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Acetylcholinesterase inhibitors are ineffective in MuSK-antibody positive myasthenia gravis: Results of a study on 202 patients

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ABSTRACT

Background: Myasthenia gravis (MG) with MuSK antibodies (MuSK-MG) represents a distinct subtype with different responses to treatments compared to patients with AChR antibodies, especially in terms of tolerance to acetylcholinesterase inhibitors (AChEI). However, AChEI are often used as first line symptomatic treatment in MuSK-MG, despite reports that they are poorly tolerated, seldom effective or even deleterious.
Methods: We analyzed demographic, clinical and therapeutic responses and side-effects in the large cohort of 202 MuSK-MG patients cared for at the MG Clinic of Azienda Ospedaliero-Universitaria Pisana.
Results: 165 patients had received AChEI at first evaluation. Only 7/165 patients (4.2%) reported an initial clinical benefit. Conversely, 76.9% of patients reported at least one side effect, most commonly neuromuscular hyperexcitability (68.4%), gastrointestinal (53.9%) and neurovegetative (35.8%) disturbances. 56 (33.9%) patients reported a concomitant worsening of muscle weakness and twelve patients (7.3%) suffered a cholinergic crisis. According to these patients, the severity of cholinergic side effects was greater at higher doses of AChEI, but side effects occurred regardless of the dose administered and ceased once the drug was discontinued.
Conclusions: This is the largest population of MuSK-MG patients reported for perceived responsiveness and tolerance to AChEI treatment. Our obervations strongly suggest avoiding this treatment in MuSK-MG.

1. Introduction

Myasthenia Gravis (MG) is a relatively rare autoimmune disease caused by autoantibodies directed against postsynaptic antigens at the neuromuscular junction (NMJ) that lead to impaired neuromuscular transmission [1]. MG is a heterogenous condition with distinct subtypes which exhibit different clinical characteristics and therapeutic needs; therefore, the clinical characterization and diagnostic testing to detect MG autoantibodies is of utmost importance. About 85–90% of patients with generalized MG (gMG) and 50% of patients with ocular MG (OMG) have autoantibodies against the acetylcholine receptor (AChR-MG). Up to 8% of the remaining MG patients have antibodies against muscle-specific receptor tyrosine kinase (MuSK-MG). The 2–10% of MG patients with neither antibody usually have milder disease and include a greater proportion of those with OMG [1]. Therefore, a proper characterization of the antibody pattern is crucial to provide appropriate treatment.

MuSK is a tyrosine kinase receptor that acts as a key organizer of the clustering of AChR and of pre- and postsynaptic neuromuscular development and maintenance. MuSK-Abs belong mostly to the IgG4 subclass and have distinct amino acid differences in the Fc region that strongly reduce the ability to bind to C1q or activating Fcγ receptors. As a result, the antibodies are unable to activate the classical complement pathway or recruit immune cells, so that their pathogenicity is mainly exerted by directly blocking of protein–protein interactions without complement activation [2–4]. MuSK Abs directly interfere, pre- and postsynaptically, with MuSK function.

The mean age of onset for MuSK patients is reported to be around 40 years and 70–80% of patients are female [5–9]. 80% of MuSK patients predominantly exhibit an involvement of the cranial and oropharyngeal muscles with dysarthria, dysphonia, rhinolalia, masticatory difficulty and dysphagia at onset. Bulbar onset is frequently acute and can lead to

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respiratory crisis or evolve slowly to respiratory failure. Limb involvement is usually less severe or absent but weakness of the extensor neck muscles can cause a 'drooping head' alone without bulbar symptoms at disease onset [9,10]. Although extraocular weakness can be the first symptom, an OMG phenotype is extremely rare [8,9].

Typical AChR-Ab positive MG patients respond to acetylcholine esterase inhibitors (AChEI) [11], thymectomy [12–14] and immunotherapies. However, in MuSK-MG symptomatic treatment with AChEI, although recommended by international guidelines [15], is generally ineffective and frequently associated with common side effects [16]. MuSK patients don't show any long-term benefits from thymectomy contrary to AChR-MG patients, in which radical surgery of thymus can lead to long-term remission. Indeed, a diagnosis of MuSK-MG is one of the main exclusion criteria for thymectomy and, by now, in the vast majority of referral centers, it is no longer recommended for these patients [17,18]. MuSK patients usually respond favorably to steroid therapy and also traditional immunosuppressants have been administered with success, even though it is typically more difficult to achieve and ensure long-term and complete remission in MuSK-MG [19–21]. Rescue therapy, such as plasma exchange (PLEX) and intravenous immunoglobulin (IVIg), are immediate-relief treatment options during exacerbations, even though a variable response to IVIg has been observed in MuSK-MG [22,23]. Recently, the use of the anti-CD20 antibody, rituximab (RTX) has shown to be more effective in MuSK-MG than in AChR-MG [24,25], and the recent consensus guideline update [26] recommends RTX as an early therapeutic option in generalized refractory MuSK-MG.

Historically, AChEI therapy has been the first-line treatment of MG. Oral pyridostigmine bromide (PB) and intravenous or intramuscular intrastigmine have been the milestone of MG management for many years [11] and are, by now, the first treatment in the majority of MG cases, irrespective of the autoantibodies identified.

The primary aims of this retrospective cohort study were to evaluate the clinical response and side-effects of symptomatic treatment with pyridostigmine bromide in MuSK-MG and identify possible clinical predictors of responsiveness and tolerance to this treatment. We analyzed the clinical data of 202 patients referring to MG Clinic in Pisa. To our knowledge, this is the largest cohort of MuSK patients ever described.

2. Methods

2.1. Inclusion and exclusion criteria

In this retrospective single cohort study, we analyzed demographic, clinical and therapeutic features of 202 MuSK patients consecutively admitted to the MG Clinic of the Azienda Ospedaliero-Universitaria Pisana from 1994 to 2022.

Patients were included if they were over 18 years of age, clinically diagnosed with MG and if they tested positive for MuSK antibodies. The clinical diagnosis of MG was confirmed in all patients by a positive test for MuSK antibodies using radioimmunoassay (RIA) and/or cell-based assay (CBA) [27,28]. Seronegative patients and those who had anti-AChR antibodies were excluded. Also patients that had a follow-up period less than one year or did not have complete data on their AChEI treatment history were excluded.

The background information of the patients was obtained from their medical records, including age, age at MG symptom onset, sex, clinical symptoms at onset (ocular, bulbar or generalized), severity of disease according to MG Foundation of America (MGFA) clinical classification at the first visit, serological results, follow-up duration, daily dose of PB, AChEI responsiveness and experience of side effects and occurrence of cholinergic crisis due to AChEI intoxication. AChEI~~s~~ side effects were divided into three main categories: symptoms of neuromuscular hyperexcitability (muscle cramps, fasciculations, tremor, eyelid myokymia), gastrointestinal (abdominal cramps, nausea, diarrhea, meteorism) and neurovegetative side effects (hypersalivation, increased lacrimation, sweating and bronchial secretion). Besides side effects, at each visit, we performed a complete neurological examination and recorded also patient self-reported improvement or deterioration of myasthenic symptoms after AChEI introduction. The first visit in our MG center was considered the baseline first evaluation and disease duration from MG onset to first visit was also recorded.

2.2. Statistical analysis

The continuous data were presented as mean (standard deviation) or median (interquartile range) depending whether the data showed normal distribution. The datasets were analyzed using student's *t*-test, one-way ANOVA or Mann-Whitney/Kruskal Wallis where appropriate. The categorical data were presented as numbers or proportions (%) and comparisons were assessed by either the Chi-Square test or Fisher's exact test. Multivariate logistic regression was performed to evaluate and identify predictors of AChEI side effects with age at diagnosis, antibody titer, sex, age, MGFA class and pyridostigmine dose and duration as covariates. *P* values were considered significant when <0.05. All statistical analyses were performed with IBM SPSS Statistics (version 27.0).

3. Results

3.1. Patients

The MuSK patients had a clear female prevalence (163 women,39 men, 4.18,1 ratio), with a median age at onset of 40.3 ± 15.6 years and of 53.7 ± 16.2 years at first evaluation. Median follow-up period was 7.8 ± 6.6 years. The duration for each patient from disease onset to first evaluation was 3.8 ± 5.9 years. The MuSK-MG clinical features were similar to those reported previously in literature with 93.5% of patients having a bulbar predominant phenotype. Demographic features of the patients are shown in Table 1. All patients were negative for AChR antibodies and were positive for MuSK antibodies; titers in 68 representative sera that were tested by serial dilutions, ranged from 0.06 to 24.96 nM (median 5.27 nM).

3.2. AChEI treatment in MuSK-MG

At first evaluation in Pisa, 91 patients (45%) were receiving AChEI (e.g. pyridostigmine bromide) at an average daily dose of 180 (158) mg/day (see Table 1). A further 74 (36.6%) had previously received AChEI but discontinued it due to poor tolerance and/or lack of effectiveness. Thus together, 165 (81.6%) of patients were currently or previously treated with AChEI. Overall, 127 (76.9%) of these patients reported at least one side effect. The most common were cholinergic symptoms of neuromuscular hyperexcitability (muscle cramps, fasciculations, tremor, eyelid myokymia) reported by 113 (68.4%) of patients and followed by gastrointestinal side effects (abdominal cramps, nausea, diarrhea, meteorism) and neurovegetative side effects (hypersalivation, increased lacrimation, sweating and bronchial secretion) in 89 (53.9%) and 59 (35.8%) of patients respectively. In addition, twelve (7.3%) cholinergic crises requiring hospitalization were recorded (Table 1).

In the study population, only seven patients (4.2%) reported an initial and transient clinical benefit after the start of AChEI therapy and 56 (33.9%) patients reported a concomitant worsening of muscular weakness. The frequency of self-reported exacerbation of muscle weakness was significantly higher in more severe MGFA classes ($p = 0.015$), in those suffering neurovegetative side effects ($p = 0.024$) and those who exhibited a cholinergic crisis ($p = 0.022$). The worsening of weakness was reported in the same muscular districts generally affected by MG. In a multivariate logistical regression analysis, however, no correlation was found between the occurrence of at least one cholinomimetic side effect and age, sex, autoantibody titer, AChEI dose or MGFA class (**Supplementary Table 1**). AChEIs were discontinued at

Table 1
Baseline characteristics of MuSK-MG patients ($n = 202$) and summary of effects of AChEIs.

General features	
Male: female (%)	39 (19.3%):163 (80.7%)
Age at onset (mean ± SD)	40.3 ± 15.6
Age (mean ± SD)	53.7 ± 16.2
MuSK-Ab titer at onset and 68 based on titration (nM range, median)	All >0.05; 0.6 to 24.96, 5.27 ($n = 68$)
Clinical symptoms at onset n (%)	
Ocular	58 (30,2%)
Bulbar and ocular	34 (17,7%)
Bulbar	35 (18,2%)
Generalized	64 (33,3%)
Other	1 (0,5%)
MGFA class at first evaluation n (%)	
I	9 (4,5%)
IIA	4 (2%)
IIB	66 (33%)
IIIB	78 (39%)
IVB	33 (16,5%)
V	10 (5%)
Previous and concurrent treatments at first evaluation	
Pyridostigmine n (%)	91 (45%)
Dose of pyridostigmine T0 - median (IQR)	180 (158) mg/day
Pyridostigmine discontinuation n (%)	74 (44.8%)
N. of patients using/have used pyridostigmine	165 (81.6%)
Prednisone at first evaluation n (%)	144 (71.2%)
Dose of prednisone, median (IQR)	25 (44.38)
Thymectomy n (%)	32 (15.8%)
Detailed effects of AChEIs	
At least one side effect n (%)	127 (76.9%)
Gastrointestinal side effects n (%)	89 (53.9%)
Neuromuscular hyperexcitability side effects n (%)	113 (68.4%)
Neurovegetative side effects n (%)	59 (35.8%)
Cholinergic crisis n (%)	12 (7.3%)
Self-reported worsening of myasthenic symptoms after pyridostigmine n (%)	56 (33.9%)
Self-reported improvement after pyridostigmine n (%)	7 (4.2%)

List of abbreviations: MuSK = Muscle-specific receptor tyrosine kinase, MG = Myasthenia Gravis, MuSK Ab = Muscle-specific receptor tyrosine kinase Antibodies, AChEI = Acetylcholinesterase inhibitors; n = number.

first evaluation in Pisa and patients acknowledged rapid resolution of adverse reactions. Time course of adverse reactions resolution was self-reported but it could be explained by the brief half-life of AChEI.

4. Discussion

MuSK-MG is a rare and distinct form of MG. It is an IgG4-autoimmune disease not related to thymic pathology and distinguished by a predominant oculo-bulbar involvement with a high tendency to respiratory failure, as we also observed in the present study. With its unique immunological profile MuSK-MG presents distinct therapeutic requirements compared to patients with AChR antibodies and the rarity of the disease makes the clinical management challenging, even at specialized MG clinics.

In this retrospective study, we made two key observations: 1) the majority of MuSK patients (81.6%) had received AChEI prior to admission to our clinic and, of these, 76.9% reported at least one side effect of AChEI therapy. 2) Overall, only 4.2% of patients treated with AChEI experienced an initial clinical benefit while 33.9% reported exacerbation of muscular weakness.

4.1. Treatment of MuSK-MG with AChEI: Current status in the literature

Current treatment guidelines focus mostly on patients with AChR-MG, but MuSK patients have distinct therapeutic requirements that are less well defined and communicated. As a result, the majority of MuSK-MG patients admitted to our clinic had been treated with AChEI, few experiencing clinical benefit. This is because, despite the absence of evidence derived from randomized controlled clinical trials [29] (one exception being a small trial on intranasal neostigmine [30,31]), AChEI are still often used as first line symptomatic treatment in MG independent of the serological pattern. Indeed, the most recent international guidelines in 2020 [26] have not changed previous recommendation to use, irrespectively of antibody status, pyridostigmine bromide as first-line symptomatic therapy at a dose that must be titrated according to clinical response. It is also stated that corticosteroids or immunosuppressive therapy should only be used in MG patients who have not improved after an adequate trial of pyridostigmine. By contrast, the recent Italian Recommendations, reflecting a higher incidence of MuSK-MG in this country [21], suggest avoiding AChEI treatment in MuSK-MG because of poor tolerance and infrequent effectiveness [32].

To date, only very few studies have investigated the effectiveness and the frequency of AChEI side effects in this category of myasthenic patients, as summarized in Table 2 and illustrated in the Fig. 2.

The first comparative study on AChEI responsiveness in MuSK-MG was conducted by Hatanaka et al. [16] who compared clinical response and adverse reactions to PB in 14 MuSK-MG, 22 SNMG and 74 AChR- MG patients, observing non-responsiveness to AChEIs in 71% of MuSK-MG compared to 18% of seronegative- and AChR- MG patients and revealing both hypersensitivity to AChEI with worsening of myasthenic symptoms and a poor tolerance in MuSK-MG. Similar results were observed in greater retrospective cohorts by Evoli et al. [19] and Pasnoor et al. [5].

In 2014 Shin et al. [33] retrospectively evaluated 17 MG patients (10 MuSK-MG, 4 AChRAb-MG and 3 seronegative) assessed with electrophysiological examination before and after neostigmine test. They observed a significantly lower rate of positive test response in MuSK-MG along with a higher appearance of adverse effects after neostigmine in this category than the 4 AChR-MG patients.

Most recently, Remijn-Nelissen et al. [34] conducted a cross-sectional study on AChEI in a population of 410 patients from Dutch-Belgian myasthenia patient registry with the administration of a questionnaire designed specifically to evaluate self-reported effectiveness and adverse effects of AChEI in all MG patients. The most significant findings were the high prevalence of side effects reported by those (both AChR-MG and MuSK-MG) taking pyridostigmine (91%) in the face of a modest efficacy. Despite the very few MuSK patients involved (only 10) in the study, Remijn-Nelissen et al. also found that the vast majority of MuSK group did not perceive any clinical amelioration on AChEI and that MuSK-Ab positivity was one of the principal features significantly associated with discontinuation of AChEI treatment.

4.2. Our experience with AChEI

In line with these previous data, in our cohort, we observed a high prevalence of AChEI intolerance (in nearly all patients), which in twelve cases was of such magnitude to trigger a cholinergic crisis. Noteworthy the symptomatic relief was entirely unsatisfactory considering that only seven patients reported an initial transient improvement of muscular weakness after AChEI introduction. We have to highlight that these patients also started a steroid therapy and this can explain their transient improvement. Other relevant finding is the potential deleterious effect of AChEI in MuSK positive patients: 33.9% of patients reported a concomitant worsening of weakness during AChEI intake. This finding should be considered cautiously because it may be challenging to distinguish whether the muscle weakness is caused by MG or as a consequence of AChEI intake.

Patients reported that the severity of cholinergic side effects was greater at higher doses of AChEI, confirming dose-dependency, which is in line with previous studies and clinical practice [11,28]. However, we observed that adverse effects occurred regardless of the dose administered, suggesting that there may be a pre-existing cholinergic

Table 2
Literature review of effects of AChEI in MuSK-MG including summary of results from Table 1.

Reference	Type of study (no. of treated patients)	Cholinergic hypersensitivity to AChEIs reported?	Beneficial response (%)	No beneficial response(%)	Adverse effects or worsening (%)	Intolerance to drug (%)
Hatanaka et al [10]	RCS ($n = 14$)	not reported	3 (21%)	10 (71%)	4 (29%)	10 (71%)
Pasnoor et al [6]	Retrospective cohort study ($n = 51$)	not reported	8 (16%)	35 (70%)	10 (20%)	15 (30%)
Evoli et al [5]	Retrospective cohort study ($N = 57$)	not reported	12 (21%)	40 (70%)	6 (10%)	5 (9%)
Shin et al [17]	Retrospective cohort study ($n = 10$)	not reported	4 (40%)	6 (60%)	8 (80%)	5 (50%)
Remijn-Nelissen et al. [18]	Cross-sectional study, n = 10)	not reported	2 (20%)	8 (80%)	90% of all MG patients	
Modoni et al, [19]	Prospective cohort study ($n = 25$)	Repetitive CMAPs observed in AChEI naïve MuSK-MG patients	7 (28%)	15 (60%)	18 (72%)	15 (60%)
The current study	Retrospective cohort study ($n = 165$)	Two of 18 AChEI- naïve pts. reported clinical signs of cholinergic hyperactivity	7 (4.2%)	158 (95,8%)	56 (33.9%) worsening symptoms, 127 (76.9%) adverse effects	127 (76.9%)

A graphical summary of the data presented here is shown in the Fig. 2.
List of abbreviations: MuSK = Muscle-specific receptor tyrosine kinase, MG = Myasthenia Gravis, AChEI = Acetylcholinesterase inhibitors, CMAPs = Compound Muscle Action Potentials.

hyperactivity in MuSK patients that makes them particularly sensitive to cholinergic side effects.

4.3. What are the mechanisms of action and side-effects of AChEI?

AChEI exert their action by slowing degradation of acetylcholine (ACh) thereby prolonging the time of action of ACh at the postsynaptic AChRs and improving neuromuscular transmission, ultimately providing a symptomatic relief in the absence of any direct impact on the underlying immunological process. AChEI's adverse effects include symptoms of muscarinic hyperactivity and symptoms derived as a result of stimulation of nicotinic receptors [34]. A cholinergic overdose could desensitize AChRs and also determine a paradoxical worsening of muscular weakness up to 'cholinergic crisis' [35]. Although rarely, there are reports describing people with a polymorphism in the promoter region of the gene that encodes the catalytic subunit of AChE showing acutely exaggerated sensitivity to conventional or even lower doses of AChEI [36].

4.4. Why do MuSK-MG patients respond poorly to AChEI?

The poor tolerance to AChEI in MuSK-MG could be explained by an inherent cholinergic hyperactivity in these patients as demonstrated in some electrophysiological studies. In fact, Shin et al. [37] found that neostigmine administration induced more frequently the appearance of R-CMAPs (Repetitive Compound Muscle Action Potentials) in MuSK-MG than in AChR-MG (90% vs. 14.3%, $p = 0.004$). Even the decrement-increment pattern induced by high frequency stimulation was greater in the MuSK-MG group (100% vs. 17.7%, $p = 0.003$).

Also, Modoni et al. [38] observed that R-CMAPs were more frequent in MuSK-MG than AChR-MG patients, irrespective of AChEI therapy but particularly evident in patients with poor tolerance to pyridostigmine. These clinical data are in line with electrophysiological findings in animal models, in which injection of anti-MuSK IgG induced a reduction in the number of AChR, a loss in AChR expression and a cholinergic hyperactivity [39,40].

4.5. Limitations

Limitations of the present study include the retrospective, observational and single center design of the study, which makes it sensitive to several bias and may limit the generalizability of the results. Further limitations include data being collected during routine clinical practice rather than a formal study setting, which meant that both quality and quantity of clinical data varied among patients. Moreover, the self-reported nature of AChEI patients experience may have hindered the results with recall bias, especially those relative to timing of onset of side effects and side effects resolution and does not allow an objective and quantitative assessment of side effects severity and its eventual correlation with weakness deterioration or the dose administered.

5. Conclusions

MuSK-MG represents approximately 10% of all forms of myasthenia, which until a few years ago were considered seronegative. This specific subtype of MG exhibits a predominance of bulbar symptoms along with an ocular involvement with ptosis and significant diplopia.

Since the anti-MuSK antibodies do not interfere with nicotinic receptors, the use of anticholinesterase therapy is useless and potentially harmful in this form of MG and it only causes significant cholinergic side effects.

AChEI's adverse reactions seen in MuSK patients are similar to those caused by AChEIs in patient with anti-AChRAb positivity when they take doses higher than those necessary, but in MuSK-MG side effects appear regardless of the dose administered.

While attending antibody results, AChEI intolerance, even at low doses, should make the clinician suspect to be dealing with a possible MuSK-MG. It could therefore be useful to suggest in treatment guidelines an early re-evaluation of MG patients after AChEI introduction or, at least, educate the patient to prompt withhold AChEI as soon as side effects occur.

To date our cohort of 202 patients represents the largest population of MuSK patients ever evaluated for perceived responsiveness and tolerance to AChEI treatment. Taken together, despite the limitations previously highlighted, our data document in detail the absence of clinical benefits and the risks related to the use of anticholinesterase therapy in this specific subtype of MG and strongly suggest that AChEIs should be avoided in MuSK patients.

Contributors

Conception and design of the study: RR. Acquisition of data: EL, RR. Statistical analysis: EL. Drafting of the manuscript: EL,RR, IK, AV, AD, MM. All authors commented on the draft and approved the final version of the manuscript. Fig. 1 was created with BioRender.com (license: I. Koneczny).

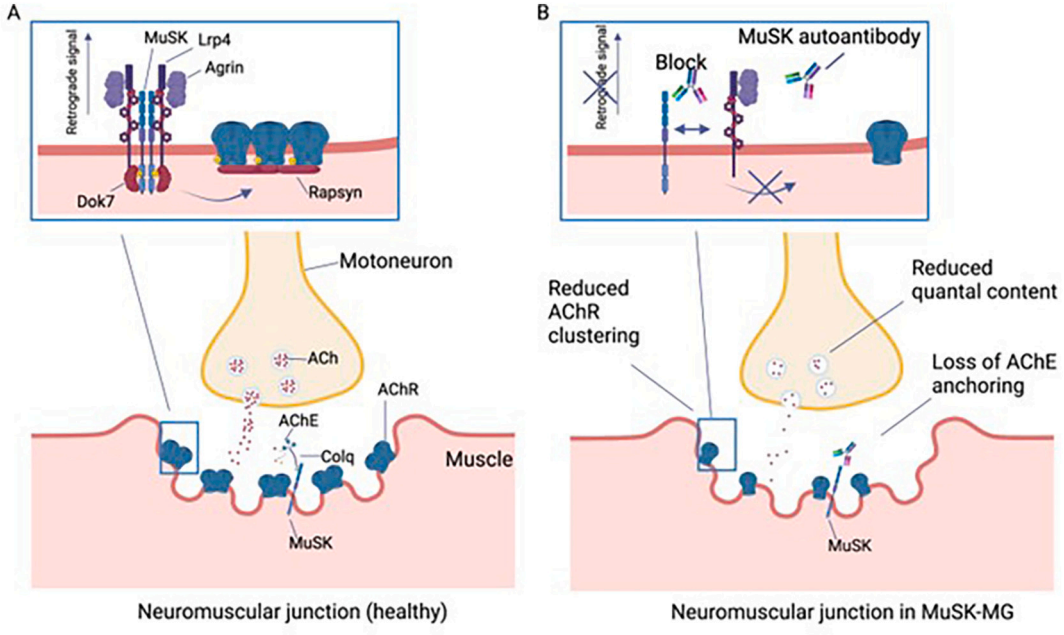

Fig. 1. Effects of MuSK autoantibodies at the neuromuscular junction. A) Healthy neuromuscular junction. B) MuSK MG: MuSK autoantibodies bind to MuSK and block binding to LRP4, therefore impairing the agrin-LRP4-MuSK-Dok7 signaling pathway and causing reduced clustering of AChRs.
List of abbreviations: MuSK = Muscle-specific receptor tyrosine kinase, MG = Myasthenia Gravis, LRP4 = Low-density Lipoprotein Receptor-related Protein 4, DoK7 = Docking Protein 7, AChRs = Acetylcholine Receptors.

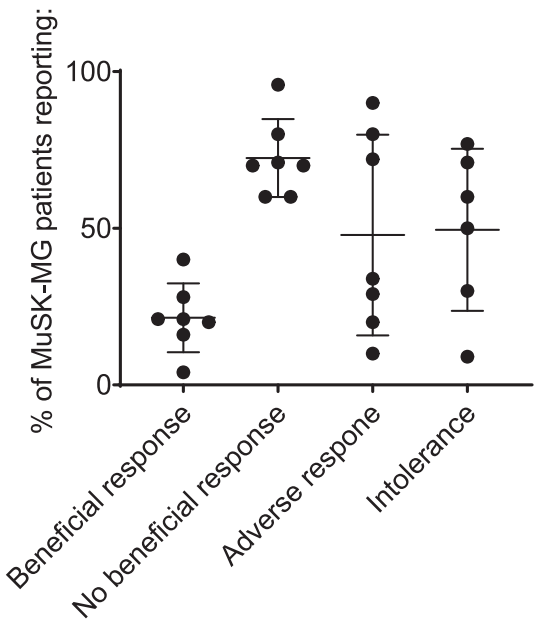

Fig. 2. Summary of effects of AChEIs on MuSK-MG patients taken from the six published and current data as summarized in Supplementary Table 2 and expressed as percentages from each study. Note that no benefit was identified in the majority of patients from each MG centre, but reports of adverse effects or intolerance to the drug were more variable. Note also that, for instance, adverse physiological effects can occur even when there is a beneficial neuromuscular response to the drug.

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Patient consent for publication

Not applicable.

Ethical approval

This study was approved by the regional ethical review board (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Sezione: AREA VASTA NORD OVEST; reference number: 3470). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

CRediT authorship contribution statement

R. Ricciardi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **E. Latini:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **M. Guida:** Writing – review & editing, Validation, Supervision. **I. Koneczny:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation. **M. Lucchi:** Writing – review & editing, Supervision. **A. De Rosa:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **A. Vincent:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation.

Declaration of competing interest

RR, EL, AD, MG, ML have nothing to disclose. AV was co-inventor of

a patent for measuring MuSK antibodies in myasthenia gravis, held by Oxford University and licensed to Athena Diagnostics USA. She received a proportion of royalties until the patent expired in 2021. She has received honoraria from Alexion, UCB and Janssen, not related to the submitted work. IK reports grants from Austrian Science Fund, lectures honoraria from Argenx and personal fees from Alexion, all not related to the submitted work. MM received lectures honoraria from Alexion and personal fees from Alexion, UCB, Indorsa all not related to the submitted work.

Data availability statement

Data are available upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123047.

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