (37)	3 (43)	6 (40)	
Thymoma	22 (20)	22 (25)	0	0	
Antibody level, nM/L**,** mean (SD)	11.9 (29.4)	16.2 (33.3)	0.01 (0.02)	0.03 (0.2)	<0.001
Severity at maximum weakness					<0.001
Ocular (MGFA Class I)	36 (13)	15 (8)	0	21 (36)	
Mild (MGFA Class 2A and 2B)	84 (31)	60 (30)	2 (15)	22 (38)	
Moderate (MGFA Class 3A and 3B)	77 (29)	65 (33)	5 (39)	7 (12)	

Severe (MGFA Class 4A, 4B and 5)	71 (27)	57 (29)	6 (46)	8 (14)	
Rate of CSR at last visit					
Thymectomy‡	13 (12)	10 (11)	1 (14)	2 (13)	0.6
Never treated	4 (1)	2 (1)	0	2 (3)	NA

MG=Myasthenia gravis, SD=standard deviation, AChR=acetylcholine receptor, MuSK=muscle-specific tyrosine kinase, nM/L=nano mol per liter, MGFA=Myasthenia Gravis Foundation of America. Percentages (%) are calculated from the total number of patients in the respective columns unless otherwise specified.*Fisher exact test was used for comparison of categorical variables and non-parametric test for continuous variables among the 3 antibody groups.†Race was unknown for 1 patient.‡(%) of all thymectomies (n=110), in AChR-positive (n=88), MuSK-positive (n=7), DN (n=15). NA=not assessed.

Table 2. Maximum AChR antibody levels.

	AChR antibody level (nM/L)				
	n (%)	mean (SD)	median	interquartile range	*P-value**
Distribution/severity†					0.01
Ocular (MGFA class 1)	15 (8)	5.4 (7.8)	1.4	0.3 - 10.6	
Mild (MGFA class 2A and 2B)	60 (30)	14.4 (23.8)	4.0	0.6 - 15.2	
Moderate (MGFA class 3A and 3B)	65 (33)	21.1 (48.1)	8.9	3.2 - 18.5	
Severe (MGFA class 4A, 4B and 5)	57 (29)	15.2 (23.2)	5.4	3.2 - 19.6	
Thymus histology‡					0.1
Normal/fatty/cystic/atrophic	34 (38)	10.9 (19.8)	3.2	0.8 - 9.1	
Hyperplastic	33 (37)	37.9 (70.6)	5.8	0.4 - 55.0	
Thymoma	22 (25)	13.7 (13.1)	9.8	3.5 - 22.6	

MG=Myasthenia gravis, AChR=acetylcholine receptor, MGFA=Myasthenia Gravis Foundation of America, nM/L=nano mol per liter.*Non-parametric rank sums tests were used to compare maximum mean AChR antibody levels across categories of distribution/severity and thymus histology.†(%) of all AChR-positives (n=197).‡(%) of all thymectomies in AChR antibody positives (n=89).

Table 3. Mode of treatment at 2, 5, and 10 years of follow-up and at the last visit for 268 MG patients, 1980-2014.

	Years of follow-up			
	Two	Five	Ten	Last visit
Treatment modality	*n=263 (98%)*	*n=213 (79%)*	*n=116 (43%)*	*n=268 (100%)*
No treatment	13 (5)	6 (3)	2 (2)	18 (7)
AChE-I only	19 (7)	8 (4)	3 (3)	12 (5)
Thymectomy only	20 (8)	18 (8)	13 (11)	20 (7)
Immunosuppressive only*	106 (40)	78 (37)	46 (40)	104 (39)
Combination therapy	105 (40)	103 (48)	52 (45)	114 (43)
AChE-I + thymectomy†	9 (8)	6 (6)	2 (4)	7 (6)
AChE-I + immunosuppressive†	15 (14)	22 (21)	9 (17)	22 (20)
Thymectomy + immunosuppressive†	64 (61)	62 (60)	34 (65)	63 (55)
All combinations†	17 (16)	13 (13)	7 (13)	22 (19)

AChE-I=Acetylcholinesterase-inhibitor.*One or more immunosuppressive drugs. Percentages (%) are calculated from the number of patients from the respective columns (the number of patients at each time point) unless otherwise specified. †Percentages (%) are calculated from the number of patients with combination therapy at each time point.

Table 4. Immunosuppressive drugs used in 268 MG patients, 1980-2014.

	Years of follow-up			
Immunosuppressive drug*	Two *n=263 (98%)*	Five *n=213 (79%)*	Ten *n=116 (43%)*	Last visit *n=268 (100%)*
Prednisone alone	67 (25)	47 (22)	22 (19)	60 (22)
Prednisone + one or more immunosuppressive drug	83 (32)	57 (27)	37 (32)	54 (20)
Azathioprine	65 (25)	61 (29)	33 (28)	65 (24)
Mycophenolate mofetil	38 (14)	42 (20)	29 (25)	67 (25)
Cyclosporin A	37 (14)	29 (14)	14 (12)	24 (9)
Rituximab	0	1 (0)	0	2 (1)
≥ 2 immunosuppressives	85 (32)	61 (29)	38 (33)	59 (22)

*Used alone or in combination with another (≥1 immunosuppressive drug. Percentages (%) are calculated from the number of patients from the respective columns (the total number of patients at each time point) unless otherwise specified.

Table 5. Predictive value of different factors for Optimal outcome.

	Years of follow-up			
	Two	*Five*	*Ten*	*Last visit*
Factor	Log-Rank test *P- value**	Log-Rank test *P- value**	Log-Rank test *P- value**	Log-Rank test *P- value**
Age at onset				
Early vs Late onset	0.001	0.001	<0.001	0.006
Gender				
Female vs Male	NS	NS	NS	NS
Race				
White vs African-American vs Other	<0.001	<0.001	NS	NS
Antibody status				
AChR-positive vs DN vs MuSK-positive	NS	NS	NS	NS
Thymectomized				
Yes vs No	0.003	0.01	0.001	0.045
Thymoma				
Yes vs No	NS	NS	NS	NS
Antibody level				
(Low vs Intermediate vs High)	NS	NS	NS	NS
Thymus histology				
Normal vs Hyperplasia vs Thymoma	NS	NS	NS	NS
Distribution				
Ocular vs Mild vs Moderate vs Severe	0.006	0.02	0.02	0.01

AChR=acetylcholine receptor, DN=double negative, MuSK=muscle-specific tyrosine kinase.*Differences in Optimal outcome between subgroups were analyzed by the Kaplan-Meier method. NS=not significant.

Table 6. Multivariate analysis of the cumulative predictive value for Optimal outcome.

	Years of follow-up											
	Two			*Five*			*Ten*			*Last visit*		
Factor	HR*	95% CI	*p*	HR*	95% CI	*p*	HR*	95% CI	*p*	HR*	95% CI	*p*
Age at onset†												
Early onset	1			1			1			1		
Late onset	1.7	1.1, 2.6	0.01	1.7	1.1, 2.7	0.01	3.9	2.0, 7.4	<0.001	1.5	1.0, 2.2	0.03
Race												
White	1			1								
Afr.-Am.	1.1	0.7, 1.8	NS	1.0	0.6, 1.6	NS	NA			NA		
Other	10.2	2.9, 35.7	<0.001	32.8	6.5, 165.4	<0.001						
Thymectomized												
No	1			1			1			1		
Yes	0.9	0.6, 1.3	NS	0.9	0.6, 1.4	NS	1.0	0.6, 1.8	NS	1.0	0.7, 1.4	NS
Distribution‡												
Severe	1			1			1			1		
Moderate	1.5	0.9, 2.3	NS	1.4	0.8, 2.2	NS	1.4	0.7, 2.7	NS	1.2	0.8, 1.9	NS
Mild	1.5	1.0, 2.4	NS	1.2	0.8, 1.9	NS	1.3	0.7, 2.4	NS	1.1	0.7, 1.1	NS
Ocular	2.3	1.3, 4.1	0.004	2.2	1.2, 3.9	0.01	2.5	1.0, 6.6	NS	2.1	1.3, 3.6	0.005

Afr.-Am.=African-American.*Cox proportional hazard regression analysis was used to evaluate significant variables in the survival analysis. †Early onset=<50 years; Late onset=≥50 years. ‡Severe=MGFA class 4A, 4B, & 5; Moderate=MGFA class 3A & 3B; Mild=MGFA class 2A & 2B; Ocular=MGFA class 1.NA=not assessed; Race was not significant for 10 years of follow-up and at last visit in the Kaplan-Meier analysis and therefore was not incorporated in the Cox models at these time points. NS=not significant.

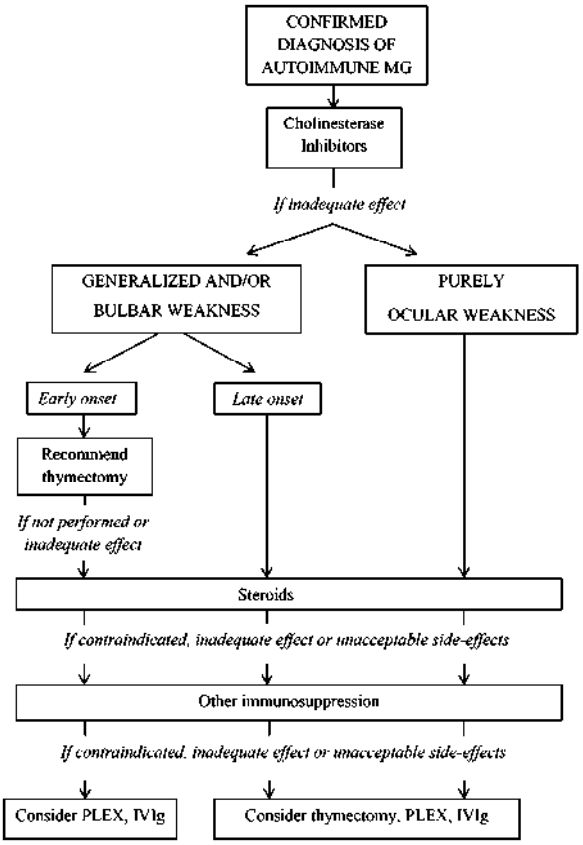

Figure 1. Treatment algorithm.
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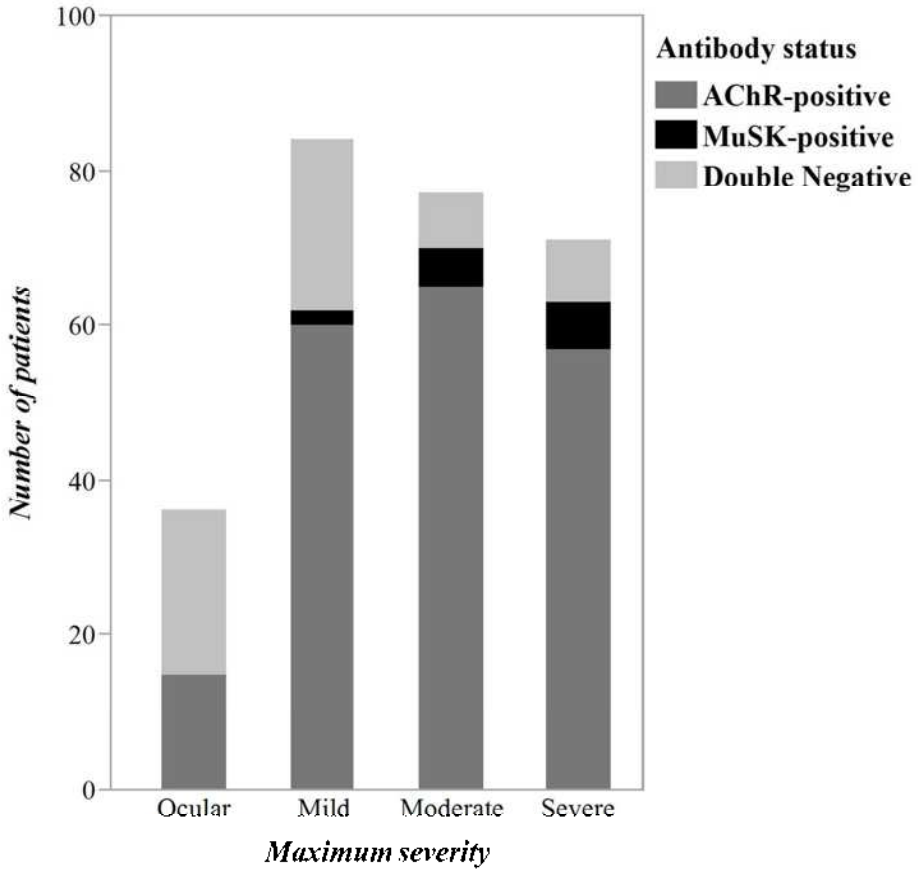

Figure 2. Maximum severity.
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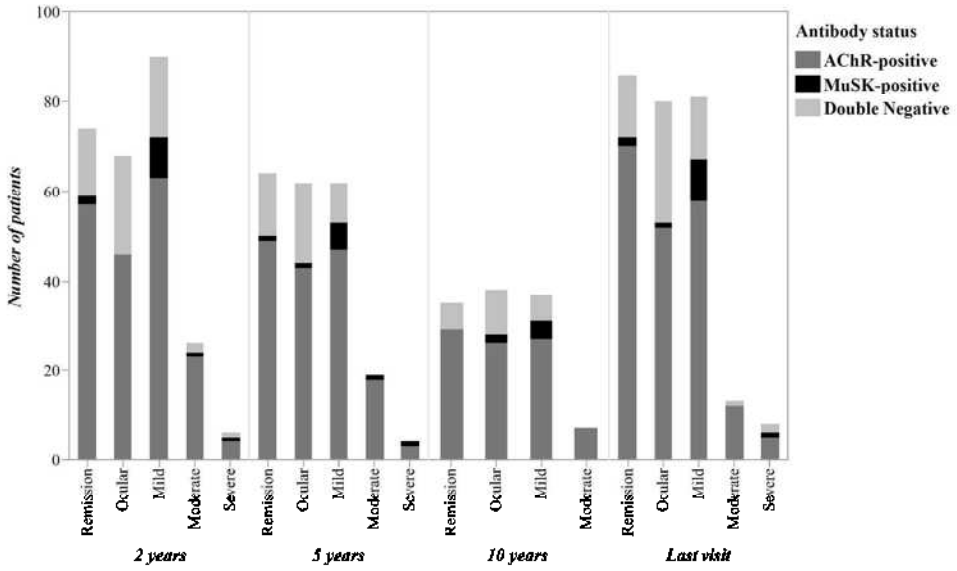

Figure 3. Clinical severity at 2, 5, 10 years of follow-up and at last clinic visit according to the different antibody status.
217x130mm (300 x 300 DPI)

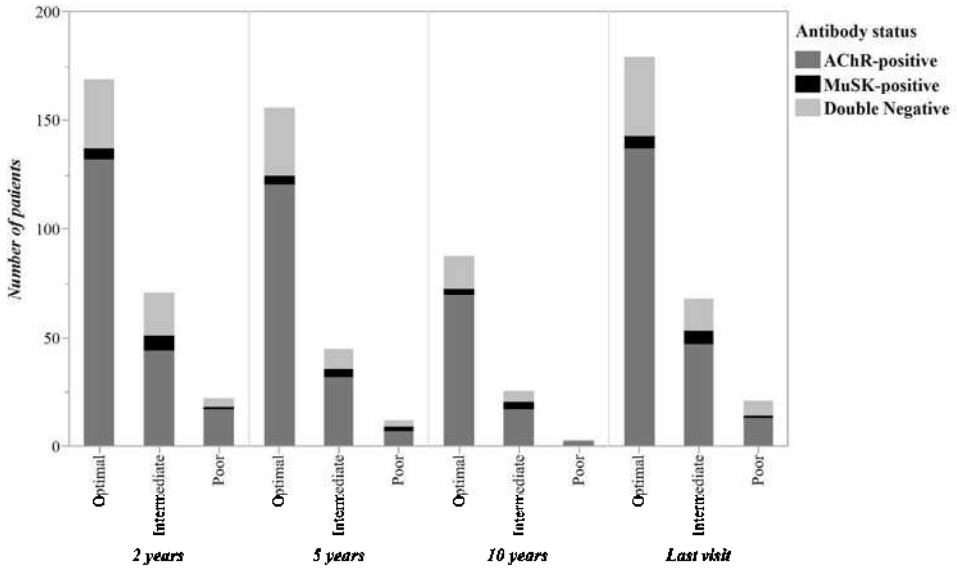

Figure 4. Outcome at 2, 5, 10 years of follow-up and at last clinic visit according to antibody status.
217x130mm (300 x 300 DPI)