OPTIMUM TREATMENT STRATEGY FOR MYASTHENIA GRAVIS: A SINGLE-CENTER EXPERIENCE

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Abstract

Background and Purpose: Patients with Myasthenia Gravis (MG) suffer from chronic fluctuating fatigue and occasionally permanent weakness despite treatment. This study aims to evaluate whether early immunotherapy and careful monitoring of MG patients in a specialized center could improve the clinical outcome.

Methods: A total of 113 patients (median age 57 years, 59 females) with ocular or generalized MG and varied autoantibody profiles were subdivided into 59 patients who had received intense and early immunotherapy from disease onset (subgroup A) and 54 patients who were initially treated conservatively and later switched to an intense approach (subgroup B). Classical scales for quantitative assessment of symptoms were employed and rescue therapy or medication switching were based on preset criteria, common for all patients.

Results: A desirable Postintervention Status was achieved in 66.4% of our patients, with no detectable weakness in 33.6% of them. Crisis occurred in 1.8% and no MG-related deaths were recorded. Subgroup A compared to subgroup B showed a significantly better Postintervention Status and a much lower chance of generalization of ocular myasthenia (7.7% versus 75.0%). Patients in subgroup B also showed better clinical outcome i.e. lower Quantitative MG score and MG Foundation of America class, following optimization of treatment.

Conclusions: The suggested approach, consisting of early initiation of immunotherapy, close monitoring, and appropriate treatment modifications, meets the main treatment objectives, i.e. prompt and sustained improvement, reducing the risk of generalization, preventing or minimizing crises and achieving a positive impact on the quality of patients' life.

Key words: myasthenia gravis, ocular myasthenia, immunosuppressive drugs, quantitative scores, clinical outcome

ΒΕΛΤΙΣΤΗ ΣΤΡΑΤΗΓΙΚΗ ΘΕΡΑΠΕΙΑΣ ΓΙΑ ΤΗΝ ΒΑΡΙΑ ΜΥΑΣΘΕΝΕΙΑ: ΕΜΠΕΙΡΙΑ ΕΝΟΣ ΚΕΝΤΡΟΥ

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Περίληψη

Οι ασθενείς με βαριά μυασθένεια (MG) υποφέρουν από χρόνια κυμαινόμενη κόπωση και ενίοτε από μόνιμη μυϊκή αδυναμία παρά την θεραπευτική αγωγή. Η παρούσα μελέτη έχει στόχο να διερευνήσει εάν πρώιμη ανοσοθεραπεία και συστηματική παρακολούθηση των ασθενών με MG σε εξειδικευμένο κέντρο μπορεί να βελτιώσει την εξέλιξη της νόσου. Συνολικά μελετήθηκαν 113 ασθενείς (μεσαία τιμή ηλικίας 57 έτη, 59 γυναίκες) με οφθαλμική ή γενικευμένη μυασθένεια και ποικίλο ανοσολογικό προφίλ και χωρίστηκαν σε 2 υπο-ομάδες: 59 ασθενείς οι οποίοι έλαβαν άμεσα μετά τη διάγνωση ανοσοθεραπεία (υπο-ομάδα Α) και 54 οι οποίοι αρχικά αντιμετωπίστηκαν πιο συντηρητικά ενώ αργότερα στην πορεία αλλάξαν σε πιο εντατική ανοσοκατασταλτική αγωγή. Εφαρμόστηκαν οι κλασσικές κλίμακες εκτίμησης της βαρύτητας και κατανομής

των συμπτωμάτων και η χορήγηση θεραπείας διάσωσης βασίστηκε σε προκαθορισμένα κριτήρια, κοινά για όλους τους ασθενείς. Τα αποτελέσματα έδειξαν ότι επιθυμητό επίπεδο βελτίωσης μετά την θεραπευτική παρέμβαση επιτεύχθηκε στο 66.4% των ασθενών μας, μάλιστα δε η πλήρης υποχώρηση της μυϊκής αδυναμίας έφθασε στο 33.6% του συνόλου. Μυασθενική κρίση εμφάνισε το 1.8% και δεν καταγράφηκε κανένας θάνατος σχετιζόμενος με MG. Η υπο-ομάδα Α συγκριτικά με την Β εμφάνισε καλύτερο επίπεδο μετά την θεραπεία και μια σαφώς μικρότερη πιθανότητα γενίκευσης της οφθαλμικής μυασθένειας (7.7% έναντι 75.0%). Οι ασθενείς της Β υπο-ομάδας έδειξαν κλινική βελτίωση (μικρότερη βαθμολογία στις κλίμακες Quantitative MG και MG Foundation of America) μετά την βελτιστοποίηση της θεραπευτικής αγωγής. Συμπερασματικά, η προτεινόμενη προσέγγιση, που συνίσταται σε πρώιμη ανοσοθεραπεία, στενή παρακολούθηση και κατάλληλες, έγκυρες τροποποιήσεις του θεραπευτικού σχήματος οδηγεί στο επιθυμητό αποτέλεσμα, δηλαδή στην άμεση και διαρκή υποχώρηση των μυϊκών συμπτωμάτων, τη μείωση του κινδύνου γενίκευσης, την αποτροπή ή ελάττωση της πιθανότητας μυασθενικής κρίσης, παρέχοντας έτσι θετικό αντίκτυπο στην ποιότητα ζωής των ασθενών.

Λέξεις ευρετηρίου: Βαριά μυασθένεια, οφθαλμική μυασθένεια, ανοσοκατασταλτικά φάρμακα, κλίμακες εκτίμησης μυϊκής κόπωσης, εξέλιξη νόσου

Introduction

Myasthenia Gravis (MG) is an antibody-mediated autoimmune disease that affects young and older persons of both sexes and characterized by a chronic fluctuating course. Focal or generalized muscle weakness and fatigue has a negative impact on patient' daily living activities and a potential risk of life threatening complications i.e. respiratory insufficiency and dysphagia.

International Task Force committees have published basic guidelines for MG treatment which are adopted by neurologists worldwide [1, 2]. However, the panel of experts underlined the heterogeneous and variable course of the disease, leaving clinicians to determine the best possible treatment on an individual basis for each patient. In this context, many questions need to be answered. How long is "an adequate trial of pyridostigmine" before deciding to start immunotherapy? Could a delayed initiation of treatment have an impact on the long-term outcome, given that eventually the vast majority of patients will require immunosuppression drugs? The definition of remission requires "absence of weakness", which is achievable in daily routine. But what about fatigability during demanding tasks, especially in young persons who want to engage in physical activities and be productive? How is the level of efficacy of a drug judged, and which are the criteria for substitution?

In practice, a suboptimal treatment effect is not uncommon and often acceptable by doctors and MG patients, who learn to live with the disability of fluctuating fatigue and even permanent weakness of some muscles. Moreover, MG crisis and admission to intensive care unit (ICU) is unavoidable in some patients. One might wonder whether these unfavorable situations can be minimized. We hypothesized that an intense treatment approach combined with close follow-up would prove to be superior to the standard, more reluctant practice in terms of controlling disease relapses and enhancing the long-term outcome. To address these issues we presented data from a single specialized center, accumulated over the last 10 years.

Materials & Methods

Participants

This is an observational cross-sectional study that presents the experience of a single neuromuscular center in a tertiary Public University Hospital. This center is attached to the Department of Neurology, which is the only public unit for neurological patients in the south-west of Greece with a general population of approximately 800.000 people. Patients who were regularly monitored in our center were studied. The most recent medical visit of all subjects extended over a period of 6 months from July 2020 to February 2021, with the exception of those who died earlier. Patients were excluded if they were lost to follow-up, moved out of the district or examined once for a second opinion. The research was performed in accordance with the 1964 Helsinki declaration with its later amendments. All participates gave their written informed consent and the study was approved by the Institutional Ethics Committee of the Patras' University Hospital (no. of approval 1134 /19-12-2019).

Diagnosis of MG was made based on clinical manifestations of fluctuating muscle weakness and fatigue after exclusion of alternative diagnoses and confirmed by the presence of 1 or more of the following paraclinical findings: 1. Antibodies, against acetylcholine receptors (AChR) or muscle specific kinase (MuSK) 2. Positive neurophysiological test, repetitive nerve stimulation (RNS) or single fiber electromyography (SF-EMG). 3. Positive neostigmine pharmacological test [3]. 4. Definite positive ice- pack test [4].

Methodology

Over the last 10 years a detailed clinical data registry has been gradually built and a treatment algorithm developed to standardize the clinical evaluation, the treatment options and the outcome assessments of MG patients. Standard clinical scales were employed to define the disease extension and severity [5]. These were: (a) Myasthenia Gravis Foundation of America (MGFA) classification I-V classes with the addition of an asymptomatic post-intervention class; (b) Quantitative Myasthenia Gravis (QMG) score (range 0-39); (c) Postintervention Status assessed at most recent visit as compared to our initial assessment, after reaching maximal disease severity; this was defined as Complete Stable Remission (CSR), Pharmacological Remission (PR) or Minimal Manifestations (MM) 0-3 when patients had no functional complains and a total QMG score of ≤3 from ≥2 items. Change in status was defined as Improved (I), Unchanged (U), Worse-Exacerbation (W/E) or Death from MG (D). The impact of MG on the patients' quality of life at the most recent visit to our center was measured by MG-QOL15 [6].

The following definitions were used during monitoring: MG crisis is defined as the need for intubation due to respiratory distress and admission to ICU. In order to define a relapse, deterioration of MG symptoms should appear after at least a month of remission and these changes should last≥ of 24 hours. Two states of relapse severity were recognized: a. Relapse, increase of QMG score by ≥3 from 1 or more items and a total QMG score of ≥6; b. Severe relapse, bulbar QMG score of 3 or respiratory of 1 or QMG total score of ≥15. Treatment decisions were taken accordingly, i.e. in most cases relapses were dealt with by modification of therapeutic regimen, whereas in severe relapses rescue therapy was always administrated.

Therapeutic interventions included data on a. thymus imaging and thymectomy with histology results and b. medication: pyridostigmine and steroid doses, additional immunosuppressive drugs and their severe side-effects. Response to treatment after an appropriate time period was characterized as:

i. favorable, reaching CSR, PR or MM stage, QoL≤ 9 and QMG score ≤3 from 2 or more items.
ii. improvement but not favorable, QMG score decrease by ≥6 but total QMG score> 3.
iii. no improvement or insignificant change. MG was defined as refractory according to Mantegazza and Antozzi [7] and to the international consensus guidance report [1], if any of the following conditions was met: (a) inadequate response to steroids and at least two other drugs; (b) prolonged need of high doses of potentially harmful therapies; (c) requirement of repeated rescue therapies; (d) occurrence of severe or intolerable medication side effects.

Patients grouping

For the aim of this study, patients were divided into two subgroups according to the management strategy they received. *Subgroup A*: included patients who were diagnosed and treated in our center from the beginning of the disease. Our approach is based on the following practices: a. immediately after the definite diagnosis, immunotherapy is administrated to all cases (with rare exceptions) regardless of the disease severity; b. close monitoring with regular visits and early addition or change of drugs is provided; c. pyridostigmine is kept at a minimum dose and used mainly for bridging between changes of treatment regimens. *Subgroup B*: included patients who were initially treated by other neurologists in the area and later attended our center because of retiring of their doctor or a non-satisfactory outcome. The initial management of these patients before we took over their care, particularly for those with ocular onset myasthenia, had one or more of the following characteristics: a. treatment with pyridostigmine alone, occasionally in an ever-increasing dose; b. administration of steroids at low dose, intermittently or for a short period of time; c. reluctance to add or change immunosuppressive medication, d. unscheduled visits, mainly at an emergency basis.

Statistical analysis

The basic descriptive statistics of the demographic and clinical variables were computed along with the frequencies of the ordinal variables for each of the two subgroups. The normality assumption of the data was tested using the Shapiro-Wilk test since it is more powerful than the commonly used Kolmogorov-Smirnov test [8]. In order to examine differences between the two subgroups independent samples t-test was utilized if the normality assumption was met and Mann Whitney U non-parametric test otherwise. For testing the difference of the first to the recent visit of the patients within each subgroup, paired samples t-test was utilized when the normality assumption was met and Wilcoxon signed rank test otherwise. For ordinal data the analysis was based on Chi-Square test with estimation of Fisher exact asymptomatic significance or, in case of non-parametric values, on Marginal Homogeneity test. The significance level for all tests was set to 5%. The data entry and statistical analysis was conducted using the software SPSS version 23 for Windows (IBM SPSS Inc., Chicago, Illinois, USA).

Results

Our registry consisted of 132 entries. Of those, 19 patients were excluded from further analysis since they did not regularly attend the clinic. In total, 113

Table 1. Clinical and laboratory features in total and two subgroups

			Total	Subgroup A	Subgroup B	P-value#
No of cases			113	59	54	
Current age, yrs*			57.0 (44.5-69.5)	52.0 (39.0-70.0)	57.5 (47.5-68.0)	0.554
Age at onset, yrs*			44.0 (34.5-61.5)	46.0 (34.0-66.0)	42.5 (34.8.0-53.3)	0.248
Female sex, no (%)			59 (52.2)	30 (50.8)	29 (53.7)	0.761
Duration from diagnosis, yrs*			6.0 (2.4-13.0)	3.5 (2.0-7.0)	11.5 (3.5-18.4)	**0.000**
Duration of our monitoring, yrs*			3.0 (2.0-7.0)	3.5 (2.0-7.0)	3.0 (2.0-6.1)	0.294
MGFA at onset, no (%)	class	I	37 (32.7)	16 (27.1)	21 (38.9)	0.650
		II	26 (23.0)	14 (23.7)	12 (22.2)	
		III	41 (36.3)	22 (37.3)	19 (35.1)	
		IV	4 (3.5)	3 (5.1)	1 (1.9)	
		V	5 (4.5)	4 (6.8)	1 (1.9)	
Auto-antibodies, no (%)	AChR		80 (70.8)	46 (78.0)	34 (63.0)	0.341
	MuSK		8 (7.1)	4 (6.8)	4 (7.4)	
	AChR+MuSK		4 (3.5)	1 (1.7)	3 (5.5)	
Thymus pathology, no (%)	hyperplasia		17 (15.0)	6 (10.2)	11 (20.4)	0.283
	thymoma		20 (17.7)	9 (15.3)	11 (20.4)	

* values expressed as median (interquartile range); #comparison between subgroups with different management approaches; no = number and (%) percentage of patients in the specified groups or otherwise indicated

patients of Caucasian race with monitoring of at least 6 months and a stable condition within the 3 months prior to their last visit were included. The scheduled visits were in average 2.6 (SD1.6, range 1 to 7) annually.

Disease profile

Data on demographics and disease characteristics are presented in total and separately for the two subgroups which were defined in the methods based on the different management attitude (Table 1). Inter-group comparison showed no statistical significant differences with the exception of longer disease duration in subgroup B. At the beginning of undertaking the medical care in our unit 6 patients were supported in ICU; 4 patients in subgroup A developed severe respiratory muscle weakness as the presenting manifestation of MG and 2 patients in subgroup B suffered a myasthenic crisis.

Management of MG patients in our center

Symptomatic treatment i.e. pyridostigmine was initially given to all patients at a mean dose of 176mg/day with the exception of anti-MuSK cases and a maximum dose of 240mg/day. At recent visit, the mean pyridostigmine dose was 83mg/day, while 32 in subgroup A and 17 patients in subgroup B discontinued this drug.

A total of 42 patients (17 in subgroup A), including all of those with thymus pathology underwent thymectomy in addition to medication. Assessment of the effectiveness of thymectomy per se was not attempted since data were not suitable for this purpose. Since the first visit in our center, together with symptomatic treatment, steroids was initiated or continued in all patients but 2 because of co-existing kidney cancer in one and very old age of the other. A favorable response was recorded in 45 patients (76.3%) in subgroup A versus 17 (32.7%) in subgroup B (p = 0.000). Steroid dependency was recorded in 30.6% of the patients during the tapering period and eventually 54% required the addition of another drug in order to improve treatment effectiveness or avoid a relapse (Table 2). Throughout the disease course, some patients, particularly in subgroup B, had to try 2 or even 3 different drugs in succession to reach the optimum condition, but none was treated concurrently with 2 immunosuppressive agents, in addition to steroids. The efficacy of immunotherapy after an appropriate time-lapse period from initiation of each drug is presented in Figure 1.

Besides the expected and manageable side-effects of medications, such as steroid induced transient hyperglycemia and cataract, the following notable events were registered. Osteoporosis and spontaneous fractures in 4 patients, rupture of large intestine in 2 and pancreatitis in 1 due to steroids; in addition two patients under steroid monotherapy were hos-

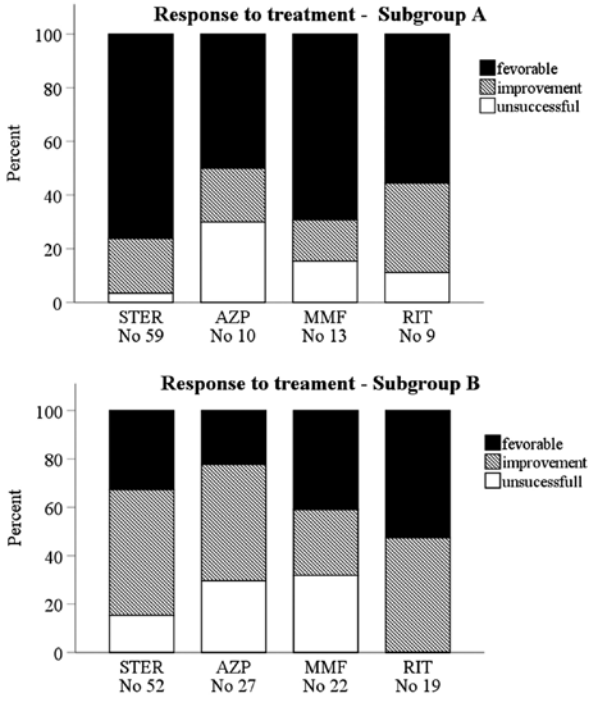
Table 2. Treatment data, disease course and clinical outcome

		Total, no 113	Subgroup A, no 59	Subgroup B, no 54	P-value*
Immunosuppressants, no of pts (%):	none steroids alone 1 or 2 more drugs 3 more drugs	2 (1.8) 50 (44.2) 53 (46.9) 8 (7.1)	0 37 (62.7) 22 (37.3) 0	2 (3.7) 13 (24.1) 31 (57.4) 8 (14.8)	**0.000**
Relapses#	no of pts (%) no of episodes	42 (37.2) 84	21 (35.6) 37	21 (38.9) 47	0.269
Severe relapses#	no of pts (%)	26 (23.0) 44	13 (22.0) 15	13 (24.1) 29	0.163
Myasthenic crises#	no of pts (%) no of episodes	2 (1.8) 5	2 (3.4) 5	0 0	
Postintervention Status, no of pts (%):	CSR PR MM1 MM2 MM3	2 (1.8) 27 (23.9) 15(13.3) 2 (1.8) 29 (25.7)	1 (1.7) 23 (39.0) 10 (16.9) 1 (1.7) 12 (20.4)	1 (1.9) 4 (7.4) 5 (9.3) 1 (1.9) 17 (31.5)	**0.019**
Change in status, no of pts (%):	I U W/E	96 (85.0) 14 (12.4) 3 (2.6)	51 (86.4) 7 (11.9) 1 (1.7)	45 (83.3) 7 (13.0) 2 (3.7)	0.783
Refractory	no of pts (%)	11 (9.7)	2 (3.4)	9 (16.7)	**0.023**
Ocular → Generalized¥	no of pts (%)	33 → 16 (48.5)	13 → 1 (7.7)	20 → 15 (75)	**0.000**
MG-QOL15 at recent visit§		5.0 (2.0-10.0)	4.0 (2.0-8.0)	8.0 (3.0-13.3)	**0.012**

* comparison between the subgroups; # referred to our follow-up; ¥ only ocular myasthenia cases with disease duration of at least two years were considered; § values expressed as median (interquartile range)

pitalized in ICU due to covid-19 infection and both had a good outcome. Withdrawal of azathioprine (AZP) was required in 10 patients; 7 within the first month of administration due to biochemistry abnormalities (megaloblastic anemia or liver enzymes elevation), and 3 after several months of treatment due to occurrence of varicella, hepatic abscess and recurrent urinary infections respectively. Mycophenolate mofetil (MMF) was early discontinued due to diarrhea in 1 patient and severe distal limb numbness in another; 1 more patient experienced over the first year of treatment recurrent episodes of herpes zoster. Rituximab (RIT) caused severe allergic reaction during administration and was discontinued in 1 patient. MG was characterized as refractory in a total of 11 patients (Table 2). Six patients failed to response sufficiently to 3 consecutive immunosuppressants, 4 required continuous high dose of potentially harmful medication, and 1 developed a life-threatening side effect of medication.

Figure 1. The efficacy of various medications in the two subgroups. The percentage was calculated in those who received a particular drug



Disease progression, relapses, and clinical status at most recent visit

Table 2 presents the main quantifiable variants during our monitoring. In general, while a similar

Figure 2. Improvement of MGFA class at the last comparing with the first visit in our Department for each subgroup

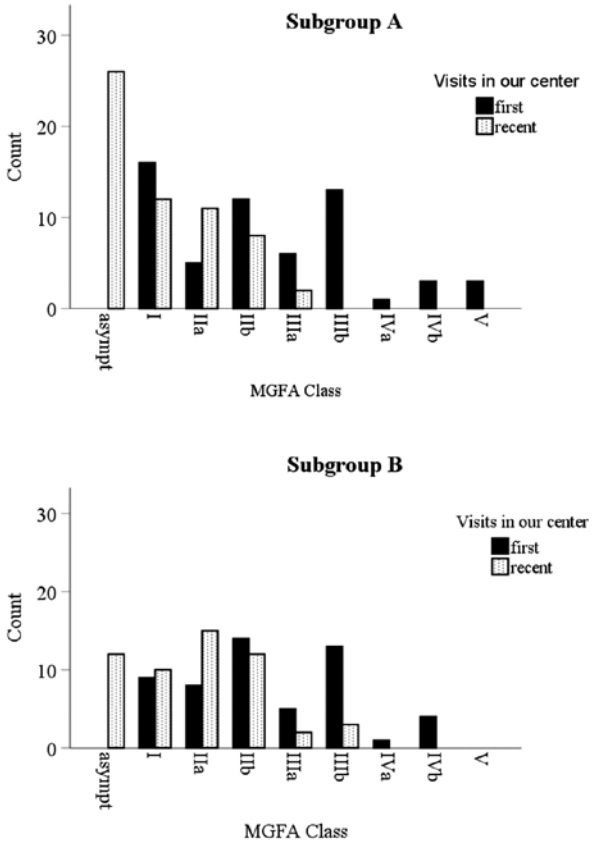


Figure 3. Changes of QMG score during our monitoring in both subgroups. Box-plots indicate median value, interquartile range and outliers

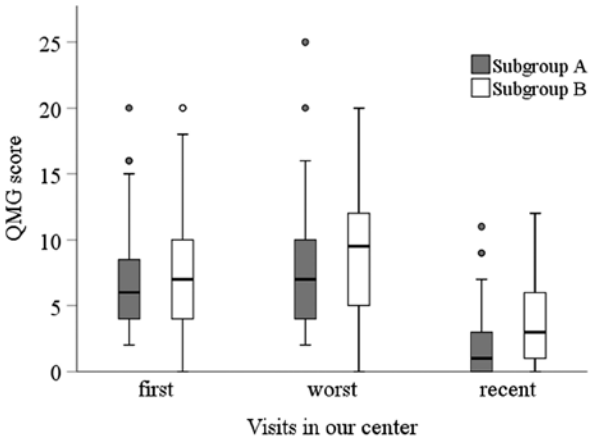
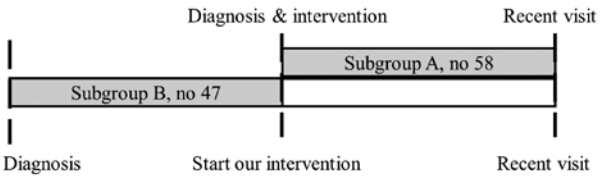


Diagram. Definition of the early disease period for each subgroup



clinical course in terms of exacerbations was observed in both subgroups, the indices of disease control and patients' satisfaction at the most recent visit were better for patients in subgroup A than subgroup B. At the beginning of our intervention MGFA class was similar in the 2 subgroups (x^2, $p = 0.698$). The intra-group change of MGFA class is presented in Figure 2. There was a statistically significant improvement, i.e. reduction in class, during our monitoring period for both subgroups (Marginal Homogeneity test for related samples, $p < 0.0005$). Figure 3 depicts the fluctuation of QMG score. In each subgroup, there was a significant difference of QMG score between the first (or worst) and the most recent visit in our center (Wilcoxon signed rank test for related samples, $p < 0.0005$). Over the last decade, 4 of our patients died. The cause of death in all cases were unrelated to MG, i.e. rupture of aortic aneurysm, stroke, complications of dementia and breast cancer.

With regard to the 8 patients with only anti-Musk antibody positivity, 3 had an onset of ocular MG and 5 experienced additional bulbar weakness. Four patients showed a moderate initial response to steroids and 4 remained dependent on this drug. At the recent visit, 5 responded well to RIT, 2 in MMT and 1 had refractory disease, with 3 patients from this group achieving asymptomatic status.

Subgroup comparison during an early disease period

The effect of treatment was evaluated after an early period i.e. our monitoring time for subgroup A and from diagnosis to the onset of our intervention for subgroup B (Diagram). To balance for disease duration between subgroups only patients with duration less than 20 years were included. The median duration (25-75 quintile) for 5 patient in subgroup A was 3.5 years (2.0-7.0) and for 47 in subgroup B 3.0 years (1.0-9.0) (Mann-Whitney test, $p = 0.367$). At the end of this early period the following differences were measured and values are presented as mean (sd): QMG score for subgroup A was 1.8 (2.6) and for subgroup B 7.6 (5.2), $p < 0.0005$; MGFA class was similar at disease onset in both subgroups but at the end of the early period became significantly lower in subgroup A as opposed to B ($p < 0.0005$). Similarly, medication daily dose was lower in subgroup A as opposed to B: for pyridostigmine was 64.0 mg (80.4) versus 178.0mg (62.7) ($p < 0.0005$), and for steroids was 10.2mg (7.7) versus 38.4mg (19.0) ($p < 0.0005$).

Discussion

A considerable proportion of patients experience MG as a devastating chronic disease associated with low physical endurance, superimposed by recurrent relapses or life-threatening events With current advances in treatment options and the increasing popularity of the 'hit hard and early' strategy, one would expect a better outcome compared to the past [9-11]. We initiated a registry for systematic recording of clinical data and follow-up measurements in order to assess the results of an intense and flexible to alterations management approach that we adopt.

Overall, at the recent visit, 33.6% of the patients had no detectable weakness, another 19.5% had symptoms restricted to eye muscles and in a total of 66.4% the Postintervention Status was evaluated as desirable (including CSP, PR, MM). Similar results were observed in a recent study of 126 MG patients in Austria by Rath et al [12] who reported after a minimum of 2-year follow-up asymptomatic stage or ocular weakness in 69.8% of patients and desirable Postintervention Status in 61.9%. Likewise, in a Japanese multi-center study including 395 MG treated patients, 30% were classified as asymptomatic and 35% as MGFA class I [13]. The Postintervention Status of 123 patients attending a single neurologic clinic in China was MM or better in 78.1% [14]. All studies emphasized the importance of immunotherapy in optimizing the outcome. In analogy to the improvement of clinical indexes, our patients satisfaction was reflected in a low score of MG-QOL (median value 5), close to 5.2 reported in a comparably designed study [10].

During our monitoring, a considerable number of relapses and severe relapses were identified according to standardized criteria. However, the prompt administration of rescue therapy and/or modification of the chronic therapeutic regimen in these cases led to the avoidance of crises in all but 2 patients who and no disease related to deaths due to MG. In the current literature the percentage of patients with crisis ranges from low values of 7.9% and 11.5% [12, 13] up to 28.5% [14] and the mortality rate varies between 1.6% [14] to 9.5% [12], and raises to 12.1% when elderly patients are included [15].

The purpose of dividing the patients into two subgroups was to better understand the immediate and long-term effects of the different therapeutic strategies: patients who were closely monitored and received optimum immunosuppressive medication soon after diagnosis were classified in subgroup A; patients who, were initially treated elsewhere with a more conservative therapeutic approach constituted subgroup B. At the end of an early disease period, during which diverse approaches were followed in the two subgroups, patients in subgroup A required lower dose of medication and showed greater improvement in clinical measurements than those in subgroup B. When the changes over the period of our neurological care for all patients in both subgroups were examined, the following conclusions were reached: (a) Both subgroups showed similarity in effectiveness of immunosuppressive agents, number of relapses/major events, change in status, and intra-group MGFA class as well as QMG score reduction. Therefore, one can assume that even in cases with a long disease duration and unsatisfactory previous status (i.e. unchanged MGFA class despite intervention), such as in subgroup B, treatment optimization is an option worth considering. (b) Achievement of favorable Postintervention Status, number of refractory cases and MG-QOL15 score were better in subgroup A than in B. The possibility of permanent, treatment-resistant weakness that developed over the years could be an explanation for the inferiority of subgroup B in the above parameters. (c) It is known that up to 80% of isolated ocular cases will go on to develop symptoms in other muscles during the first two years [16, 17]. In subgroup A, where all patients received immunotherapy immediately after the diagnosis, including those with pure ocular symptoms, only 7.7% of patients with ocular MG and a minimum 2-year follow-up experienced generalization. On the contrary, in subgroup B, the disease became generalized in 75.0%, a percentage close to that expected by the natural course of MG in the Caucasian population [18, 19]. Our results suggested that early initiation and continuation of immunotherapy, as applied in subgroup A, lowered the risk of generalization in cases of ocular myasthenia, confirming the results of previous retrospective studies [20, 21].

Pyridostigmine was kept at the lowest effective dose at all stages. The need for doses higher than 180mg on a daily basis constitutes a "red flag" for treatment modifications. At the recent visit, pyridostigmine was withdrawn in 43.4% of all patients and remained at low dose (≤ 120mg/day) in 27.4%. A similar approach towards symptomatic treatment has been reported recently by Rath et al. [12], who estimated pyridostigmine free patients 34.8% in the treatment responsive group and 14.3% in the refractory cases. The efficacy of immunosuppressive drugs in our patients was in agreement with that reported previously [16, 22]. The small number of patients treated with a particular drug did not allow statistically supported conclusions. However, in agreement with the literature [23-25], RIT appeared to have a very good effectiveness in 27 out of 28 treated patients. The adverse drug events were predictable [26, 27] and manageable due to the frequent clinical and laboratory surveillance. In our cohort 9.7% of patients fulfilled at least one of the criteria for refractory MG, which is close to the lower values of

previous reports that range from 10% [7] and 14.8% [28], to as high as 27.4%, which was observed in patients with at least 1 crisis [29].

Limitations

The main limitation is the study design which is a common drawback of many MG studies as was pointed out in a recent article by Tannemaat and Verschuuren [30]. Our data collection, which was partly retrospective for subgroup B, did not intend to evaluate the effect of certain treatment regimen over a restricted time period as presented in a recent single blind study from France [31]. In our view, in diseases such as MG, which might have unexpected clinical fluctuations, and relapses after long periods of remission and no certain final outcome, a cross sectional observation study provides a realistic presentation of a patient cohort at any given time. Another noticeable point is that the cohort of patients attending a specialized center could introduce a possible bias in favor of severe cases which might have compromised the outcome. Nevertheless, as the only Neurology department in the district, the grand majority of patients with MG of any severity are diagnosed and followed up by us.

Conclusion

In summary, a physician treating MG patients aims at a fast and steady improvement in severe cases, an avoidance of weakness expansion in ocular cases, while keeping myasthenic crises to a minimum and thus providing an optimum long term-outcome and good quality of daily living. Our results indicated that all these goals were better achieved in a specialized unit, where two necessary steps were taken in order to decide on the best possible treatment and at the right time: (a) well-defined criteria to quantify the degree of deterioration/ improvement and the effectiveness of treatment were set. (b) medical decisions were made in accordance to preset rules ensuring equality in treatment options for all patients with similar clinical status and resulting in immediate interventions and treatment modifications.

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