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Dear colleagues,

It is a great pleasure to introduce you to a new issue of "Archives of Clinical Neurology". In the current issue you may find 3 articles, including one consensus paper and 2 case reports.

In the consensus paper, Chroni E. together with a group of experts in the field present the treatment recommendations of the Hellenic Neurological Society for myasthenia gravis. The authors critically reviewed the literature and provide current evidence on drugs available in Greece and rules/guidelines for induction and long term treatment. This consensus paper may serve as useful guide in every day practice of neurologist and residents treating patients with myasthenia gravis.

In a case report, Papagiannopoulou et al. present a young female patient with scapular winging due to involvement of the long thoracic nerve. High-resolution magnetic resonance neurography reveled diffuse hyperintense signal across the long thoracic nerve, highlighting the importance of imaging in such patients. The patient responded well in an intensive physiotherapy program with complete resolution of symptoms within 9 months.

In the 2nd case report, Petrou et al. describe an older male patient with a former diagnosis of mycosis fungoides (in remission), presenting with rapidly progressive cognitive decline and generalized seizures. Both 14-3-3 and RT-QuIC were positive. However, CSF T-cell lymphocytic pleocytosis together with multiple contrast enhancing lesions in neuroimaging, led to a brain biopsy revealing brain infiltration by a highly malignant T-cell lymphoma. This case report reminds that, despite a high specificity of RT-QuIC for Creutzfeldt-Jakob disease, alternative diagnoses should be considered in some unusual clinical settings.

I would like to thank all authors for sharing with us their clinical experience and research findings, offering treatment guidelines and diagnostic considerations.

George Paraskevas, MD, PhD

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TREATMENT RECOMMENDATIONS FOR MYASTHENIA GRAVIS: A CONSENSUS PAPER OF THE HELLENIC NEUROLOGICAL SOCIETY

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ABSTRACT

Given the recent development in the therapeutics of myasthenia gravis (MG), the Hellenic Neurological Society sought to present the available treatment options to achieve the goals as they have been set in the present era in a consensus document.

The authors of this article, all experienced in treating MG patients, prepared a guide for MG treatment strategies as has been modified recently and discuss the effectiveness and adverse reactions of the available drugs in Greece including those of the new categories that have been approved by European Medicines Agency. The information provided was based on a critical review of the recent literature mainly including articles on international and other countries' guidelines and expressing personal views.

A definite diagnosis of MG and subtyping according to the MG Foundation of America (MGFA) classification, immunological profile, thymus pathology, or co-existing other medical conditions should precede treatment. When choosing a treatment approach, a balance should be kept between drug effectiveness i.e. successfully managing acute symptoms and sustaining remission and drug burden, including adverse effects and patient's discomfort. Response to treatment is better quantified using structured clinical scales and a commonly agreed definition of deterioration on one side and the optimum post-intervention status on the other.

No uniform treatment regimen exists to be recommended for all patients with MG. However, there are general rules for induction and long-term treatment, which should then be individualised based on clinical symptoms, disease severity, and patient's age, and after careful consideration of each patient's requirements in social and professional life. Steroids remain the first-line treatment for the majority of MG patients, followed by azathioprine and, alternatively, other immunosuppressive medications that serve to lower the dose or replace steroids. For patients with MuSK-positive antibodies, rituximab is particularly effective. Novel immunomodulatory, fast-acting drugs (i.e. complement C5 inhibitors and FcRn blockers) can be added to various therapeutic regimens, on an individual basis to improve the outcome. The impending and established myasthenic crisis requires emergency treatment with plasmapheresis or IVIG. We expect this first attempt to codify MG therapy recommendations to be helpful for clinical practice and form the basis for future revisions upon fruitful criticism.

Keywords: myasthenia gravis, clinical scales, immunotherapy, new drugs, drug adverse effects, thymus, auto-antibodies, MG in pregnancy, myasthenic crisis, treatment guidelines, consensus, Greece

ΚΑΤΕΥΘΥΝΤΗΡΙΕΣ ΟΔΗΓΙΕΣ ΓΙΑ ΤΗΝ ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΒΑΡΕΙΑΣ ΜΥΑΣΘΕΝΕΙΑΣ: ΕΝΑ ΑΡΘΡΟ ΟΜΟΦΩΝΙΑΣ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΝΕΥΡΟΛΟΓΙΚΗΣ ΕΤΑΙΡΕΙΑΣ

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Περίληψη:
Δεδομένης της πρόσφατης εξέλιξης στη θεραπευτική της βαρείας μυασθένειας (MG), είναι χρήσιμο να παρουσιαστούν οι διαθέσιμες θεραπευτικές επιλογές για την επίτευξη των στόχων όπως αυτοί έχουν τεθεί στη σημερινή εποχή μέσα από αυτό το άρθρο ομοφωνίας της Ελληνικής Νευρολογικής Εταιρείας.
Οι συγγραφείς αυτού του άρθρου, όλοι έμπειροι στη θεραπεία ασθενών με MG, ετοίμασαν έναν οδηγό για στρατηγικές θεραπείας της MG όπως τροποποιήθηκαν πρόσφατα και συζητούν την αποτελεσματικότητα και τις ανεπιθύμητες ενέργειες των διαθέσιμων στην Ελλάδα φαρμάκων, συμπεριλαμβανομένων εκείνων που ανήκουν στις νέες κατηγορίες και εγκρίθηκαν από τον Ευρωπαϊκό Οργανισμό Φαρμάκων (EMA). Οι πληροφορίες που παρέχονται βασίστηκαν σε μια κριτική ανασκόπηση της πρόσφατης βιβλιογραφίας, συμπεριλαμβανομένων κυρίως άρθρων για διεθνείς και κατευθυντήριες γραμμές άλλων χωρών και εκφράζοντας προσωπικές απόψεις.
Η βέβαιη διάγνωση της MG και ο προσδιορισμός του υπότυπου σύμφωνα με την ταξινόμηση του MG Foundation of America (MGFA), το ανοσολογικό προφίλ, η παθολογία του θύμου αδένα, οι συνυπάρχουσες άλλες ιατρικές καταστάσεις θα πρέπει να λαμβάνονται υπόψη πριν την έναρξη της θεραπείας. Κατά την επιλογή μιας θεραπευτικής προσέγγισης, θα πρέπει να διατηρείται μια ισορροπία μεταξύ της αποτελεσματικότητας του φαρμάκου, δηλαδή της επιτυχούς διαχείρισης των οξέων συμπτωμάτων και της διατήρησης της ύφεσης και των αρνητικών επιδράσεων ενός φαρμάκου, συμπεριλαμβανομένων των ανεπιθύμητων ενεργειών και της συμμόρφωσης του ασθενούς. Η ανταπόκριση στη θεραπεία ποσοτικοποιείται καλύτερα χρησιμοποιώντας δομημένες κλινικές κλίμακες και έναν κοινά αποδεκτό ορισμό της επιδείνωσης από την μία πλευρά και της βέλτιστης κατάστασης μετά την παρέμβαση από την άλλη.
Δεν υπάρχει ενιαίο θεραπευτικό σχήμα που να συνιστάται για όλους τους ασθενείς με MG. Ωστόσο, υπάρχουν γενικοί κανόνες για την έναρξη και τη μακροχρόνια θεραπεία, οι οποίοι στη συνέχεια θα πρέπει να εξατομικεύονται με βάση τα κλινικά συμπτώματα, τη σοβαρότητα της νόσου και την ηλικία του ασθενούς και μετά από προσεκτική εξέταση των απαιτήσεων κάθε ασθενούς στην κοινωνική και επαγγελματική ζωή. Τα στεροειδή παραμένουν η θεραπεία πρώτης γραμμής για την πλειοψηφία των ασθενών με MG, ακολουθούμενα από την αζαθειοπρίνη και εναλλακτικά άλλα ανοσοκατασταλτικά φάρμακα που χρησιμεύουν για τη μείωση της δόσης ή την αντικατάσταση των στεροειδών. Για ασθενείς με θετικά στο MuSK αντισώματα, η ριτουξιμάμπη είναι ιδιαίτερα αποτελεσματικό φάρμακο. Νέα ανοσοτροποποιητικά, ταχείας δράσης φάρμακα, δηλαδή αναστολείς C5 του συμπληρώματος και αναστολείς FcRn μπορούν να προστεθούν σε διάφορα θεραπευτικά σχήματα, σε ατομική βάση για τη βελτίωση του αποτελέσματος. Η επικείμενη και εγκατεστημένη μυασθένεια κρίση απαιτεί επείγουσα θεραπεία με πλασμαφαίρεση ή IVIG. Αναμένουμε ότι αυτή η πρώτη προσπάθεια κωδικοποίησης των συστάσεων θεραπείας της MG θα είναι χρήσιμη για την κλινική πρακτική και θα αποτελέσει τη βάση για μελλοντικές αναθεωρήσεις μετά από γόνιμη κριτική.

Λέξεις ευρετηρίου: Μυασθένεια Gravis, κλίμακες αξιολόγησης, ανοσοθεραπεία, νέα φάρμακα, ανεπιθύμητες ενέργειες φαρμάκων, θύμος αδένας, αυτοαντισώματα, MG και εγκυμοσύνη, μυασθενική κρίση, κατευθυντήριες οδηγίες, συναίνεση, Ελλάδα

ΕΛΛΗΝΙΚΗ ΝΕΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

INTRODUCTION

Myasthenia Gravis (MG) is the most common among the acquired autoimmune disorders of the neuromuscular junction. The European prevalence of MG has recently been estimated to vary between 11 and 36 per 100.00 persons,[1] and therefore, in the Greek population, approximately 1100 to 3500 people are expected to suffer from MG.

MG is clinically characterised by fluctuating and alternating muscle weakness and fatiguability. It can practically affect all striated muscles, although there is a selectivity for the extraocular muscles which are the first and more frequently affected (in 60-75% of cases), followed by the facial, bulbar, and neck, and thereafter the respiratory and proximal limb musculature.[2,3] MG is caused by a defect in the transmission of acetylcholine (ACh) through the neuromuscular junction, which is due to the presence of pathogenetic auto-antibodies. In about 85% of patients with generalised MG (gMG) and 50% of those with ocular MG (oMG) antibodies against ACh Receptors (AChR) were detected, whereas antibodies against MuSK or LRP4 are much less frequent, being present in 5% and 1-4% of patients respectively. Finally, in approximately 10% percent of patients, no detectable antibodies are found.[2,4] A definite diagnosis is necessary before any treatment attempt. Diagnosis is set by clinical appraisal and confirmed by serological tests to define the auto-antibody profile, and/or neurophysiological tests.[3]

Currently, MG has no cure.[2] Treatment aims to ease the MG symptoms during acute exacerbation and prolong remission phases by addressing immunopathology while maintaining a fair balance between quality of life and treatment-related burden. Therapeutical decisions are challenging due to the variety of available drugs, some of which have novel mechanisms of action, the number of possible drug combinations or drug switches, and the undefined duration of treatment necessary for disease control. Factors, that should be taken into account when deciding on drugs suitable for each patient are: disease characteristics i.e. weakness distribution and severity, antibody profile; the presence of thymoma; patient's age; comorbidities; personal needs, for example, family planning; professional requirement; and patient's compliance.[5]

The scope of this article is to outline the general framework of recommendations on the therapeutic approach of patients diagnosed with MG in Greece. For this purpose, the Hellenic Neurological Society sought to present the available treatment options to achieve the goals as they have been set in the present era in a consensus document. Specifically, a team of MG experts and senior neurologists who often treat MG patients was organised at a national level. In September 2024, a face-to-face meeting was held to assign the deliverables. Subsequently, a literature search was performed, focusing on high-quality articles that reported treatment guidelines implemented in other countries or published by international consortia up to December 31, 2024. These articles were critically reviewed and served as the foundation for this article. Finally, virtual rounds to exchange views on various therapeutic topics were organised. All team members are the authors of this article, who contributed to the writing of the first draft and approved its final version. All recommendations presented in the current consensus paper were unanimously approved by all authors.

Evaluation scales

Several structured, widely accepted scales are necessary to assess the spreading and severity of muscle weakness and to evaluate the effect of treatment.

Myasthenia Gravis Foundation of America (MGFA) Clinical Classification: This classification roughly divides the patients into V classes according to the disease's severity and the distribution of muscle involvement.[6]

Quantitative Myasthenia Gravis (QMG) Scale: This scale objectively evaluates the strength and endurance for 13 selected motions at a specific time point (during the patient's visit). It requires 16 minutes, and the total QMG score ranges from 0 (normal) to 39 (worst possible).[6]

Myasthenia Gravis Activities of Daily Living (MG – ADL): The patient's reported questionnaire, combines 2 items of daily living activities with 6 items of physiological functions concerning the prior week. The total score ranges from 0 (normal) to 24 (worst possible).[7]

Myasthenia Gravis Composite (MGC) Scale: It combines 3 items from the patient's reported history and 7 items from the physician's examination. The total score ranges from 0 (normal) to 50 (worst possible) and constitutes a merging of QMG and ADL scale.[8]

Definitions of status related to treatment

To rate the status after treatment interventions the following definitions are adopted:

Classical evaluation of treatment

The ***classical evaluation of treatment*** efficacy is based on the determination of the post-intervention status (PIS), which is graded as: Complete Stable Remission (CSR); Pharmacological Remission (PR); Minimal Manifestations (MM); Improved (I) (but not reaching the previous higher grades); Unchanged (U); Worse (W); Exacerbation (E) or Death from MG (D).[6]

Optimum outcome after treatment

Remission, or at least MM with grade 1 Common Terminology Criteria for Adverse Events (CTCAE)

medication side effects i.e. asymptomatic or only mild symptoms, no intervention is indicated.[9]

I. Remission: The patient has no symptoms or signs of MG. Careful examination showing isolated weakness of eyelid closure is acceptable. Patients in daily need of taking cholinesterase inhibitors (ChEIs) are not considered to be in remission.[9]

II. MM status: The patient has no functional limitations but some weakness in some muscles during the examination[9]; a total QMG score of ≤3 from ≥2 items is acceptable.

Alternative way to grade treatment response

Recently, an ***alternative way to grade treatment response*** has been suggested in the German Guidelines. Achievement of disease control is graded into four levels: (1) Full disease control with no disease activity and no residual symptoms. (2) Full disease control with no detectable disease activity, but minimal residual symptoms with stability (incomplete remission). (3) Incomplete disease control with disease activity: instability, deterioration, fluctuation with residual symptoms and continuous new or developing symptoms, ± fluctuations, ± crises. (4) No disease control with high disease activity (including refractory MG): continuous symptoms with or without crises or crisis-like deteriorations, resistance to therapy.[10]

In the 4-level classification of disease control, level 1 approximately corresponds to Remission and level 2 corresponds to MM status.

The ***optimum patient satisfaction*** can be expressed through scoring in the ADL scale, with Minimum Symptom Expression (MSE) defined as a score 0 or 1.[11]

Relapse or Exacerbation: A deterioration of MG symptoms appearing after at least a month of remission and lasting no less than 24 hours. The following severity grades of acute deterioration are recognised:

Relapse, defined as an increase of QMG score by ≥ 3 from 1 or more items and a total QMG score ≥ 6.

Impending Crisis, defined as a rapidly deteriorating status that may lead to a myasthenic crisis in the short term (days to weeks).[9] The term Severe Relapse provides a quantification of Impending Crisis and is defined as an increase of bulbar and neck QMG score ≥ 3 or respiratory ≥ 1 (irrespectively of total QMG score), or increase of QMG score by ≥ 3 from 1 or more items and QMG total score ≥ 15.[12]

Myasthenic Crisis, defined as severe worsening of respiratory function requiring intubation or non-invasive ventilation.[9] It is a medical emergency and a life-threatening condition.

Refractory MG: Failure of conventional treatment due to one of the following: 1. Inadequate response, defined as PIS unchanged or worse, to steroids and at least one other IS, applied in adequate doses and for an adequate duration; 2. Requirement of repeated rescue therapies (IVIG or Plex), at least 3 times within 12 months; 3. Prolonged need for high doses of potentially harmful therapies (drug dependency); 4. Severe or intolerable adverse effects from immunosuppressive therapy (treatment intolerance) leading to treatment discontinuation; 5. Comorbidities as a consequence of which myasthenia treatment is contraindicated.[9,12,13]

TREATMENT

Medical treatment includes 2 major categories: ***symptomatic treatment***, which aims to restore neuromuscular transmission quickly but temporally; and ***immunomodulatory and immunosuppressive drugs (collectively referring as ISs)***, which aim to terminate the immune attack on the neuromuscular junction. Next, the mechanism of action, the dosage, and any adverse events of the frequently used drugs for the treatment of patients with MG during acute and chronic phases are described.

Symptomatic treatment

It comprises the administration of acetylcholinesterase inhibitors (AchE-I) and, occasionally, beta-2 adrenergic agonists.[14]

Pyridostigmine

Indications & mechanism of action: Pyridostigmine is strongly recommended as symptomatic treatment for all forms of MG. It is a synthetic acetylcholinesterase inhibitor (AchE-I) that acts by retarding the hydrolysis of Ach at the neuromuscular cleft thereby facilitating neuromuscular transmission.[2,10,14,15]

Effectiveness & Contraindications: In early or less severe disease pyridostigmine has a significant and rapid clinical effect whereas in chronic and/or advanced cases, its' action may be insufficient. It has been suggested,[16] but not universally agreed (Farmakidis et al., 2018), that the effectiveness of pyridostigmine diminishes over time and the wearing off was ascribed to the expression of a soluble splice variant of the acetylcholinesterase gene, that is not inhibited as effectively by the drug.[17] The effectiveness of pyridostigmine is generally moderate[18] but varies amongst different MG populations. For instance, it is less prominent in anti-MuSK cases, compared to patients with AChR autoantibodies,[19] whereas it is particularly robust in juvenile MG.[20] The maximum blood concentration (Cmax) of pyridostigmine is attained 1.5–3 h after oral ingestion but symptom improvement may start within 15-30 min.[21] The drug should be avoided in cases of gastrointestinal or urinary obstruction and used cautiously in patients with renal impairment (the clearance of the drug is reduced, and dosages need adjustment), obstructive respiratory disease, cardiac arrhythmias

or recent coronary artery occlusion. Elderly patients may be particularly prone to develop cardiac adverse effects and develop syncope even with very low doses of the drug.

Dosing schedule: A typical starting dose is 30mg qid for 2-4 days subsequently increased to 60 mg qid for 5 days while adjusting the time of administration to match the patient's activity needs. If necessary, the dose may be increased to 90 mg qid over one week or even higher trying always to identify the lowest effective dose. Since there is interindividual variation in the duration of action, some patients may require 5 rather than 4 daily dosages. Usual daily doses range from 180-450 mg/24h although occasional cases may need up to 720 mg/24h.[10] If the patient with gMG becomes asymptomatic on steroids,[2] it is possible to taper pyridostigmine at a rate of 30–60 mg per week until complete withdrawal or, if this is not feasible, until reaching the lowest effective dose.

Adverse Effects: Pyridostigmine is commonly associated with muscarinic side effects which are dose-dependent and may lead to drug discontinuation in up to 26% of patients.[18] The most common adverse effects are gastrointestinal (nausea, diarrhoea, abdominal cramps, and flatulence). These symptoms tend to abate over time but can be persistent in a number of cases. Other side effects include urinary urgency, muscle cramping, blurred vision, increased sweating, bronchial secretions, hypotension, and bradycardia.[18,21] The management of persistent or troublesome symptoms involves the administration of propantheline 15 min prior to pyridostigmine. This antimuscarinic agent counteracts many cholinergic adverse effects of pyridostigmine without affecting its facilitatory action on neuromuscular transmission. Importantly, although the Summary of Product Characteristics of propantheline states that the drug is contra-indicated in MG (SMPC), this is clearly incorrect as it is a standard treatment for counteracting the toxicity of pyridostigmine. Other agents that may be used to this end include oral glycopyrrolate 1 mg, hyoscyamine 0.125 mg, or loperamide 2 mg to be given concurrently with pyridostigmine up to thrice daily.[21] At doses higher than those regularly used, pyridostigmine may induce a paradoxical worsening of muscular weakness that may lead to bulbar palsy and respiratory insufficiency due to drug excess rather than MG per se. This entity, termed "cholinergic crisis", is now rarely encountered because currently available, highly efficacious immunotherapies obviate the need for use of excessively high dosages of the drug.[15] It should be noted that the intravenous injection of edrophonium in order to decide whether weakness is due to pyridostigmine excess or MG is not reliable and the optimal strategy in those rare cases where cholinergic weakness is indeed probable is the temporary withdrawal of the AchE-I while monitoring the patient for improvement. Parenthetically, in ventilated patients with myasthenic crisis, it is recommended to withdraw pyridostigmine in order to limit oral and bronchial secretions.

In rare instances of ineffectiveness or intolerance to pyridostigmine, ambenonium,[14] neostigmine, or distigmine may also be tried.[10]

Beta-2 adrenergic agonists

There is limited clinical and neurophysiological evidence from small scale, placebo-controlled trials that low-dose beta-2 adrenergic receptor agonists, such as terbutaline or salbutamol, may improve the symptoms of MG.[22,23] Accordingly, these drugs may be used as adjuvant symptomatic agents in selected cases, provided no contraindications exist (i.e. significant cardiovascular disease, uncontrolled hyperthyroidism, hypokalaemia).

Steroids

Mechanism of action: Steroids have an immunomodulatory effect. They promote apoptosis in T cells, particularly in CD4+ T cells that are required to interact with B cells, suppress the transcription of inflammatory cytokines, and exert a moderate effect on B cells by reducing their total number resulting in decreasing AChR-antibody levels.[24]

Indications and effectiveness: Steroids have been introduced in the treatment of MG since the decades 1950 and 1960 leading to a dramatic reduction of mortality. To this day, they remain the backbone of treatment strategy.[25] The initial small case series, demonstrating the benefits of steroids, were followed by larger, long-term studies that showed improvement in 70-80% of patients.[24,25] Steroids constitute the first-line disease-modifying treatment for all patients with MG irrespective of antibody profile, age, thymus pathology, or disease severity.[10,26] Onset of response is expected in 2-4 weeks[25] and the maximum possible response may be delayed up to six months.

Dosing schedule: The steroid prednisolone is commonly used in Greece instead of prednisone employed by the International Consensus Guidance.[9] It is suggested to start treatment with prednisolone 10-20 mg/day in a single morning administration, increasing the dose by 5 mg/day weekly until the treatment goal is achieved based on the judgment of the treating physician, or to a maximum of 60mg/day.[2,25] Steroids initiation at high doses is not generally recommended since it can cause transient clinical worsening in 50% of the patients, occasionally resulting in a myasthenic crisis.[9] The worsening, which can also be seen in some patients at lower doses, usually occurs within the first 2 weeks and can last for several days, therefore during that time hospitalisation is recommended, particularly in elderly patients with

bulbar symptoms or thymoma.[9,24]

After achieving the optimum goal, according to the international guidelines, a slow alternate day tapering by 5mg/day dose equivalent per month is suggested.[9] However, a more recent single-blind, parallel, randomised clinical trial showed that an earlier and rapid decrease (lowering 10mg from daily dose every 10-15 days) is feasible, well tolerated, and with a good outcome until a plateau of 20-15mg equivalent daily dose.[27] Once a dose of 30mg on alternate days is reached, a slower rate of tapering by 2.5 mg every 2 weeks is suggested until a maintenance dose of 10mg or lower is achieved.[24] Complete cessation of steroids is not advised, since forever continuation of a low dose (5mg/day) protects from relapses.[9] The maximal initial dose and the rate of titration can be adjusted on an individual patient basis considering the clinical features and extent of symptoms.[25] Daily steroids administration, instead of an alternate day scheme, is more appropriate in patients with diabetes mellitus for better blood sugar control.

A nonsteroidal IS agent should be administered alone when corticosteroids are contraindicated or in conjunction with a low dose of corticosteroids when there is a high risk of steroid side effects. A nonsteroidal IS agent should be added to standard treatment with corticosteroids when: a. significant steroid side effects appear; b. the treatment response to steroids is less than optimum; c. a steroid-dependency is developed, demonstrated by exaggeration of symptoms in an attempt to lower the dose.[9]

Adverse effects: Steroids can cause a variety of systematic adverse effects ranging from mild to severe, some of which are frequent and unavoidable. These are: weight gain, cataracts, glaucoma, hypertension, diabetes mellitus, osteoporosis, osteonecrosis, skin fragility, gastrointestinal ulcers, mood changes, insomnia, hirsutism, hypothalamic-pituitary axis suppression, cushingoid appearance, growth retardation in children.[9,24]

Precautions and monitoring during steroid treatment: Before steroids' initiation, testing for latent or active tuberculosis and hepatitis B & C (HBV/HCV), measurement of intraocular pressure and bone density, and performing the required vaccinations are the necessary actions.

During steroids treatment the patient should be strongly advised to follow a diet of low carbohydrates and salt and should be given medication for gastroduodenal prophylaxis and supplements for calcium and vitamin D; the blood sugar and glycated haemoglobin (HbA1C), the blood pressure, the intraocular pressure, the bone density should be periodically monitoring.[9]

Azathioprine

Indications and mechanism of action: Azathioprine is a purine analogue that inhibits the synthesis of nucleic acids. It interferes with T and B cell proliferation and lowers AChR antibodies in patients with MG. Azathioprine (along with mycophenolate mofetil) are the most commonly used glucocorticoid-sparing therapies in patients with MG (MuSK, LRP4, or acetylcholine receptor (AChR) antibody positive or seronegative). For MuSK-positive MG: If cost or access to rituximab is prohibitive, azathioprine (and mycophenolate mofetil) remains reasonable to use as first-line steroid-sparing therapies.[9,26,28]

With a lack of data from comparative trials, yet azathioprine is supported as a first-line glucocorticoid-sparing agent by expert consensus, observational data, and limited randomised trial evidence. In observational studies, azathioprine reported to improve MG symptoms in 70% to 90% of patients, but the onset of any beneficial effect seems to be delayed 6 to 12 months, with a maximal effect often not seen until one to two years of treatment. This was demonstrated in a three-year randomized trial of prednisolone plus azathioprine versus prednisolone plus placebo in 34 patients with generalised MG. At one year, the median prednisolone dose required to maintain remission was similar between groups (37.5 versus 45 mg prednisolone every other day for azathioprine and placebo groups, respectively). By three years, however, azathioprine azathioprin lowered the median prednisolone dose (0 versus 40 mg every other day), the proportion of patients still requiring prednisolone (20 versus 63 percent), and the number of relapses and treatment failures.[29]

Before using the drug: Before starting azathioprine, it is prudent to screen patients for variants in the thiopurine methyltransferase (TPMT) gene that causes TPMT deficiency. One in 300 individuals is homozygous for a genetic variant and has very low or absent enzyme levels. Such patients should not receive azathioprin because they cannot metabolise the drug and may develop life-threatening bone marrow suppression. Patients who are heterozygous for a genetic variant generally have low enzyme activity but can tolerate azathioprine at lower than usual doses. Either genotype and/or phenotype (such as erythrocyte enzyme level assay in serum) testing for TPMT deficiency may be done.[30]

Dosing schedule: Azathioprine, whether used alone or in combination with glucocorticoids, is begun at a dose of 50 mg daily for two to four weeks. If it is tolerated without systemic side effects, it can be increased by 50 mg increments every two to four weeks to a maintenance dose of 2 to 3 mg/kg body weight. In most patients, this is typically 150 to 200 mg each day.

Adverse effects and monitoring: Monthly monitoring of complete blood counts (CBCs) and liver function tests are recommended for the first six months

and then less frequently if values remain stable.[31]

The most common side effect with azathioprine is a flu-like syndrome with fever, nausea, vomiting, and malaise, developing in 10 percent of patients. Less frequent adverse events include hematologic, gastrointestinal, or liver problems. The initial flu-like illness is idiosyncratic and develops within the first few weeks of treatment. The drug should be discontinued in the patient, and the symptoms quickly abate.

Hepatotoxicity, suppression of the white blood count, and pancreatitis are less common but serious potential adverse effects. For these reasons, it is useful to monitor with a CBC and liver function tests weekly and then at least monthly for at least six months, and then appropriately. The azathioprine dose should be decreased and the CBC monitored more frequently if the white blood count falls below 3500-4000 cells/mm^3. Azathioprine should be discontinued if the white blood cell count falls below 2500-3000 cells/mm^3. Azathioprine should also be discontinued if the liver function studies are more than mildly abnormal or continue to rise. Serum amylase should be performed if symptoms develop that are consistent with pancreatitis, andazathioprine-should be discontinued if the amylase is elevated in this setting.

Azathioprine causes a macrocytosis (increased mean corpuscular volume (MCV) of the erythrocytes). This is usually not clinically significant, but some use it as a means to assess dosing and compliance.

Although it is quite uncommon in patients with MG, the risk of malignancy with long-term azathioprine use may be increased for non-Hodgkin lymphomas and non-melanotic skin cancer. The malignancy risk is likely relatively low and analogous to the experience seen with its use in rheumatoid arthritis.[32]

There is an important drug interaction between azathioprine and the xanthine oxidase inhibitors allopurinol and febuxostat. Xanthine oxidase inhibitors interfere with the metabolism of 6-mercaptopurine, the active metabolite ofazathioprine. Therefore, xanthine oxidase inhibitors should not be used in combination with azathioprine if possible.

Older adults: There are few studies that look at the treatments in this particular age group. However, the usefulness of immunotherapy is supported by a study of outcome at one year or longer in 149 patients with disease onset after age 60 who were treated with azathioprine with or without prednisone. Better outcomes and fewer side effects were observed when prednisone was avoided or was combined with azathioprine. In general, the use of azathioprine can be considered in older patients.[33]

Pregnancy: There are limited data from azathioprine use in pregnancy, mainly in transplant recipients and patients with autoimmune diseases other than MG. Azathioprine has been linked to spontaneous abortion, preterm labor, low birth weight, chromosomal damage, and hematologic suppression. In patients who cannot be adequately controlled on prednisone, cannot tolerate glucocorticoids, or have significant comorbidities that may worsen with glucocorticoid administration, selective use of azathioprine during pregnancy could be considered when the benefits of immunosupression with this agent appear to outweigh the risks. In general,azathioprine is considered safer in pregnancy than other immunosuppressant drugs, including mycophenolate mofetil, cyclosporine, and tacrolimus.

The risk of continuing azathioprine should be weighed against the benefit of controlling myasthenic symptoms.

Active metabolites of azathioprine have been detected in milk of women receiving azathioprine treatment. Breast-feeding and concomitant use of azathioprine are contra-indicated.

Mycophenolate Mofetil

Mechanism of Action: Mycophenolate Mofetil (MMF), as a prodrug of mycophenolic acid, affects the proliferation primarily of lymphocytes, through the inhibition of inosine monophosphate dehydrogenase, an enzyme with a crucial role in the de novo synthesis of guanosine nucleotides. MMF was primarily used as an immunosuppressive agent to prevent rejection in organ transplantation. By reducing both T and B cells, MMF can decrease the levels of the pathogenic autoantibodies in MG patients. In addition, the ability of MMF to diminish lymphocyte activity and to decrease pro-inflammatory cytokines production further contribute to its immunosuppressive effect.[34]

Indications: There have been several studies investigating the efficacy of MMF in MG. Several open-label clinical trials and retrospective studies have reported clinical improvement, less relapses, and corticosteroid dose reduction when MMF was added to the treatment of MG patients.[35-37] However, two subsequent randomised controlled clinical trials failed to any statistically significant difference between MMF and placebo, in MG patients on prednisolone treatment.[38,39] MMF is not currently approved for the treatment of MG. Nevertheless, MMF is a common alternative as immunosuppression in MG patients experiencing adverse effects from corticosteroids or azathioprine, as a steroid-sparing agent and in refractory MG patients as an add-on treatment [9].

Dosing schedule: MMF is administered orally. The starting dose usually used for MG treatment is 500–1000 mg twice daily. An increase of total daily dose to 2000-2500 mg is considered reasonable according to patient tolerance and clinical response. To increase absorption MMF should be taken before meals on an empty stomach.

Contraindications/ Safety: In most patients, MMF

is well-tolerated. There are several MMF contraindications such as hypersensitivity, pregnancy, breastfeeding, severe active infections, pre-existing immunodeficiency, active gastrointestinal diseases, severe liver dysfunction, and renal impairment. Regarding pregnancy, MMF is teratogenic and in women of childbearing potential effective contraception is required.[40] Regarding infections, patients under MMF treatment are susceptible to opportunistic infections and early detection of signs and symptoms of infection is of great importance.

Adverse effects: Most common adverse reactions of MMF include gastrointestinal symptoms, such as vomiting, nausea, diarrhoea, and abdominal pain, haematological disturbances like leukopenia, anaemia, and thrombocytopenia. To detect the adverse effects mentioned earlier during MMF treatment, regular full blood counts, liver and renal function tests are crucial.

Cyclosporine

Mechanism of Action: Cyclosporine selectively inhibits calcineurin, impairs the production of interleukin-2, and inhibits T lymphocyte-dependent immune responses.[9,26,28]

Observational studies and small placebo-controlled trials have demonstrated the efficacy of cyclosporine both in newly treated patients with MG and in prednisone-treated patients.[41-43]

In the largest trial, 39 patients with prednisone-dependent MG were treated with either prednisone plus placebo or prednisone plus cyclosporine at a dose of 5 mg/kg per day (in two divided doses). At six months, the cyclosporine group showed greater improvement in quantitative strength testing. This group also had a nonsignificantly lower mean prednisone dose. Over the subsequent 18 months of open-label follow-up, progressive nephrotoxicity led to discontinuation of cyclosporine in 10 percent, and cumulative side effects led to discontinuation in a total of 35 percent [42].

Cyclosporine may achieve results faster than azathioprine or mycophenolate, but concerns about kidney toxicity, hypertension, and drug interactions limit its use as first-line steroid-sparing agent. In rare patients with contraindications to both drugs (eg, active liver disease for azathioprine and lymphopenia for either azathioprine or mycophenolate), cyclosporine may be used as an initial oral glucocorticoid-sparing agent.[9,26,28]

Dosing schedule: When used in patients with MG, cyclosporine is typically started at 2.5 mg/kg per day in divided doses. The dose can be increased in 0.5 mg/kg per day increments every four to eight weeks as tolerated to a maximum of 5 mg/kg per day. Clinical practice varies with regard to monitoring of cyclosporine levels; some have suggested aiming for trough levels <300 ng/mL.

Clinical benefit in MG can often be appreciated as early as one to two months after starting cyclosporine, with the full effect usually achieved on average after 6-7 months of continuous treatment.

Adverse effects and monitoring: Hypertension and nephrotoxicity are the most common limiting adverse effects of cyclosporine. Progressive nephrotoxicity occurs in up to 10 percent of patients. Before initiation of treatment a baseline level of renal function should be established by at least two measurements. The estimated glomerular filtration rate (eGFR) can be used for estimation of renal function and should be repeated frequently. If eGFR decreases by more than 25% below baseline at more than one measurement, the dosage should be reduced by 25 to 50%. If the eGFR decrease from baseline exceeds 35%, further reduction of the dose should be considered. These recommendations apply even if the patient`s values still lie within the laboratory`s normal range. If dose reduction is not successful in improving eGFR within one month, cyclosporin treatment should be discontinued. In addition, liver function tests, serum lipids, potassium, magnesium and uric acid are advisable before treatment and periodically during treatment, along with regular monitoring of blood pressure. Other cyclosporine side effects include tremor, nausea, gingival hyperplasia, myalgias and flu-like symptoms, and hypertrichosis. The risk of malignancy, primarily squamous cell skin cancer and lymphoma, may also be increased with long-term use.

Through its metabolism via the cytochrome P450 system, cyclosporine interacts with many other medications as a substrate of CYP3A4 and an inhibitor of CYP2C8/9 and 3A4. Some drugs reduce the serum cyclosporine levels, whereas others raise the levels. It is important to check trough cyclosporine levels after any of these medications are added to or withdrawn from the patient's regimen.

Older adults: Due to the potential kidney side effects, the use of cyclosporine is not commonly recommended in these patients.[33]

Pregnancy: There are no adequate or well-controlled clinical studies in pregnant women using ciclosporin. There is a moderate amount of data on the use of ciclosporin in pregnant patients from postmarketing experience, including transplantation registries and published literature with majority of cases available from transplant recipients. High doses of cyclosporine have been linked to spontaneous abortion, preterm labour, low birth weight, chromosomal damage, and hematologic suppression. As with azathioprine, selective use of cyclosporine during pregnancy may be considered when the benefits of immunosuspression with this drug appear to outweigh the risks. It could be considered for pregrant patients who are not controlled, cannot tolerate

glycocorticoids, or have significant comorbidities that may worsen with glucocorticoid administration. The risk of continuing this medication should be weighed against the benefit of controlling myasthenic symptoms. In general, cyclosporine should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Cyclosporin passes into breast milk. Mothers receiving treatment with cyclosporin should not breast-feed because of the potential of the drug to cause serious adverse drug reactions in breast-fed newborns/infants.

Methotrexate

Mechanism of Action: Traditionally used for treating various autoimmune disorders, methotrexate is an immunosuppressive agent, that works through inhibition of dihydrofolate reductase, leading to a decrease of DNA, RNA, thymidylates, and proteins synthesis. Thus, a reduction of the proliferation of immune cells, especially lymphocytes, is achieved, mitigating the immune response against neuromuscular junction components occurring in patients with MG.

Indications: Among the treatments currently used for MG, methotrexate is considered an off-label treatment, and its use could be beneficial as a steroid-sparing agent in refractory cases with intolerance to other first-line immunosuppressants. According to a randomised, placebo-controlled trial in 2016 that included 50 patients with AChR-positive generalised MG receiving stable dose of prednisone, there was no significant difference between methotrexate and placebo groups regarding reduction of prednisone dose over the 12-month period and there were also no significant changes in MG activities of daily living (MG-ADL) score and quantitative MG (QMG) scores. [44] Although there is a lack of evidence from RCTs, its use could be preserved for patients who do not respond clinically to first-line treatments, or who experience significant adverse effects.[26]

Dosing schedule: Methotrexate can be administered either orally or via subcutaneous or intramuscular injection in weekly intervals. While its use in MG treatment is still under investigation, there is guidance on dosing originating from several studies and reports of clinical experience, as well as from studies for several rheumatic diseases.[44-46] Usually, the initial dose of methotrexate is 7.5mg taken orally every week, with increments of 2.5mg every 1 to 2 weeks according to tolerance and clinical response, up to a maximum dose of 20-25mg once weekly. A crucial consideration is that methotrexate disrupts folic acid metabolism, making folic acid supplementation important to reduce adverse effects. Typically, 1 mg of folic acid is recommended orally every day except on the day of methotrexate administration.[45]

Contraindications/ Safety: In general, methotrexate is well-tolerated at low doses, but it can cause several side effects such as bone marrow suppression, hepatotoxicity, gastrointestinal disorders and pulmonary toxicity. To limit these adverse effects, regular monitoring with complete blood counts, liver and renal function tests every 2 to 4 weeks in the first few months after the initiation of treatment and every 1-3 months thereafter is of utmost importance. [47] Furthermore, patients on methotrexate should undergo periodic chest x-rays to evaluate pulmonary toxicity. Methotrexate use is contraindicated in pregnancy and lactation, in severe or chronic liver disease, in renal impairment, in bone marrow suppression, in active infections and in cases of hypersensitivity to the drug. Several other conditions should be considered as relative contraindications like peptic ulcers, mild to moderate renal and liver impairment, elderly patients, concomitant use of other immunosuppression, and interstitial lung disease.[47]

Adverse effects: Common adverse effects of methotrexate treatment include nausea, fatigue, mouth sores, and increase of liver enzymes. Aforementioned less common but more serious adverse events include hepatotoxicity, pulmonary toxicity, suppression of the bone marrow, and an increase in susceptibility to infections.

B-cell depleting therapies

Adaptive immunity and particularly B-cells play an important role in the pathogenesis of myasthenia gravis (MG). Autoantibodies against specific neuromuscular junction components such as nicotinic acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (LRP4) are produced via a CD4 dependent, B cell-mediated immune response.[48] Antibodies against AChR belong to the IgG1 and IgG3 subclasses, they activate the complement, leading to the destruction of the postsynaptic neuromuscular junction membrane. Anti-MuSK MG is considered as an IgG4-mediated autoimmune disease singe the majority of the antibodies belong to the IgG4 subclass. [49] Monoclonal antibodies that target B-cells such as rituximab have shown significant efficacy in reducing the levels of autoantibodies and improving muscle strength in patients with MG, which emphasizes the pivotal role of B-cells in the pathogenesis of the disease.[50,51]

Mechanism of action: Rituximab is a chimeric monoclonal antibody that binds the CD20 receptor expressed in B-cells and thus it induces an antibody-dependent cellular cytotoxicity of circulating B-cells. [52] Besides the production of antibodies, B-cells have also an antigen-presenting role participating in T-cell activation, as well as the ability to secrete cytokines responsible for T-cell differentiation. Rituximab suppresses the early stages of humoral response, through

depletion of circulating B-cells and plasmablasts, leads to alteration of balance of cell populations in the periphery, by depleting memory B cells and increasing T regulatory cells. By reducing these B cells populations, Rituximab decreases the levels of autoantibodies against AChR and MuSK. Although plasma cells, the antibody-producing cells, do not express CD20, a strong reduction in autoantibody levels can be achieved through depletion of precursor B cells. Suppression of the early humoral response could further explain the difference in effectiveness of Rituximab between MuSK and AChR-positive MG. As IgG4 type, antibodies against MuSK are believed to be produced by cell populations that are in a constant dependence of the precursor B cells. On the other hand, with regard to MG patients with AChR antibodies, it appears that initiation of Rituximab treatment earlier in the course of the disease can prevent the development of plasma cells that secrete pathogenic autoantibodies, leading to a stronger therapeutic response.[52]

Indications: According to the most recent comprehensive international consensus guidelines updated in 2021,[26] efficacy of Rituximab remains uncertain in the treatment of AChR-positive MG patients, but it can be considered as a treatment option for patients failing to respond or tolerate other immunosuppressive agents.[53] In contrast, despite the lack of clinical trials, Rituximab is recommended as an early treatment option for MuSK-positive MG patients.[54] Regarding seronegative MG patients, evidence for the use of Rituximab is limited, although successful use in refractory patients has been reported.[12,55]

Dosing schedule: Rituximab is administered through intravenous infusion. There is conflicting evidence regarding the adequate dosage of Rituximab in MG. Despite the great variety of regimens used in different clinical protocols, the most commonly used is either the two doses of 1g with an interval of 15 days between them or four doses of 375mg/m2 with a weekly interval among them.[56] Furthermore, lower dose regimens have been used with contradictory results.[57] Regarding retreatment, it is usually guided by evidence of disease relapse or less frequently in some protocols by the use of CD20+ cell counts in the peripheral blood.[58] In general, refractory patients could benefit from higher and more frequent doses.[59]

Contraindications/ Safety: Overall, Rituximab is contraindicated in patients with known hypersensitivity reactions to the drug, active severe infections, active hepatitis B infection, history of progressive multifocal leukoencephalopathy (PML), and during pregnancy and lactation. While not an absolute contraindication, patients with history of immunosuppression should be carefully evaluated. In recent decades, there has been increasing experience with the use of Rituximab, with a large amount of safety data collected.[60,61] Most common side effects include infusion-related reactions such as fever, chills, headache, and flu-like symptoms. Infections are a potential concern regarding Rituximab treatment. In MG patients, serious infections like gastrointestinal, respiratory, skin, and herpes zoster have been reported with an overall risk of 0.05 per 100 patient-years. Rituximab treatment has also been linked with hypogammaglobulinemia, a condition that may increase the risk of serious infections.[60] Concerning PML, a serious with poor prognosis infection of the central nervous system caused by John Cunningham virus, there have been three cases reported in Rituximab-treated MG patients.[62] Finally, there are limited data available regarding Rituximab exposure during pregnancy. While Rituximab could cross the placenta and cause B-cell depletion, there is no proof of certain malformations or severe neonatal complications.[63]

Adverse effects: Infusion-related reactions are the most common adverse events in Rituximab treatment. Symptoms may include fever, chills, nausea, headache, urticaria, angioedema, and bronchospasm. The majority of patients will experience any of these symptoms during the first infusion. A pre-treatment administration of acetaminophen and antihistamines, slower initiation of infusion, and temporary stopping and slowing of the infusion could alleviate these symptoms. Moreover, several hematologic toxicities, like neutropenia, thrombocytopenia, anaemia, and late-onset neutropenia might also occur following Rituximab infusion. Finally, rarer are adverse events like gastrointestinal perforation, severe mucocutaneous reactions, and other severe hypersensitivity reactions.

FcRn Inhibitors

Mechanism of Action: Neonatal fragment crystallisable receptors (FcRn) are expressed on several cell types, such as endothelial, epithelial, and antigen-presenting cells.[64] The primary role of FcRn is to prolong the half-life of serum IgG by binding IgG immunoglobulins and preventing their degradation in lysosomes, thus facilitating long-term circulation of IgG in the blood.[64] Two new humanised anti-FcRn molecules have been approved so far, an IgG1 Fc fragment (Efgartigimod; Vyvgart@), and an IgG4 monoclonal antibody (Rozanolixizumab; Rystiggo®), which target the IgG-binding domain of FcRn, thereby accelerating the loss of IgG immunoglobulins including the AChR-specific antibodies.

Efgartigimod

The approval of Efgartigimod is based on the multicentre, randomised, placebo-controlled phase 3 clinical trial, ADAPT,[65] in which Efgartigimod met the primary endpoint of the study. The ADAPT study

included 167 MG patients, 129 (77%) of which were positive for anti-AChR antibodies (AChR-MG), while 38 (23%) were seronegative for anti-AChR antibodies, of whom 6 were positive for antibodies to the muscle-specific kinase MuSK. Half of the patients received Efgartigimod (10mg/kg IV) as adjunctive therapy, once weekly for 4 weeks, while the other half received placebo as adjunctive therapy, with the primary endpoint being the proportion of patients responding to treatment based on the MG-ADL scale in patients with AChR-MG in the first 8 weeks. In AChR-MG patients treated with Efgartigimod as adjunctive therapy, MG-ADL scores improved by at least two points for four consecutive weeks in 68% of the patients (44/65), compared to 30% (19/64) in the placebo group. Specifically, among AChR-MG patients treated with Efgartigimod, 40% experienced minimal or no symptoms, as indicated by an MG-ADL score of 0 or 1, whereas only 11% in the placebo group experienced minimal or no symptoms.

Indications: Efgartigimod was approved by the FDA in 2021 and by the EMA in 2022 as an add-on therapy to standard therapy for adult patients with MG and anti-AChR antibodies.

Dosing schedule: The required dose of Efgartigimod is based on patient body weight with a recommended dose of 10 mg/kg as an intravenous infusion over 1 hour. For patients weighing more than 120 kg, the maximum dose is 1,200 mg (3 vials). It is administered in infusion cycles once weekly for 4 weeks and subsequent treatment cycles should be administered according to the ADAPT clinical trial. The safety of starting subsequent cycles earlier than 7 weeks has not been established. No dose adjustment is required for patients with mild renal or hepatic impairment.

Contraindications/Safety: Efgartigimod should not be administered to patients with hypersensitivity to the active substance or to any of the excipients listed in the Summary of Product Characteristics (SPC).

In patients with active infection, the benefit-risk balance of maintaining or temporarily interrupting Efgartigimod therapy until the infection has resolved should be considered. Vaccinations should be administered at least 2 weeks after the last infusion of a treatment cycle and 4 weeks before the start of the next cycle. Vaccination with live or live attenuated vaccines is not recommended for patients on treatment. No dose adjustment is required in elderly patients, and no data are available for the paediatric and adolescent population.

No interaction studies with other drugs have been performed. As Efgartigimod interferes with the FcRn recycling mechanism of IgG, serum concentrations of IgG class medicinal products (e.g. monoclonal antibodies and intravenous immunoglobulin [IVIG]) and Fc peptide fusion proteins are expected to be decreased if administered concomitantly or within 2 weeks of Efgartigimod administration. It is recommended to initiate these therapies 2 weeks after Efgartigimod administration and monitor for decreased efficacy of these medicinal products when administered concomitantly.

In addition, treatment with intravenous or subcutaneous immunoglobulins, plasmapheresis and immunoadsorption may reduce circulating levels of Efgartigimod.

Clinical data on the use of Efgartigimod in pregnant women and during lactation are limited. Treatment of pregnant women and during lactation with Efgartigimod should be applied only if the clinical benefit outweighs the risks.

Adverse effects: According to the ADAPT clinical study, 65 (77%) of 84 patients in the Efgartigimod group and 70 (84%) of 83 patients in the placebo group experienced adverse reactions. The most common adverse reactions were headache (Efgartigimod 29% vs. placebo 28%) and nasopharyngitis (Efgartigimod 12% vs. placebo 18%). Four (5%) Efgartigimod treated patients and 7 (8%) patients in the placebo group experienced serious adverse events (thrombocytosis, intestinal adenocarcinoma, exacerbation of MG, and depression). Three patients in each treatment group (4%) discontinued treatment during the study. There were no deaths. Efgartigimod may be associated with allergic reactions, febrile movements, and myalgia during infusion, and has been uncommonly reported to increase serum triglycerides and lipids.

Rozanolixizumab

The approval of Rozanolixizumab is based on the multicentre, randomised, placebo-controlled, phase 3 clinical trial, MycarinG,[66] in which Rozanolixizumab met the primary endpoint of the study. The MycarinG study included 200 MG patients, of whom 90% were anti-AChR positive and 10% anti-MuSK positive. One third of the patients received subcutaneous treatment once a week at 7mg/kg, one third received 10mg/kg and one third received placebo as adjunctive therapy, always once a week, with the primary endpoint being the change in MG-ADL score on day 43 of treatment compared to baseline in patients with anti-AChR antibodies, as well as in patients with anti-MuSK antibodies (n=21). The MG-ADL score also decreased similarly for both doses of Rozanolixizumab. The study also demonstrated a significant difference in favour of rozanolixizumab in the total QMG score change from baseline. In addition, significant improvements in secondary endpoints were detected in QMG and MG composite score among participants receiving both doses of rozanolixizumab, further supporting the potential benefits of rozanolixizumab in the management of MG.

Rozanolixizumab has been shown to cause a reduc-

tion in all four IgG subclasses, including IgG4, which may help explain the drug's efficacy in patients with MuSK antibodies.

Indications: Rozanolixizumab received FDA approval in 2023 and EMA approval in 2024 for adults with MG and anti-AChR or anti-MuSK antibodies as add-on therapy to pre-existing therapy.

Dosing schedule: Rozanolixizumab is administered via subcutaneous infusion. A treatment cycle consists of 1 dose per week for 6 weeks. Subsequent treatment cycles should be administered according to clinical assessment. The recommended total weekly dose of Rozanolixizumab is determined by patient body weight (280 mg in patients weighing ≥ 35 to < 50 kg; 420 mg in patients ≥ 50 to < 70 kg; 560 mg in patients ≥ 70 to < 100 kg and 840 in patients ≥ 100 kg). No dose adjustment is required in elderly patients, while no data are available in the paediatric and adolescent population.

Contraindications/Safety: Rozanolixizumab is not recommended for use in patients with hypersensitivity to the active substance or to any of the excipients listed in the SPC. This medicinal product contains 29 mg of proline per ml. Use in patients with hyperprolinaemia should be restricted to patients with no alternative treatment. Infusion pumps, syringes and infusion sets suitable for subcutaneous administration of medicinal products should be used. During the administration of the first course of treatment as well as of the first dose of the second course of treatment with Rozanolixizumab, appropriate treatment for injection-related and hypersensitivity reactions should be readily available. Rozanolixizumab treatment should not be administered to patients with a clinically significant active infection. As it causes a decrease in IgG levels, vaccination with live attenuated or live viruses is not recommended during treatment. All other vaccines should be administered at least 2 weeks after the last infusion of a treatment cycle and 4 weeks before the start of the next cycle.

No interaction studies with other drugs have been performed. As Rozanolixizumab interferes with the IgG FcRn recycling mechanism, serum concentrations of IgG class medicinal products (e.g. monoclonal antibodies and IVIG) and Fc peptide fusion proteins are expected to be decreased if administered concomitantly or within 2 weeks of Rozanolixizumab administration. It is recommended to initiate these treatments 2 weeks after Rozanolixizumab administration and monitor for reduced efficacy of these products when administered concomitantly.

In addition, treatment with intravenous or subcutaneous immunoglobulins, plasmapheresis, and immunoadsorption may decrease circulating levels of Rozanolixizumab.

Clinical data on the use of Rozanolixizumab in pregnant women and during lactation are very limited. Treatment with Rozanolixizumab in pregnant women and during lactation should only be considered if the clinical benefit outweighs the risks.

Adverse effects: In the Mycarin G clinical trial, adverse reactions related to Rozanolixizumab treatment were reported by 81% and 83% of participants treated with 7 mg/kg and 10 mg/kg rozanolixizumab, respectively, compared to 67% (45/67) of those treated with placebo (Bril et al., 2023). The most common adverse reactions were headache (45%, 38%, and 19% of patients in the 7 mg/kg, 10 mg/kg, and placebo groups, respectively), diarrhoea (25%, 16%, and 13%, respectively), and fever (13%, 20%, and 1%, respectively). Serious adverse events occurred in 8%, 10%, and 9% of patients, respectively. Adverse events that led to discontinuation of Rozanolixizumab in 6 patients were: arthralgia, headache, diarrhoea, upper abdominal pain, vomiting, oral herpes, metastatic squamous cell carcinoma, pruritus, and deep vein thrombosis. There were no deaths.

Infusion reactions, such as rash or angioedema, may also occur, and patients should be monitored during treatment with Rozanolixizumab and for 15 minutes after completion of administration. Treatment with Rozanolixizumab may be rarely associated with an increase in serum triglycerides and lipids.

Complement inhibitors

Complement inhibition targeting specific complement proteins (e.g., C3 and C5) has emerged as a promising therapeutic approach for complement-mediated diseases, including MG. The primary strategy consists of using monoclonal antibodies to target complement proteins and/or regulators to prevent the formation of the MAC, which normally mediates tissue damage and inflammation.[67]

Ravulizumab

Mechanism of action: Ravulizumab is a recombinant monoclonal antibody IgG2/4K that specifically binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]), and preventing the generation of theC5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes. thereby reducing inflammation and tissue damage.[68]

Pharmacodynamic effects: The time to maximum observed concentration (tmax) is expected at the end or soon after of infusion. Therapeutic steady-state drug concentrations are reached after the first dose.

Biotransformation and elimination. As an immunoglobulin gamma (IgG) monoclonal antibody,

ravulizumab is metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways). Ravulizumab contains only natural occurring amino acids and has no known active metabolites. In adult patients with gMG the terminal elimination half-life is 56.6 days with mean (SD) 8.36 days.

Clinical efficacy: Ravulizumab is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody positive. The efficacy and safety of ravulizumab in adult patients with gMG was assessed in a Phase 3, randomised, double-blind, placebo-controlled, multicentre study (ALXN1210-MG-306). Patients participating in this study were subsequently allowed to enter an Open-Label Extension Period during which all patients received ravulizumab. The primary endpoint was the change from Baseline to Week 26 in the MG-ADL total score. The secondary endpoints, also assessing changes from Baseline to Week 26, included the change in the Quantitative Myasthenia Gravis (QMG) total score, the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively, as well as changes in quality-of-life assessments.[69]

A clinical responder total score was defined as having (a) in the MG-ADL at least a 3-point improvement and (b) in the QMG at least a 5-point improvement.

The proportion of clinical responders at Week 26 in Ravulizumab demonstrated a statistically significant change in the total score as compared to placebo:

(a) in MG-ADL: the proportion of clinical responders was 56.7% on ravulizumab compared with 34.1% on placebo (nominal p=0.0049).

(b) in QMG The proportion of clinical responders was 30.0% on ravulizumab compared with 11.3% on placebo (p=0.0052).

Dosing schedule: Ravulizumab is to be administered by intravenous infusion using a syringe-type pump or an infusion pump over a minimal period of 0.17 to 1.3 hours (10 to 75 minutes). Total dose is depending on body weight range. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration. Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ravulizumab), but the subsequent dose should be administered according to the original schedule.

Plasma exchange (PE), plasmapheresis (PP) and IVIg have been shown to reduce ravulizumab serum levels. A supplemental dose of ravulizumab is required in the setting of PE, PP or IVIg, within 4 hours following each PE or PP intervention.

Contraindications/Safety

Common adverse events including headache and nasopharyngitis.

Vaccinations. Prior to initiating ravulizumab therapy, it is recommended that patients initiate immunizations according to current immunisation guidelines. Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Meningococcal infections. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to initiating ravulizumab unless the risk of delaying ravulizumab therapy outweighs the risk of developing a meningococcal infection. Vaccines against serogroups A, C, Y, W135 and B, where available, are recommended. Patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. The optimal duration of chemoprophylaxis and the exact regimen to be employed is still a matter of conjecture. The International Consensus Guidance for Management of Myasthenia Gravis (21) quotes penicillin VK 250–500 mg bid as the first-line chemoprophylaxis and erythromycin 500 mg bid, azithromycin 500 mg qd, or ciprofloxacin 500 mg qd as alternatives for penicillin-allergic patients. At the same time, however, the authors note that fluoroquinolones and macrolides may lead to exacerbation of MG (***vide infra*** "4. Drugs to avoid"). It should be noted that National Guidelines for the prevention of meningococcal meningitis in this particular setting vary significantly. For instance, the German Guidelines do not specify particular antibiotics (10) whereas the French Guidelines mention penicillin V (or macrolides in case of allergy) and suggest that chemoprophylaxis may be prescribed for part or the entire period of complement inhibitor treatment.[70] With regard to chemoprophylaxis against Neisseria Meningitidis in general, the CDC and the American Academy of Paediatrics mention that rifampin, ciprofloxacin, and ceftriaxone are 90% to 95% effective in reducing nasopharyngeal carriage of ***N. meningitidis*** and, along with azithromycin, are all acceptable antimicrobial agents for chemoprophylaxis in children and adults.[71,72] The ultimate selection amongst these agents will have to depend on their safety profile particularly in MG patients as well as other characteristics such as the route of administration. Greek Chemoprophy-

laxis Guidelines for complement inhibitor -treated patients are not yet in place so it is recommended that treating neurologists request infectious disease consultation locally.

Fertility, pregnancy, and lactation. Women of childbearing potential should use effective contraception methods during treatment and up to 8 months after treatment. There are no clinical data from the use of ravulizumab in pregnant women. Human immunoglobulin G (IgG) are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the foetal circulation. It is unknown whether ravulizumab is excreted into human milk.

Zilucoplan

Mechanism of action: Zilucoplan is a 15 amino acid, synthetic macrocyclic peptide that inhibits the effects of the complement protein C5 through a dual mechanism of action. It specifically binds to C5, thereby inhibiting its cleavage by the C5 convertase to C5a and C5b, which results in a downregulation of the assembly and cytolytic activity of the membrane attack complex (MAC). Additionally, by binding to the C5b moiety of C5, zilucoplan sterically hinders binding of C5b to C6, which prevents the subsequent assembly and activity of the MAC, should any C5b be formed.

Pharmacodynamic effects: Following single and multiple daily subcutaneous administration of the zilucoplan recommended dose in healthy subjects, zilucoplan reached peak plasma concentration generally between 3 to 6 hours post-dose. Zilucoplan as a peptide, is expected to be degraded into smaller peptides and amino acids via catabolic pathways. The mean plasma terminal elimination half-life was approximately 7-8 days.

Clinical efficacy: Zilucoplan is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Zilucoplan has not been studied in gMG patients with a Myasthenia Gravis Foundation of America (MGFA) Class V.

The safety and efficacy of zilucoplan were evaluated in a 12-week multicentre, randomised, double-blind placebo-controlled study RAISE and the open-label extension study RAISE-XT.[73,74] In this study patients were treated once daily with either zilucoplan or placebo. The primary endpoint was the change from baseline to week 12 in MG-ADL total score. Key secondary endpoints were the change from baseline to week 12 in QMG total score, in Myasthenia Gravis Composite (MGC) total score and in MG Quality of Life (MG-QoL15r) total score.

Zilucoplan improved the MG-ADL score beyond the clinically meaningful threshold of 3 points in nearly three-quarters of patients compared with just under half of those who received placebo. MG-ADL clinical responders were defined as having at least a 3-point decrease and QMG responders were defined as having at least a 5-point decrease without rescue therapy.

The treatment effect in the zilucoplan group for all 4 endpoints started rapidly at week 1, further increased to week 4 and was sustained through week 12.

At week 12, a clinically meaningful and highly statistically significant improvement in MG-ADL total score and in QMG total score was observed for zilucoplan versus placebo.

At week 12, 73.1% of the patients in the zilucoplan group were MG-ADL clinical responders without rescue therapy, vs. 46.1% in the placebo group (p<0.001). Fifty-eight percent (58.0%) of the patients in the zilucoplan group were QMG clinical responders without rescue therapy, vs. 33.0% in the placebo group (p=0.0012). At week 12, the cumulative portion of patients that needed rescue therapy was 5% in the zilucoplan group and 11% in the placebo group. Rescue therapy was defined as intravenous immunoglobulin G (IVIG) or plasma exchange (PLEX).

In RAISE-XT, that was the open-label extension study in which all patients received zilucoplan. Primary objective was long-term safety. Secondary efficacy endpoints were change from double-blind study baseline in MG-ADL, QMG, MGC and MG-QoL15r score at week 24. In patients who received zilucoplan further improvements in MG-ADL score continued through to Week 24 (least squares mean change [95% confidence interval] from double-blind baseline -6.06 [-7.09, -5.03]) and were sustained through to Week 60 (-6.04 [-7.21, -4.87]). In patients who switched from placebo in the parent study, rapid improvements in MG-ADL score were observed at the first week after switching to zilucoplan; further improvements were observed at Week 24, 12 weeks after switching (-6.46 [-8.19, -4.72]), and were sustained through to Week 60 (-6.51 [-8.37, -4.65]). Consistent results were observed in other efficacy endpoints.

Dosage/method of administration: The total daily dose is depending on body weight range. The recommended dose should be given as a subcutaneous injection once daily/same time every day.

Contraindications/Safety

Vaccinations. Before starting therapy, patients must be vaccinated against ***Neisseria meningitidis.***

If treatment needs to start less than 2 weeks after vaccination, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose.

The most frequently reported adverse reactions were injection site reactions (injection site bruising (13.9%) and injection site pain (7.0%)) and upper respiratory tract infections (nasopharyngitis (5.2%), upper respiratory tract infection (3.5%) and sinusitis (3.5%)).

Fertility, pregnancy, and lactation. There are no clinical data from the use of zilucoplan in pregnant women.

Intravenous Immunoglobulin (IVIG)

Mechanism of action: IVIG consists of a pool of human immunoglobulins from many healthy donors, and therefore it contains all IgG subclasses (IgG1, 2, 3, and 4). The mechanism of action of IVIG in MG is not clear, although it potentially has multiple modes of action, such as inhibiting complement activity and causing FcRn blockade, reducing the half-life of IgG in the blood. It may also contain anti-idiotypic antibodies that may bind and neutralize pathogenic autoantibodies including antibodies against AChR.[75]

Indications: In MG, IVIG is mainly used as a rescue therapy in myasthenic crisis. However, it is sometimes used in other situations, such as in patients who are refractory to conventional treatments.[9,76,77]

Efficacy: The significant efficacy of IVIG in patients with myasthenic crisis is mainly supported by clinical trials,[78] observational studies,[79] systematic reviews, and meta-analyses[80] in which IVIG was compared with plasmapheresis. The efficacy of IVIG usually occurs in less than a week and the benefit can last for three to six weeks. Plasmapheresis appears to be more effective than IVIG in MuSK MG.[9]

Dosage/route of administration: The total dose of IVIG is 2 g/kg of patient body weight, and usually it is administered in a period of two to five days (at a dose of 0.4–1 g/kg of body weight daily) [81].

Contraindications/Safety: IgA deficiency is a relative contraindication for IVIG treatment, as it can be complicated by a severe anaphylactic reaction. Conversely, a history of a previous allergic reaction to IVIG is an absolute contraindication for new IVIG treatment. In addition, IVIG should be used with caution in patients with renal dysfunction or a history of thrombotic events (coronary artery disease or ischemic stroke).

Based on the above, it is recommended to check total immunoglobulin and immunoglobulin subtypes to exclude selective IgA deficiency before starting IVIG treatment. [9, 81].

Adverse effects: Approximately 10% of patients receiving IVIG may experience adverse effects, which are generally mild. The most common adverse effects include headache, neck pain, nausea, fatigue, low-grade fever, rash, and neck stiffness, and can usually be improved by adjusting the infusion rate. Uncommon but with serious adverse effects include anaphylactic shock, autoimmune haemolytic anaemia, aseptic meningitis, thrombotic events such as deep vein thrombosis and pulmonary embolism, renal failure, pulmonary oedema, acute coronary syndrome, and acute ischemic stroke [82, 83].

Therapeutic Plasma Exchange

Therapeutic PLEX, also called plasmapheresis, is an extracorporeal method where whole blood is removed and then it is separated into components by centrifugation or membrane filtration. Plasma is taken away and is replaced mainly with albumin and saline for avoidance of hypotension. PLEX needs specialized apheresis unit with well-trained and experienced personnel.[84]

Mechanism of action: Plasma Exchange is an immunomodulatory treatment and its mechanism of action in the treatment of autoimmune diseases is more than the removal of pathological autoantibodies. Proposed mechanisms are sensitization of antibody-producing cells to immunosuppressants by increased lymphocyte proliferation, alterations in the Th1/Th2 ratio with a shift to a Th1 dominant pattern, removal of immune complexes and improvement of monocyte/macrophage function, removal of cytokines, increase T and decrease B lymphocytes, increase T-regulatory cells and T-suppressor activity.[85]

The first report of beneficial effect of PLEX in acquired myasthenia gravis (MG) was made in 1976. [86] The unequivocal improvement of fatigable muscle weakness was evident within a few days after initiation of treatment, indicating that a humoral factor is causative for the disordered neuromuscular transmission.

Administration schedule: Typically, five sessions of PLEX over 10 days remove approximately 90% of IgG antibodies (Abs). The rapid removal of IgG Abs results in early clinical improvement of myasthenic symptoms which may be a lifesaving process. Concomitant immunosuppressive therapy is recommended for maintenance of therapeutic effect of PLEX and avoidance of antibodies overshoot following plasmapheresis. [86,87] Therapeutic PLEX has also impact on the levels of IgA and IgM, which are also reduced approximately 70% and 79%, respectively. Among the four subclasses of IgG, IgG3 recover faster usually by 3 weeks after the last session of PLEX.

Adverse effects: The side effects are usually minor and include hypotension, hypocalcaemia with paraesthesia and muscle cramps, nausea, vomiting. Bleeding and allergic reactions are rare. Peripheral venous access is the preferred route, because the severe complications (usually thrombosis and infection)

are related with the placement of central venous line.

Indications and contraindications: PLEX is indicated in gMG. PLEX should not be used in sepsis or in hemodynamically unstable patient. Generalised MG has an excellent response to PLEX irrespective of antibody status.[88] In particular, in MuSK-MG there is a dramatic response to PLEX, which is considered therapy of choice for rapid improvement of potentially life threatening bulbar and/or respiratory symptoms. In MuSK–MG the prompt and great improvement following PLEX is due to removal of MuSK Abs (IgG4), which have a functional role by blocking the interaction between lipoprotein-related protein 4 and MuSK with subsequent reduction of AChR clustering.[89]

The ***indications*** of PLEX in gMG are:

1. Myasthenic crisis (rescue therapy)
2. Impending myasthenic crisis (rescue therapy)
3. At the onset of corticosteroids in moderate gMG, especially with prominent bulbar and/or respiratory muscle involvement (bridging therapy)
4. In severe clinical deterioration during the disease course
5. Presurgical or postsurgical muscle strengthening

Although clinical trials suggest that IVIg and PLEX have comparable efficacy and duration of effect, in myasthenic crisis (MC) and impending MC, PLEX is first-line treatment because of rapid onset of action and predictable response.[90,91]

Presurgical strengthening is not required for all MG patients. Prognostic factors for post-thymectomy MC include bulbar symptoms, history of MC, reduced vital capacity (VC<2-2.9 L), and chronic pulmonary disease. In clinical practice, well-controlled patients with sustained clinical improvement can undergo surgery safely without pre-surgical short-term immunotherapy.[9,92,93]

In the aforementioned clinical settings, PLEX is a short-term therapy. The use of PLEX as a chronic-maintenance treatment is rare and concerns refractory MG along with escalation treatment with rituximab or pulsed cyclophosphamide.[9]

Immunoadsorption (IA) has been increasingly recognized as an alternative to therapeutic PLEX for the treatment of autoimmune neurological disorders. IA is a blood purification technique which enables the selective removal of humoral factors from separated plasma through a high -affinity absorbent with tryptophan or phenylalanine. In the treatment of MG, IA is of comparable therapeutic efficiency with PLEX and with favourable safety profile.[94]

Novel immunotherapies called "chemical plasma exchange" are antagonists of FcRn. They interfere with FcRn - mediated IgG recycling with resultant selective reduction of serum IgG levels but no affection of IgA, IgM and albumin. In practice, the introduction of FcRn antagonists in clinical settings where PLEX is indicated is challenging. Although FcRn antagonists may be effective treatment as bridging therapy or presurgical muscle strengthening, in acute setting of MC or impending MC, PLEX is the first-line lifesaving treatment. After all, FcRn antagonists have not been studied in patients with severe and life threatening bulbar and/or respiratory muscle involvement.[95]

Thymectomy

The presence of thymoma (thymoma associated myasthenia gravis) is an absolute indication for thymectomy, where surgical removal of thymoma and surrounding thymic tissue is performed.[9] In this case, thymectomy is performed for oncological reasons and not for therapy of myasthenia gravis which necessitates lifelong immunosuppressive therapy.

In non-thymomatous myasthenia gravis, thymectomy is recommended in early onset (onset<50 years), generalized myasthenia gravis with positive titre of acetylcholine receptor antibodies (AChR Abs) and duration of symptoms < 5 years.[96] The therapeutic effect of thymectomy is delayed (>12 months) and thymectomy does not substitute for medical treatment.

Thymectomy is not recommended in MG with muscle specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4) Abs.

In seronegative MG and ocular MG with positive titre of AChR Abs, thymectomy is a therapeutic option when there is no response to immunosuppressants or when side effects or contraindications exclude immunosuppressive therapy.[26]

In thymomatous and no-thymomatous MG, thymectomy is never performed on an emergency basis. Patients undergo thymectomy when they are in a sustained clinical improvement according to judgement of treating physician.[38]

Presurgical strengthening with intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) is performed when needed for minimising the risk for post thymectomy MG exacerbation or myasthenic crisis. Prognostic factors for post-operative MC are pre-operative bulbar symptoms, decreased vital capacity, disease severity, history of MC.[92] Generally, well-controlled patients with sustained clinical improvement can undergo thymectomy without prior therapy.[93,97] However, in thymomatous myasthenia gravis presurgical strengthening is often applied.[98]

The goal of thymectomy is the complete removal of all thymic tissue. Extended transsternal thymectomy has been the gold standard for thymoma resection and management of non thymomatous myasthenia gravis. [99] Minimally invasive thymectomy approaches, video-assisted thoracoscopic thymectomy (VATS) and robotic-assisted thoracoscopic thymectomy (RATS) are increasingly performed with safety and good results in experienced centres. [100]

Myasthenic patient is sensitive to any neuromuscular blockade and there is risk for prolonged neuromuscular blocking and respiratory insufficiency. There is an increased sensitivity to non-depolarising muscle relaxants (rocunorium, vecunoriu, cisatracurium) and these should be avoided. If a nondepolarizing muscle relaxant is used, dose should be reduced and sugammadex should be available (fast and predictable reversion of neuromuscular blockade).[101] Succinylcholine as a depolarising muscle relaxant can be used in myasthenia gravis but the response is reduced and higher doses are need. The metabolism of succinylcholine is affected by preoperative use of pyridostigmine and the duration of neuromuscular blockade may be prolonged. A safe alternative is the intubation with propofol and remifendanil.[102]

Adequate corticosteroid-stress doses (hydrocortisone) are administered presurgical, during surgery and postsurgical because of adrenal insufficiency which occurs with daily prednisolone dose ≥5 mg for more than 20 days.

Perioperative and postoperative analgesic regimen is a therapeutic challenge in patients with myasthenia gravis. Post-surgical pain affects respiratory function, causes intense stress which may provoke clinical exacerbation and may delay patient's recovery. Pain is associated with shallow inspiration, decreased cough, retention of secretions and increased risk for atelectasis and pneumonia. Opioids administered via intravenous patient-controlled analgesia are effective but harbour the risk of respiratory depression. On the other hand, hypoventilation may be caused by untreated pain.[103]

RECOMMENDATIONS FOR TREATMENT - TREATMENT ALGORITHM

MG is not a uniform disease in all patients but presents variations based on the localisation of symptoms, the age and gender, the autoimmune profile and the presence of thymoma. Seven main sub-types are recognised: Ocular MG (oMG); Early Onset MG (EOMG); Late Onset and Very Late Onset MG (LOMG and VLOMG); MuSK antibody positive MG (MuSK MG); seronegative Mg (snMG); Thymoma-associated MG (TAMG); MG in pregnancy. Therapeutic suggestions will be presented separately for each sub-type.

Ocular Myasthenia

This subgroup constitutes approximately 10% of all MG cases[3] and includes patients with isolated weakness or/and fatigue of ocular muscles, presenting with ptosis or/and diplopia at any time from disease onset. Careful clinical examination does not reveal weakness in any other muscle group (including neck flexors). Patients, who initially had symptoms of gMG that were resolved after treatment, while the ocular symptoms remained, should not be included in this category.

Treatment Recommendations: All patients should start with pyridostigmine at 30 – 60 mg 3 times/ day and titrated up to 60mg 4 times/day, as determined by its efficacy and side effects.[104] Withdrawal of pyridostigmine is recommended after remission or MM status is achieved. Prednisolone should also be administered to all patients from diagnosis to avoid permanent weakness and atrophy of ocular muscles and, more importantly, to eliminate the possibility of generalisation occurring in up to 80% of untreated patients within 3 years from onset.[105,106] Prednisolone should be started at low doses 10 –20 mg /day increasing by 5–10 mg every 3 days until symptoms resolve or up to 40mg/day for a month followed by a careful long tapering.[2,15,104] Complete cessation of steroids in oMG is rarely suggested and under close follow-up; in the majority of oMG patients, the aim is to reach a maintenance dose of 2.5 -10mg / day. Exceptions to the above strategy: 1. when life expectancy is short, treatment with pyridostigmine alone is suggested. 2. when steroids are strictly contraindicated or fail to demonstrate an adequate response or relapses occur upon steroids-tapering, another IS is administered [15, 26]. Based on retrospective studies and empiric use of ISs in gMG, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil or rituximab are agents to be considered for oMG treatment.[10,104] Until this day, no data is available regarding the efficacy of medications in the categories of FcRn inhibitors and Complement C5 inhibitors in oMG. Thymectomy is recommended when thymoma is present, whereas in all other oMG cases thymectomy decision should be considered on an individual basis since there is no evidence to support a general recommendation[104] and it is often suggested when steroids or other ISs have failed.[26]

Early Onset Generalised MG (EOMG)

This subgroup includes patients between 18 and 50 years of age at the onset of MG symptoms, positive for antibodies against AChR or LRP-4.

Symptomatic treatment with pyridostigmine should be given to all patients from disease onset until remission and during deterioration phases.[10,38]

First-line treatment: prednisolone administration should start soon after diagnosis to increase the possibility and reduce the time to achieve MM status.[107] It is noted that higher doses of steroids and longer treatment periods do not necessarily lead to a better outcome.[108] Additionally, in patients where, at the time of the diagnosis, they present severe weakness, particularly affecting the bulbar, neck flexors, and respiratory muscles, that may lead to impending crisis, hospitalisation, and rescue therapy (PLEX of IVIG) may be considered necessary.[15]

Patients with non-thymoma-associated MG and abs against AChR should be provided with the option of thymectomy (transsternal or minimally invasive) soon after stabilisation of their status, ideally within 2 years and no later than 5 years from diagnosis. [10,26] However, recent data support that there is still a benefit of thymectomy performed after a longer disease duration.[2] There is no evidence to support or reject the effect of thymectomy in MG patients with LRP-4 antibodies.[26]

Second-line treatment: Limited literature data exist regarding the order of drug choice for supplementary or steroid replacement treatment. Azathioprine remains the most frequently used among the steroids sparing agents based on favourable effects in some RCT and the experts' opinion. Alternatively, mycophenolate mofetil, cyclosporine, or rituximab can be considered.[9] Particularly Rituximab, which acts faster than the other classical ISs agents, should be considered as an alternative drug to steroids or azathioprine in newly diagnosed patients or patients in a refractory phase.[14]

In the era of new, targeted medications, while awaiting the results of real-world data studies to find their place in the therapeutic algorithm, these drugs can be carefully selected on an individual basis, considering factors such as the patient's age, antibody profile, the adverse reactions and contraindications of ISs, and disease burden. Compared to classical ISs, the FcRn and Complement C5 inhibitors are expected to act faster and have fewer long-term risks. These can be combined with any existing treatment regimen of symptomatic, steroids, and/or ISs, at any time from onset or during the disease course, to improve the outcome or to allow safe reduction of the latter. Caution should be exercised in a few drug combinations. For example, monoclonal antibodies like rituximab or a C5 complement inhibitor may be counteracted by PLEX or FcRn inhibitors, which enhance the lysosomal degradation of IgG antibodies, if administered close together. Until today, there has been no European approval for the use of FcRn and complement C5 inhibitors in LRP-4 positive patients.

According to Japanese guidelines, cyclosporine and tacrolimus are more effective in patients with shorter disease history and, therefore, are suggested to be administrated in the early stages of the disease. [108] A dilemma remains whether to treat a patient with steroids along with a second-line drug, either classical ISs or FcRN and Complement C5 inhibitors, from the beginning, or to wait for the response of steroids (and of thymectomy) before considering adding a 2nd drug. It rests with the treating physician to judge on an individual basis the risks and benefits of such a decision. [15]

Late Onset and Very Late Onset Myasthenia Gravis

Late onset Myasthenia Gravis (LOMG with onset >50 and ≤ 64 years)

In this age-group the treatment of myasthenia gravis (MG) is medical and surgical only when thymoma is detected.

The basis of the medical treatment is immunotherapy (immunosuppression and immunomodulatory treatment).

The first line immunosuppression is prednisolone. Introduction of non-steroidal immunosuppression (usually azathioprine, mycophenolate mofetil) is recommended for achievement of early steroid-sparing effect. The main drawback of the conventional non-steroidal immunosuppressants, especially of azathioprine, is that the beneficial effect takes months to appear. Advanced age, comorbidities, and polypharmacy affect the therapeutic decisions.

Rituximab is the first line immunosuppressive therapy in myasthenia gravis with muscle specific tyrosine kinase antibodies (MuSK Abs) with resultant dramatic response and long-lasting remission.[50] Rituximab may also be effective as steroid sparing agent in a proportion of patients with positive titres of acetylcholine receptor antibodies (AChR Abs).[55] Rituximab is advantageous to conventional non-steroidal immunosuppressants because of early clinical effect (1-3 months). Unfortunately, there are no factors to predict who patients with AChR Abs (+) MG may benefit more with rituximab. Single dose of 500 mg rituximab seems to be effective in generalised MG when duration of symptoms is <12 months (newly diagnosed MG patients).[109]

Immunomodulatory treatment with intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) is recommended for treatment of severe clinical exacerbation or myasthenic crisis (rescue therapy) and at the onset of immunosuppression as bridging therapy. The choice between IVIg and PLEX depends on availability and patient's comorbidities.

When thymoma is detected, thymectomy is planned when the patient is in sustained clinical improvement. Some neuromuscular experts recommend pre-surgical strengthening with IVIg or PLEX before thymectomy in thymoma-associated myasthenia gravis (TAMG), to minimise the risk of MG exacerbation or myasthenic crisis.[98] In non-thymomatous MG, according to last update of international consensus guidance for management of myasthenia gravis, thymectomy is recommended for adult patients ≤ 50 years with AChR Abs (+) generalised MG of < 5 years duration.[26] Consequently, there is no formal guidance for thymectomy in non-TAMG of late onset.

Very Late Onset Myasthenia Gravis (VLOMG, onset ≥ 65 years)

In this age-group, multiple coexisting medical conditions and polypharmacy with drug-interactions and

drug-side effects, affect treatment plan, and dictate individualisation of therapy and close monitoring.

Because of atrophic thymus and rare occurrence of thymoma, treatment of VLOMG is only medical (unless thymoma is present).

The duration of action of pyridostigmine is prolonged in the elderly and also the occurrence of cholinergic adverse events (diarrhoea, increased bronchial secretions and salivation) is increased in the aged.[110,111] Lower daily doses of pyridostigmine and longer intervals between doses are applied in the elderly for improvement of tolerance.

In VLOMG, the distribution of myasthenic weakness is predominantly bulbar and there is increased risk for myasthenic crisis. Consequently, accurate diagnosis and early initiation of immunotherapy, in an inpatient setting, is crucial for better short- and long-term outcome.[112]

Prednisolone is the first -line immunotherapy, which it should be slowly increased because advanced age and bulbar phenotype are predictors for steroid-induced clinical deterioration ('steroid dip').[8] Also, advanced age correlates with increased response to steroids and increased incidence of steroid-induced side effects (cataract, glaucoma, osteoporosis, diabetes, arterial hypertension, infections). The effective prednisolone dose in VLOMG is much lower than in early onset (EOMG) and late onset MG (LOMG).[113]

Immunomodulatory treatment with intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) is recommended for prompt alleviation of potentially life-threatening symptoms. This treatment serves as a rescue therapy in case of severe affection or as a bridging therapy until the beneficial effect of non-steroidal immunosuppressants is evident (after months). Very old patients often have poor peripheral venous access and placement of central venous line is needed for completion of PLEX. In this case, caution is warranted because of catheter-associated adverse events (bleeding, infection, thrombosis). On the other hand, thromboembolic complications associated with infusions of IVIg, are higher in very old patients with additional risk factors for thrombotic episodes.[114]

In VLOMG, the immunosuppressive therapy is lifelong and early initiation of non-steroidal immunosuppressant is strongly recommended as steroid-sparing agent. The choice between conventional immunosuppressants depends mainly on patient's comorbidities and length of latency period for the appearance of therapeutic effect. Azathioprine has been increasingly used in MG therapy as steroid-sparing agent and the combination with prednisolone is highly effective.[29] The main drawback of azathioprine is the long latency effect (approximately 6-8 months). In the meantime, the patient remains on prednisolone with increased risk of severe side effects. Liver dysfunction and bone marrow depression are azathioprine side effects which are usually reversible with drug discontinuation. Close and long term follow up of full blood count and liver function tests is required for early detection of hepatotoxicity or/and myelotoxicity and dose adjustment. Probably in older patients there is vulnerability to side effects of azathioprine in contrast to favourable safety profile among younger individuals.[115] Mycophenolate mofetil has a favourable side effect profile and beneficial effect appears earlier.

Rituximab is safe and effective in elderly MG patients where low doses may be more appropriate, especially in newly diagnosed MG patients (<12 months).[112,116]

Antagonists of FcRn interfere with IgG recycling with resultant reduction of serum IgG levels. Although only a small number of elderly patients have been studied with novel immunotherapies, FcRn antagonists [efgartigimod-alpha for AChR Abs (+) MG or rozanolixizumab for AChR Abs (+) or MuSK Abs (+) MG] could be an alternative to PLEX when this is not available, not feasible via peripheral venous access or when cardiovascular instability is present.

MuSK-MG

Antibodies against MuSK are found in 5-8% of MG patients and this subtype is more frequent in Mediterranean countries (Rodolico 2020). Of note, these antibodies belong to the IgG4 subclass and, unlike those of the IgG1-IgG3 subclasses, do not activate the complement cascade.[4] Therefore, MuSK-positive MG patients are unlikely to benefit from treatments with complement inhibitors. The disease manifests acutely with progression over a few weeks. Compared to other subtypes, onset with bulbar and respiratory symptoms followed by generalised limb weakness is more common, requiring fast treatment decisions.[117] Pyridostigmine may be offered shortly after diagnosis. However, unlike the AChR -Abs positive patients, the benefit is expected to be mild or absent with frequent drug intolerance.[2] An increasing number of reports and empirical impressions support the successful use of rituximab in this particular MG sub-group. The most recent International Guidelines suggested that rituximab should be considered as a good alternative to the standard combination of steroids and azathioprine.[26] An open-label study from a Greek centre including 24 refractory MG and 6 MuSk-MG patients who were treated with cycles of rituximab for a mean duration of 33.3 months, showed that MuSK-MG patients benefitted the most.[12] The German guidelines proposed rituximab as a treatment option only for highly active MuSK-MG.[10] In this approach, however, one should be confident that there is enough time for steroids and azathioprine to act, risking the possibility of a rapid deterioration of dysarthria, dysphagia, and respiratory crisis. Recently, a new drug in the category of

FcRn inhibitors, rozanolixizumab, was approved by EMA for MuSK-positive patients and can be added to any therapeutic regimen but not in combination with rituximab. No evidence supports a beneficial effect of thymectomy in MuSK-MG.[26]

Seronegative MG (snMG)

This group includes patients negative for antibodies against AChR, MuSK, and LRP-4. In a study from a Greek centre, the percentage of refractoriness to treatment is higher among seronegative compared to seropositive patients.[76] In contrast, a study from Mexico reported mild symptoms with no refractory cases, and another from China showed a good response to steroids with about one-third of patients achieving CSR or PR.[57,118] This discrepancy reflects the subgroup heterogeneity, possibly related to ethnicity, patient's age, and auto-immunity. It has been suggested that immunotherapy should be initiated soon after diagnosis since deterioration within the first year of the disease is not uncommon.[119] Based on the limited information on the best treatment options for SNMG and as a general rule, the guidelines for gMG with AChR antibodies are followed. There is no evidence favouring thymectomy in snMG,[119] but, it can be offered anytime during the disease course when conventional ISs prove ineffective.[15] At present, no one of the novel medications has been approved by the authorities for the snMG subtype. However, the results of several ongoing clinical trials assessing the usefulness of FcRn and complement inhibitors are expected.[119]

Thymoma associated myasthenia gravis (TAMG)

About 10-15% of myasthenia gravis patients harbour thymoma. Thymoma associated myasthenia gravis (TAMG) is a paraneoplastic disorder, affecting both sexes and all age groups, although occurrence above 70 is rare.

TAMG is usually severe and rapidly progressive with predominant involvement of bulbar and respiratory muscles. Due to the distribution and severity of myasthenic weakness, early and aggressive immunotherapy is mandatory. Prednisolone is the first-line immunosuppressive treatment and the dose is slowly increased because of the risk of prednisolone-induced clinical deterioration ("steroid dip"). Immunomodulatory therapy [plasma exchange (PLEX) or intravenous immunoglobulin (IVIg)] alleviates rapidly the potentially life-threatening myasthenic symptoms and serves as "bridging therapy".[98,120] Novel, targeted and approved immunotherapies (FcRn antagonists and complement inhibitors) have not been studied in MG patients with active or untreated thymoma. However, there are a few reports with favourable outcome of TAMG treated with eculizumab and ravulizumab (C5 complement inhibitors).[121,122]

The presence of thymoma is an absolute indication for surgical removal of thymoma and the surrounding thymic and fatty tissue. The surgery is performed for oncological reasons and it is not cure for TAMG.[9]

In TAMG immunosuppressive treatment is chronic and usually lifelong and for that reason non-steroidal immunosuppression (e.g. azathioprine, mycophenolate mofetil, rituximab) should be introduced early as steroid-sparing agent.

Thymectomy is performed when sustained clinical improvement of MG has been achieved and the treating physician believes that the patient is safe and can tolerate the compromised respiratory function due to pain and mechanical factors. Many neuromuscular experts recommend presurgical muscle strengthening (with IVIg or PLEX) before thymectomy in cases of TAMG.[98]

The goal of surgery is to remove all thymic tissue possible; extended transsternal thymectomy has historically been the gold standard for thymoma resection. Minimally invasive techniques (video-assisted and robotic-assisted thoracoscopic surgery) reduce pain and length of hospital stay and they are considered safe and effective for early-stage thymomas in experienced centres.[100] Further thymoma treatment (radiotherapy, chemotherapy) is decided upon histological examination findings (WHO and Masaoka classification) and degree of surgical excision.

MG in pregnancy

General principles

Myasthenia gravis (MG) per se does not affect fertility and most MG treatments do not affect fertility with the notable exception of cyclophosphamide. Female MG patients should be encouraged to have babies, but planned pregnancy is recommended. Pregnancy should be avoided within two years from MG diagnosis and be postponed until sustained clinical improvement of the disease. The precautions and recommendations about pregnancy and delivery are the same for patients with and without detectable antibodies. Female patients in reproductive age and their partners should be informed early, extensively and repeatedly for pregnancy, delivery, transient neonatal myasthenia gravis, arthrogryposis, puerperium, and breastfeeding.[123]

Pyridostigmine is safe during pregnancy and breastfeeding. Female MG patients in reproductive age need immunosuppressive treatment for the optimal and sustained control of myasthenic symptoms. A great concern is the safety of immunosuppressive drugs during pregnancy and if they have teratogenic effects. MG is a rare disease and relevant information is limited. However, data can be extrapolated, from the use of immunosuppressants in other autoimmune diseases (e.g. inflammatory bowel disease, renal and connective tissue disease) and organ transplant

recipients in pregnancy.

The initiation of non-steroidal immunosuppressant is not recommended during pregnancy because there is no clinical benefit as the onset of therapeutic effect is delayed.

Pregnant women who were taking prednisolone for control of MG should not discontinue it in pregnancy but the lowest effective dose should be maintained. Prednisolone is metabolised by the placenta and <10% crosses in foetal circulation. Prednisolone dose ≤ 20 mg daily is safe during pregnancy and lactation. With higher doses, intrauterine growth restriction, preterm birth and premature rupture of membranes have been reported. Also, with higher corticosteroids doses than 20 mg daily, the time of breastfeeding is preferentially be adapted to corticosteroid intake. Concerning pregnant women on corticosteroids, there is an increased risk of gestational diabetes mellitus, elevation of blood pressure, infections and especially urinary tract infections. Importantly, there is evidence that neonatal adrenal suppression because of corticosteroids exposure in utero does not occur.

Azathioprine is safe during pregnancy and lactation. Azathioprine is a prodrug that is metabolized in 6-mercaptopurine which is converted intracellularly in active nucleotides. The immature foetal liver does not express the enzyme for this metabolic process and for that reason the foetus is relatively protected from the clinical effect of azathioprine.

Cyclosporin and tacrolimus are not teratogenic. Hypertension and gestational diabetes mellitus are side effects of calcineurin inhibitors.

Mycophenolate mofetil, methotrexate and cyclophosphamide have teratogenic effect and should not been given in females in reproductive age.

MMF has a teratogenic effect and causes a typical clinical syndrome with microtia, micrognathia, cleft lip and palate, shortened fifth fingers, hypoplastic nails, diaphragmatic hernia, congenital heart defects. Mycophenolate mofetil should not been prescribed in females in reproductive age. If a woman receives MMF should be strongly advised to switch to another immunosuppressant with safer profile (azathioprine, cyclosporine, tacrolimus) at least 3 months before conception. Otherwise, she must be fully informed about the risks for the foetus.

Methotrexate and cyclophosphamide are absolutely contraindicated in pregnancy and breastfeeding. If a woman is taking one of these drugs before pregnancy, a washout period of at least 3 months is needed before conception.

Teratogenicity is not a risk factor for rituximab. Newborns of mothers treated with rituximab have a transient B-cell depletion which is normalised after 6 months. The elimination half- life of rituximab is about 3 weeks and it is thought to be fully cleared in 15 weeks (5 times the elimination half -life). Rituximab is an IgG antibody that crosses the placenta and till the 22 week of gestation the amount in foetal circulation is <5-10% of the maternal concentration.[124-126]

According to the manufacturer, rituximab is contraindicated during pregnancy and 12 months before pregnancy. However, consensus-treatment guidelines and recommendations have reduced this time to 3 months before pregnancy.[127]

Novel immunotherapies (FcRn antagonists and C5 complement inhibitors) have not been studied in pregnancy. There are reports of pregnant women with favourable response to eculizumab in MG and other autoimmune disorders. Eculizumab is an IgG antibody with the same kinetic during pregnancy as other monoclonal IgG antibodies. Available data do not indicate reduced complement activity in the newborn.[128,129]

Thymectomy should be performed before planned pregnancy and it should not be undertaken during pregnancy.

IVIg has been used for treatment of several autoimmune diseases during pregnancy including autoimmune thrombocytopenic purpura and immunodeficiency syndromes and is considered safe. PLEX has been used in pregnancy to treat thrombotic thrombocytopenic purpura and haemolytic uremic syndrome and is also considered safe. PLEX and IVIg can be used to treat clinical deterioration of MG symptoms during pregnancy.[123,125]

Delivery

Provided that MG is well-controlled, the aim is vaginal delivery with spontaneous onset of labour. When the pregnant woman receives ≥ 7.5 mg prednisolone daily (or 15 mg on alternate) for ≥ 2 weeks, then stress-dose parenteral hydrocortisone should be given in labour. Caesarean section should be performed only for obstetric indications and whenever possible epidural analgesia is preferable to general anaesthesia. A multidisciplinary team involvement of obstetrician, anaesthetist, neonatologist and neurologist is recommended.[123]

Transient Neonatal Myasthenia Gravis (TNMG)

About 10-15% of newborns of mothers with MG have transient muscle weakness due to maternal antibodies against AChR or MuSK that cross placenta and enter the foetus circulation. TNMG has also been reported in seronegative mothers. Previous thymectomy reduces the risk of neonatal myasthenia. Symptoms usually appear within the first hours (12-48h) after birth, but sometimes the onset may be delayed. Close observation of newborn is recommended for at least the first 3 days. Hypotonia, weak cry, poor sucking and feeding difficulty are

the usual symptoms while respiratory involvement is rare. Symptoms progressively improve as the titre of maternal antibodies falls and the disorder is usually resolved within 3-4 weeks.

Supportive therapy and therapy with small doses of pyridostigmine or neostigmine is sufficient in most cases. IVIg or PLEX are needed for the exceptional cases of severely affected infants with respiratory or severe bulbar involvement.[130,131]

Foetal Acetylcholine Receptor Inactivation Syndrome (FARIS)

Although TNMG is by definition transient, persistent myopathy with generalized or localised muscle weakness may occur. This condition is called Foetal Acetylcholine Receptor Inactivation Syndrome (FARIS) and is caused by the effect of maternal AChR Abs on the γ subunit of foetal AChR during a critical period of foetal development. Mothers with high proportion of Abs against γ-subunit of the foetal AChR are usually pauci-symptomatic or asymptomatic and often the diagnosis is made after the detection of foetal syndrome.[131]

Arthrogryposis multiplex congenita is a rare but severe condition characterized by skeletal abnormalities and joint contractures due to foetal hypokinesia in utero. Intrauterine or neonatal death may occur due to pulmonary hypoplasia and polyhydramnios. There are many causes of arthrogryposis including MG where the cause is the effect of maternal AChR Abs on the foetal type of AChR with γ-subunit.

Pregnant women should be instructed to follow foetal movements and regular ultrasound evaluation is important for monitoring of foetal movements and early detection of joint contractures and polyhydramnios.[131]

A previous newborn with severe neonatal myasthenia, foetal acetylcholine receptor inactivation syndrome or arthrogryposis represents a definite risk for next pregnancy. In these cases, IVIg or PLEX is the recommended treatment in all later pregnancies.

Breast-feeding should be encouraged in all MG mothers, excluding those receiving mycophenolate mofetil, methotrexate and cyclophosphamide. All other MG treatments which are regarded safe during pregnancy are safe during lactation. Drugs concentration in breast milk is further reduced with proper adjustment of lactation time to drug intake.[131]

Special Conditions

Myasthenic Crisis

MC is the most severe, life-threatening complication of gMG. The mortality is about 3-5% and death is usually the result of comorbid conditions such as cardiac arrythmia, sepsis, multi-organ failure or acute respiratory distress syndrome.

The definition of MC is severe involvement of respiratory and/or bulbar muscles with urgent need for respiratory support. About 20% of MG patients suffer a myasthenic crisis during the disease course, usually within two years from onset. In a small proportion of patients, MC can be the first presentation of MG and MG should be included in the differential diagnosis of unexplained respiratory failure in the emergency department. Post-operative MC is a delay in extubation beyond 48 h post-surgery.[131]

Myasthenic crisis is reversible but early and aggressive therapeutic interventions are crucial. The first step is patient's transmission to Intensive Care Unit (ICU) for respiratory support (intubation and mechanical ventilation or non-invasive ventilation). Non-invasive ventilation (NIV) can be helpful in patients prior to intubation and in the immediate post-extubation period. Hypercapnia (PaCO2>50 mmHg), pneumonia or older age predict NIV failure. Clinical signs dictating the need for intubation is respiratory distress with increasing tachypnoea and declining lung volume and/or severe bulbar weakness with weak cough and difficulty to clear secretions. The decision to intubate is always a clinical one and emergency intubation should be avoided. If there is evidence of infection, proper antibiotics are started immediately.[132]

Immunomodulatory treatment is introduced with IVIg or PLEX. IVIg 2gr/kg is administered over a period of 5 days. One study found no difference between 1 or 2 gr as total IVIg dose. The usual scheme of PLEX is a course of 5 exchanges every other day over 10 days. Clinical trials suggest that IVIg and PLEX are comparable in terms of efficacy. However, some studies suggest that PLEX leads to faster clinical improvement and shorter ICU stay. Most neuromuscular experts prefer PLEX in overt myasthenic crisis due to rapid onset of action. In clinical practice, the choice between PLEX and IVIg depends on availability and patient's comorbidities. Sepsis and cardiovascular instability are contraindications for PLEX while in recent history of pulmonary embolism, risk for cardiac overloading or renal dysfunction IVIg should be avoided. The preferred route for PLEX is peripheral venous access. Severe complications (thrombosis, pneumothorax, infections) are associated with central line placement.

If there is insufficient response to the initial treatment, PLEX can be given after IVIg and IVIg can be administered after PLEX. As the effect of IVIg may be delayed it is reasonable to wait at least 7 days after completion of IVIg before pursuing PLEX.[9,78,133]

Peros pyridostigmine is discontinued in intubated patient because its use doesn't offer clinical benefit while oral and bronchial secretions may block feeding and endotracheal tube and cause mucus plugging with resultant atelectasis. Intravenous pyridostigmine is discouraged because significant and often

fatal cardiac complications may occur (arrhythmia, coronary vasospasm, myocardial infarction).

If the patient was taking steroids, they should not be stopped; if not, IV prednisolone is introduced (1 mg/kg/day is the usual target dose). There is no rational for initiation of non-steroidal immunosuppression in ICU because of the delayed onset of action. Thymectomy is not performed in intubated patient, unless the extremely rare need for urgent removal of thymoma because of cardiopulmonary complications.

Based on the results of phase III studies, FcRn and complement inhibitors have an early (within the first week), sustained clinical effect and favourable safety profile. Because of these features, novel immunotherapies are attractive options in acute setting of MG especially when there is no response to standard "rescue" therapy (PLEX/IVIg). FcRn antagonists (intravenous infusion efgartigimod alpha and subcutaneous infusion rozanolixizumab) interfere with IgG recycling process and the result is reduction of serum antibodies including acetylcholine receptor antibodies (AChR Abs) and muscle specific tyrosine kinase antibodies (MuSK Abs). Theoretically, FcRn antagonists could be an alternative to PLEX in case of hemodynamic instability or when PLEX is not available. Efgartigimod-alpha was the first approved FcRn antagonist for adult gMG as add-on therapy and there are reports of favorable outcome in cases of myasthenic crisis or impending myasthenic crisis.

C5 complement inhibitors (intravenous infusion eculizumab and ravulizumab and subcutaneous injection zilucoplan) inhibit the formation of Membrane Attack Complex (MAC) and its destructive effects on neuromuscular junction. So far, there are a few reports of successful treatment of refractory MC with eculizumab and one report of favorable outcome in refractory MC with ravulizumab.

Although there is evidence from real-world clinical practice for a favourable outcome,[134-138] recommendations cannot be made for the use of these novel immunotherapies in MC because patients suffering from MC (MGFA V) were excluded from the clinical trials.

General critical care is important for avoidance or treatment of systemic complications which increase patient's morbidity and mortality. Adequate nutrition is important to avoid negative energy balance. Care is needed for deep vein thrombosis prophylaxis, electrolyte imbalance, anaemia, prevention of atelectasis with chest physiotherapy and frequent suctioning, and infections including ventilator-associated pneumonia and urinary tract infections.

Approximately 20-40% of patients fail extubation and re-intubation is needed. The extubation failure is higher in older patients, in patients with pneumonia or atelectasis or in those with prolonged care in ICU. Close observation for at least 48- 72 h in ICU is recommended before transfer to the general ward. The observation period may be longer for less stable patients. Tracheostomy is considered when prolonged intubation (>2 weeks) is required.

Continuous inspiratory muscle training and breathing exercises are helpful for the improvement of respiratory muscle strength and endurance.

In the long term, patients who survived MC can achieve pharmacological remission or minimal manifestation status and return to fully productive lives.

Impending Myasthenic Crisis

MC does not occur suddenly and without warning. The experienced physician should recognize the early signs of incipient myasthenic crisis. Impending Myasthenic Crisis (IMC) is the severe and rapidly evolving clinical deterioration which, based on the physician's judgment, can result in short time (days to weeks) in overt myasthenic crisis. IMC is an emergency situation and it necessitates aggressive management like overt myasthenic crisis. Patients with IMC should be transmitted to ICU where immunomodulatory and corticosteroid therapy should be promptly initiated. When the patient's respiratory status is in doubt, elective intubation is recommended.[9]

DRUGS TO AVOID

There is an increasingly long list of drugs that have the potential to exert negative effects in MG and are mechanistically categorised as follows[139]:

A) Drugs that induce de novo or exacerbate pre-existing MG by interfering with the homeostatic immunological mechanisms that guard against the emergence of autoimmune diseases, including MG.

Prime examples in this category include immune checkpoint inhibitors, penicillamine, statins, tyrosine kinase inhibitors and interferons (the latter two only rarely incriminated).

- Immune Checkpoint inhibitors are being increasingly used in the management of metastatic cancers and are associated with numerous immune-related adverse effects. The ICIs associated with MG are programmed cell death-1 (PD-1) blockers (such as pembrolizumab or nivolumab) and, less frequently, blockers of cytotoxic T cell lymphocyte-associated antigen-4 (CTLA-4), such as ipilimumab, or of programmed cell death-ligand 1 (PD-L1) (avelumab, atezolizumab). The ICI-induced MG can be severe, causing respiratory failure in up to 45% of patients or even leading to death in 25–40% of those affected.[140] Patients who experienced ICI-induced MG should avoid these drugs thereafter but if it is imperative to use them, pre-treatment with steroids, IVIGs or plasma exchange is advised.

- D-Penicillamine, a pyridoxine antagonist, is associated with MG, which is mild in severity and primarily ocular, in approximately 1–7% of treated patients. The drug should be avoided in pre-existing MG and discontinued in cases of penicillamine-induced MG. In the latter case, complete resolution of myasthenic symptoms is expected in the majority (70%) of cases.[141]
- Statins can rarely induce de novo MG and infrequently exacerbate pre-existing disease or lead to MG-like symptoms. Gras-Champel et al. identified in the WHO database of adverse drug reactions 169 cases of possible statin-induced MG amongst 3967 MG patients.[142] These data indicate an increased likelihood (2.66-fold greater odds ratio) of MD exacerbation or induction amongst statin users. In these cases, statins should be discontinued and patients should resort to alternatives that have not been associated with induction of MG such as nicotinic acid (niacin), bile acid sequestrants (cholestyramine, colestipol, and colesevelam), PCSK9 inhibitors (alirocumab and evolocumab).[139]

B) Drugs that interfere with neuromuscular transmission, thereby exacerbating muscular weakness in MG patients or even inducing MG-like symptoms in patients not previously suffering from MG.

The usual culprits in this category are particular antibiotics, antihypertensives and antiarrhythmics, magnesium, neuromuscular blocking agents, inhalation anaesthetics, and sedatives/analgesics as well as botulinum toxin.

- Antibiotics. In view of the fact that antibiotics are quite commonly used in patients with MG, it is important to stress that particular agents are associated with a definite risk of exacerbating myasthenic symptoms. Macrolides (azithromycin, telithromycin, erythromycin), fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, moxifloxacin, levofloxacin) and aminoglycosides (neomycin, amikacin, gentamycin but with the exception of tobramycin) should be avoided in MG, if possible. If not, patients should be closely monitored for the emergence or exacerbation of myasthenic symptoms. On the other hand, on the basis of rare or absent reports of myasthenic reactions to penicillins, cephalosporins, sulfa drugs, clindamycin, tetracyclines, polymyxin B, and nitrofurantoin, it is suggested that these antibiotics can be safely used in MG.[139]
- Antihypertensives and Antiarrhythmics. Antihypertensives, such as adrenergic or calcium channel blockers, can be cautiously administered to MG patients that are in remission or satisfactorily controlled, provided that the lowest effective doses are used and the patient is closely monitored for worsening of MG. Class Ia Antiarrhythmics, such as quinine or procainamide, as well as Class Ic, like propafenone, should be avoided, if possible, or otherwise the patient should be closely monitored for exacerbation of myasthenic symptoms. On the other hand, class Ib antiarrhythmics, like flecainide, potassium channel blockers (like amiodarone and dofetilide) and moricizine have not been implicated in the induction or exacerbation of MG.[139]
- Magnesium has been reported to exacerbate myasthenic symptoms, including precipitation of myasthenic crisis in the context of parenteral magnesium administration for pre-eclampsia.[143] Accordingly, it should be used extremely cautiously in MG under close patient monitoring.
- Neuromuscular blocking (NMB) agents, inhalation anaesthetics & sedatives/analgesics. Succinylcholine, a depolarising NMB, is not absolutely contraindicated in MG.[144] In contrast, non-depolarising NMBs (such as rocuronium, mivacurium, vecuronium, and pancuronium) and inhalation anaesthetics (such as halothane, isoflurane, enflurane, and sevoflurane) should be avoided, if possible.[139,145] If not, close postoperative monitoring is imperative and administration of an ACh-I or sugammadex (a y-cyclodexterin, which encapsulates and reverses the action of NMBs) [146] may be considered. With regard to sedatives, benzodiazepines at high doses should better be avoided or, if necessary, administered with close monitoring of respiratory function.[147] Opioid agents (such as fentanyl, buprenorphine, hydromorphone, methadone, morphine, oxycodone, and oxymorphone) can be used in patients with MG as sedatives/analgesics although, at high doses, monitoring of respiratory rate and pulse oximetry is mandatory.[139]
- Botulinum Toxin should better be avoided in MG for cosmetic purposes as it may unmask subclinical disease,[148] exacerbate pre-existing symptoms or cause weakness distally mimicking ocular or generalised MG. On the other hand, it may be cautiously used for the treatment of cervical dystonia[149] or blepharospasm[150] in cases with stable MG of mild severity, provided the dose is gradually titrated and the patient is closely monitored.

AREAS OF UNCERTAINTY

Over the last 7 years, and after a long period of indolence, the therapeutic landscape of generalised myasthenia has changed dramatically. Following the successful completion of phase III trials, numerous drugs that target complement activation or interfere with FcRN-mediated antibody recycling were approved by regulatory agencies and entered clinical practice. In addition, a number of novel molecules

and cell-based therapies (e.g. CAR T-cells) are at various stages of development. All in all, these innovative advances revolutionised the management of patients with gMG that were hitherto considered refractory or intolerant to traditional approaches. It would be fair to say that we are probably entering a "golden" era in the treatment of gMG.

On the other hand, there are numerous areas of uncertainty that urgently need to be clarified. As of today, it is unknown which particular patient is going to benefit most from a given drug (or a combination of drugs) and when exactly in the evolution of the disease these novel drugs should be introduced. Further, in the absence of head-to-head comparisons, the relative effectiveness and side-effect profile is unknown and can only be deduced, to a certain degree, indirectly (e.g. by meta-analyses). Finally, the external validity of the pre-registration trials needs to be expanded by generating data on patient populations that are traditionally excluded from participation- patients with seronegative or purely ocular MG, patients in whom the dosages of baseline immunosuppressants are not kept stable and patients with significant medical comorbidities. Last but not least, robust health economic data that analyse comparatively and in a holistic manner the significant cost of innovative treatments as well as the potential economic benefits derived by reduction of the burden of the disease and the burden of treatment are urgently needed to guide neurologists and health authorities.

The answer to these lingering questions requires concerted action by scientists and clinicians. We urgently need prognostic biomarkers, so as to identify early on patients with potentially aggressive disease course, and predictive biomarkers, so as to select the most appropriate treatment on a rational rather than empirical basis.[151] We also need MG registries (to capture data in a structured manner) and quality real-world studies so as to fill the gap on the effectiveness of these treatments in every-day practice. Thus, we may get closer to achieve the mantra of personalised medicine: The right drug for the right patient at the right time.[152]

SUPPORTIVE MEASUREMENTS

Any type of physical exercise in patients with severe weakness or MG crisis should be avoided. However, when patients are in remission or stable with mild or moderate weakness, exercise may enhance muscle endurance and it is recommended to follow an individualised exercise program.[14] Moreover, moderate-intensity aerobic and resistance exercise has been proposed in patients on high doses or long-use of steroids to avoid or even reverse the steroids-induced myopathy.[153]

The percentage of MG patients experiencing anxiety, chronic stress, and depression is much higher than in the general population, further degrading the patients' quality of life, and these symptoms should be recognised and treated appropriately.[154]

BRIEF GUIDE TO MG TREATMENT

The recommendations were formulated based on the data from the literature as mentioned above in this article and the authors' clinical experience (Tables 1-3).

Table 1: General recommendations

- All MG subtypes is expected to benefit from pyridostigmine + steroids
- IVIg or PLEX should be readily available for all cases of myasthenia gravis in a status of myasthenic crisis or impending crisis. The effectiveness of fast-acting FcRn and C5 complement inhibitors in severe MG exacerbations remains to be seen in clinical practice.
- An innovative approach, which, however, has not yet been incorporated in any European or International guidelines, would be to start early after disease diagnosis with fast-acting drugs (IVIg, PLEX) or ISs to achieve earlier disease control and possibly use low doses of steroids avoiding their side effects.[108,109]
- Thymectomy should be performed in all cases with thymoma, while in non-thymomatous patients it should be considered according to specific indications
- Pregnant women with MG should be close monitoring by a neurologist expert in the field.
- Application of the structured scales for the evaluation of clinical status and treatment response at the scheduled visits are useful for treatment decisions, facilitates monitoring, and better detects a possible deterioration that can potentially result in a myasthenic crisis.
- In the real world, treatment decisions, in addition to the scientifically proven data, should consider drugs' availability, treatment cost, and the patients' perspective.
- Patients with MG, like other chronic diseases, require sufficient time to discuss alternative treatment options with their doctors before they agree on the optimal treatment recommended to them.
- The phrase "one size fits all" does not apply to MG treatment. The therapeutic regimen should be individualized according to immunological type, disease severity, comorbidities, patient's age, and his/her personal and professional needs.

Table 2: Recommendations for MG subtypes treatment according to currently prevailing literature

Ocular MG: ISs other than steroids are rarely needed. If the results of ongoing trials on FcRn inhibitors are positive, a reduction in the necessary steroid dose (or ISs) may be possible
Generalised MG with Abs AChR, LRP4, or snMG: when steroids have a suboptimal response, show a dependency effect, or should be drastically reduced due to major adverse effects, it is suggested to switch to any of the following choices: Add azathioprine or mycophenolate mofetil, methotrexate, cyclosporine or rituximab Add an FcRn inhibitor or a complement C5 inhibitor Combined a. and b.
MuSK-MG: treatment initiation with rituximab + low steroid dose. If Rituximab is unavailable or unsuccessful, substituted it with another IS, preferably azathioprine. An alternative to the rituximab suggestion, the result of which remains to be seen in real life, is the use of rozanolixizumab, an FcRn inhibitor, as add on to steroids or ISs

Table 3: Recommendations for considering treatment regimen unsuccessful and for potentially modifying treatment strategy

Treatment related problems	• Drug is contraindicated • Drug has major adverse effect • Drug dependency • Drug requires a long time to show a positive response
Uncontrolled disease for a period longer than that required for a drug to show a positive response	• Clinical status unchanged or worsening • Clinical improvement is minimal (affects personal or professional life) • Disease fluctuation phase with frequent relapses/ crises

Table 4: Newer agents under evaluation for MG treatment

Investigation Product	MoA	Clinical Trial	MG subtypes	Pts No	RCP	Status	Outcome
Nipocalimab	FcRn inhibitor	Vivacity-MG3	AChR, MuSK, LRP4	199	24 weeks	Completed Nov 2023	meaningful & sustained efficacy as add-on drug[155]
Satralizumab	IL-6 receptor inhibitor	LUMINESCE	AChR+, MuSK+, LRP4+	188	24 weeks	Completed Aug 2023	Small improvement[156]
Efgartigimod	FcRn inhibitor	ADAPT oculus	oMG	124	7 weeks	Recruiting	Clinical Trials.gov[157]
Efgartigimod	FcRn inhibitor	ADAPT SERON	Triple snMG	110	8 weeks	Recruiting	Clinical Trials.gov[158]
Batoclimab	FcRn inhibitor	FLEX trial	gMG, all subtypes	240	12 weeks	Active	Clinical Trials.gov[159]
Gefurulimab	Complement C5 inhibitor	PREVAIL	AChR+	254	26 weeks	Active	Clinical Trials.gov[160]
Pozelumab	Complement C5 inhibitor	NIMBLE	AChR+, LRP4+	235	24 weeks	Recruiting	Clinical Trials.gov[161]
Iptacopan	Complement factor B inhibitor	NCT06517758	AChR+	146	6 months	Recruiting	Clinical Trials.gov[162]
Inebilizumab	Anti-CD19 monoclonal antibody	MINT	AChR+, MuSK+	230	26 weeks	Active	Clinical Trials.gov[163]
Telitacicept	B & plasma cell depletion	RemeMG	AChR+, MuSK+	180	24 weeks	Recruiting	Clinical Trials.gov[164]
Cladribine	Selective disruption of T- and B-cells	MyClad	gMG, all subtypes	240	24 weeks	Recruiting	Clinical Trials.gov[165]
Descartes-08	mRNA CAR T-cell therapy	AURORA	AChR+	100	4 months	Recruiting	Clinical Trials.gov[166]

MoA: mechanism of action; RCP: randomised control period.

EMERGING DRUGS AND ONGOING CLINICAL TRIALS

MG remains at the centre of interest of the pharmaceutical industry for developing several novel targeted drugs. These are being tested in clinical trials for their efficacy compared with existing therapies, and their potential to minimise treatment burden. At the same time, efforts are being made to develop formulations that are more patient-friendly, for example, by switching from intravenous administration to subcutaneous or oral administration. A list of selected phase III clinical trials that have recently been completed or are in progress is presented in Table 4.

CONCLUSION

This article provides informative guidance for Neurologists treating MG patients in Greece. Over the past few years, the field of MG treatment has been changing rapidly. Several new immunomodulatory agents have recently been approved by the European and United States Authorities (EMA and FDA) and remain to be integrated into therapeutic regimens along with (or instead of) the empirically used 1st and 2nd line drugs. At present, although the various published guidelines and their updates differ slightly from each other, they propose common general rules that should be followed for the benefit of the MG patients.

The expectations of patients and neurologists are higher than those in the distant past and aim to achieve the MM status and MSE. The ideal drug will be able to control the disease as quickly as possible, minimising the pharmaceutical burden and ensuring long-term remission. Although recent clinical studies shed light on the immediate efficacy of a drug or a combination of drugs for a predetermined period of time, much less is known about the need to continue, change, or reduce a medication over the years. MG, which affects young and older people, presenting fluctuating and alternating muscle weakness, with exacerbations and remissions, constitutes a great example of practicing individualised medicine to tailor the specific needs of a single patient at any given time.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ΠΤΕΡΥΓΟΕΙΔΗΣ ΩΜΟΠΛΑΤΗ ΣΕ ΕΔΑΦΟΣ ΝΕΥΡΟΠΑΘΕΙΑΣ ΜΑΚΡΟΥ ΘΩΡΑΚΙΚΟΥ ΝΕΥΡΟΥ – Η ΣΥΜΒΟΛΗ ΤΗΣ ΜΑΓΝΗΤΙΚΗΣ ΝΕΥΡΟΓΡΑΦΙΑΣ

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η πτερυγοειδής ωμοπλάτη μπορεί να προκληθεί από πάρεση του μακρού θωρακικού νεύρου, του παραπληρωματικού νεύρου ή του ραχιαίου νεύρου της ωμοπλάτης, οδηγώντας σε αδυναμία του πρόσθιου οδοντωτού μυός, του τραπεζοειδούς ή των ρομβοειδών μυών, αντίστοιχα. **Μέθοδοι**: Στην παρούσα εργασία παρουσιάζουμε ένα περιστατικό με πτερυγοειδή ωμοπλάτη σε έδαφος νευροπάθειας μακρού θωρακικού νεύρου. **Παρουσίαση Περιστατικού:** Γυναίκα 23 ετών με ελεύθερο ατομικό ιστορικό παρουσίασε από εξαμήνου σταδιακά επιδεινούμενο άλγος στην περιοχή του δεξιού ώμου, με συνοδό μυϊκή αδυναμία. Κατά την αδρή νευρολογική εξέταση, διαπιστώθηκε απόσπαση της ωμοπλάτης από το οπίσθιο θωρακικό τοίχωμα, ανύψωση της άνω γωνίας και μετατόπιση του έσω χείλους προς τα μέσα. Από τον ηλεκτροφυσιολογικό έλεγχο, η μελέτη αγωγιμότητας των νεύρων ανέδειξε μειωμένο ύψος κινητικού προκλητού δυναμικού από τον πρόσθιο οδοντωτό μυ δεξιά, χωρίς στοιχεία ενεργού απονεύρωσης. Η Μαγνητική Νευρογραφία, με ειδικές ακολουθίες T2-weighted short-tau inversion recovery (STIR), ανέδειξε διάχυτα αυξημένο σήμα κατά μήκος του μακρού θωρακικού νεύρου, χωρίς παθολογική σκιαγραφική ενίσχυση. Περίπου εννέα μήνες μετά την έναρξη των συμπτωμάτων και έπειτα από εντατική φυσικοθεραπεία, η ασθενής παρουσίασε πλήρη υποχώρηση των συμπτωμάτων. **Συμπεράσματα:** Η παρούσα περιγραφή περιστατικού αναδεικνύει τη χρησιμότητα της μαγνητικής νευρογραφίας ως μια αξιόπιστη απεικονιστική μέθοδο στην ανίχνευση προσβολής του μακρού θωρακικού νεύρου σε ασθενείς με πτερυγοειδή ωμοπλάτη.

Λέξεις-κλειδιά: πτερυγοειδής ωμοπλάτη, μακρό θωρακικό νεύρο, νευροπάθεια, μαγνητική νευρογραφία

SCAPULAR WINGING DUE TO LONG THORACIC NERVE NEUROPATHY DETECTED WITH HIGH-RESOLUTION MR NEUROGRAPHY

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ABSTRACT

Background: Scapular winging may be caused by palsies of long thoracic, spinal accessory or dorsal scapular nerves, leading to serratus anterior, trapezius, or rhomboid muscles weakness, respectively. **Methods**: We report a case of scapular winging due to long thoracic nerve neuropathy. **Case report:** A 23-year-old woman with unremarkable medical history presented with 6-month history of right shoulder pain and weakness. Neurologic examination revealed scapular protraction and upward rotation impairment associated with medial displacement of the right scapula. Nerve conduction study showed decreased compound muscle action potential (CMAP) amplitudes exclusively over the right serratus anterior, without

acute denervation of the muscle. High resolution Magnetic Resonance Neurography (MRN) disclosed T2-weighted short-tau inversion recovery (STIR) diffuse hyperintense signal across the long thoracic nerve without gadolinium enhancement. Approximately nine months following symptoms onset and intensive physiotherapy, neurological examination revealed complete symptom resolution. **Conclusion:** This case highlights the high resolution MRN utility, as promising and versatile technique on detecting isolated long thoracic nerve palsy in patients with scapular winging.

Keywords: scapular winging, long thoracic nerve, neuropathy, magnetic resonance neurography

INTRODUCTION

Scapular movements of rotation, abduction, and tilting contribute to optimal shoulder function and accurate placement of upper extremity. Scapular pathology leads to scapular winging with shoulder dysfunction and weakness in elevation of the arm.[1] Scapular winging can mainly result from long thoracic nerve palsy leading to serratus anterior dysfunction and medial winging, with an incidence ranging from 0.003% to 0.210%.[2,3] Additionally, spinal accessory and dorsal scapular nerves involvement, leading to trapezius and rhomboid muscles dysfunction, respectively, causes lateral winging.[3] Herein, we report the case of a 23-year-old woman who presented with pain and weakness in her right arm and clinical manifestation of right scapular winging. Nerve conduction study confirmed isolated long thoracic nerve involvement and high-resolution Magnetic Resonance Neurography (MRN) demonstrated diffuse hyperintense signal across the long thoracic nerve without gadolinium enhancement. Approximately nine months after symptom onset and following intensive physiotherapy, complete resolution of symptoms was noted.

CASE REPORT

A 23-year-old woman with an otherwise unremarkable medical history presented with right shoulder pain and weakness with progressive worsening during the past six months. She reported no history of trauma, infection, or systemic illness. Her symptoms had progressively worsened, leading to significant functional impairment in her daily activities. On neurological examination, the patient exhibited notable weakness in her right shoulder, scapular protraction and upward rotation impairment, indicating potential dysfunction of the serratus anterior muscle, which is primarily innervated by the long thoracic nerve. There was a visible medial displacement of the right scapula, commonly referred to as scapular winging (**Figure 1**). Lumbar puncture was performed with unremarkable cerebrospinal fluid (CSF) findings and comprehensive diagnostic workup for autoimmune and other neuromuscular disorders was negative.

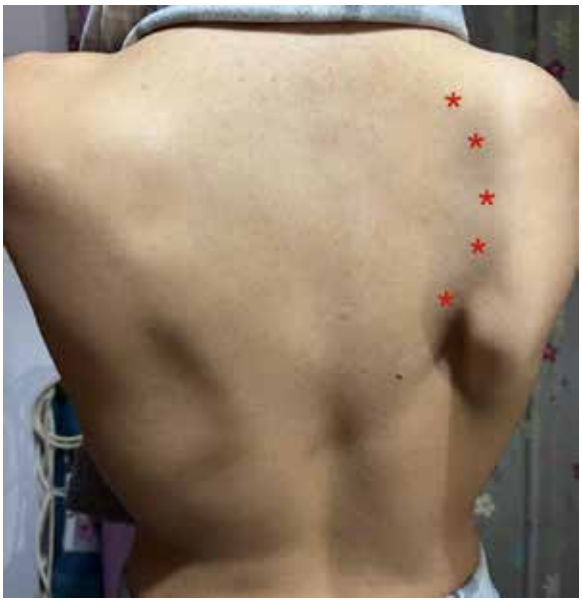

Figure 1: Clinical features. Neurological examination revealing medial displacement of the right scapula, caused by weakness of the right serratus anterior muscle.

Detailed nerve conduction studies were also performed, revealing decreased compound muscle action potential (CMAP) amplitudes exclusively in the right serratus anterior, indicative of isolated long thoracic nerve involvement. Notably, there was no evidence of acute denervation in the muscle, suggesting a subacute or chronic process rather than an acute nerve injury. To further elucidate the underlying pathology, high-resolution MRN was employed. T2-weighted short-tau inversion recovery (STIR) sequences disclosed diffuse hyperintense signal across the right long thoracic nerve (**Figure 2**). Absence of gadolinium enhancement suggested that there was no active inflammation or structural nerve lesion.

The patient was enrolled in an intensive physiotherapy program aiming at strengthening the shoulder girdle muscles and improving scapular stabilisation. Approximately nine months following symptom onset and consistent physiotherapy, the patient experienced complete resolution of her symptoms. Neurological examination at this point revealed full restoration of scapular function with no residual weakness or winging.

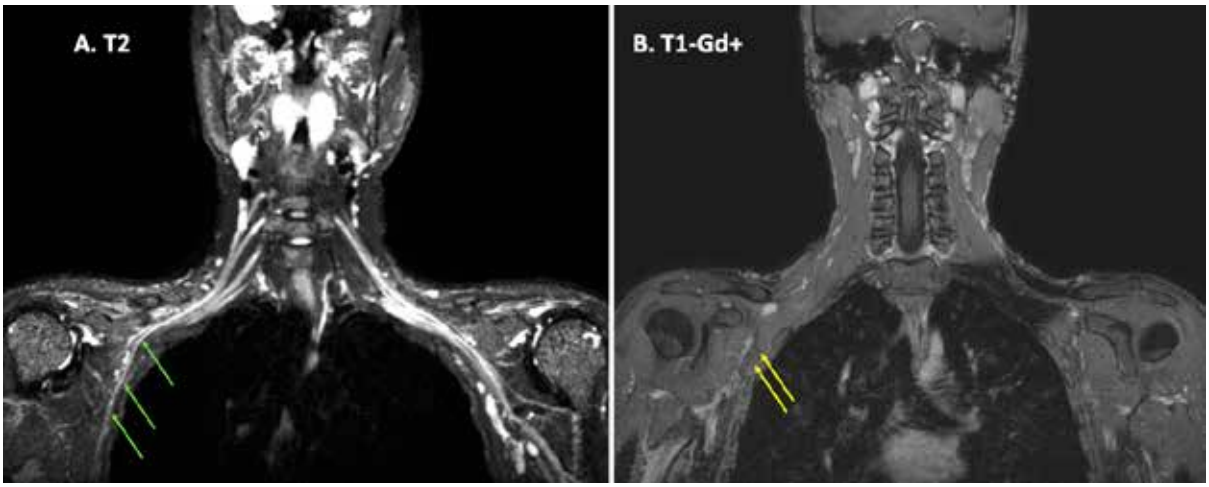

Figure 2: High resolution 3 Tesla Magnetic Resonance Neurography. Coronal T2-weighted STIR sequences demonstrating characteristic diffuse hyperintense signal across the right long thoracic nerve (Panel **A**; green arrows), without distinct gadolinium enhancement (Panel **B**; yellow arrows).

DISCUSSION

The first description of scapular winging was reported by Winslow in 1723.[4] Scapular winging leads to loss of strength and restricted flexion and abduction of the upper extremity, often causing significant pain.[5] It can result from various aetiologies, including iatrogenic, traumatic, infectious, neoplastic, or idiopathic causes.[1] When medical history is taken, it is important to include questions regarding occupation, hobbies and sports, recent injuries and surgeries especially in the neck and thorax, as well as inflammatory or neoplastic diseases.[5] In our case, the isolated long thoracic nerve involvement without clear precipitating factor along with unremarkable diagnostic investigation, suggested an idiopathic neuropathy.

Scapular winging can result from long thoracic, spinal accessory, or dorsal scapular nerve palsies, which innervate the serratus anterior, trapezius, and rhomboid muscles, respectively. Detailed clinical examination is the first step towards the localisation of the lesion. Long thoracic nerve palsy, manifested with arm flexion difficulty leads to medial displacement of scapula, which becomes more pronounced when arms are flexed to horizontal position against a wall, as illustrated in our case.[6] Spinal accessory nerve palsy affects arm abduction and in clinical examination, drooping of the effected shoulder is present along with lateral sifting of the superior scapula angle that is more prominent in arm abduction.[7] Dorsal scapular nerve palsy may lead to scapular winging with scapula's inferior angle shifted laterally and may be more evident when extending elbow backwards.[2,8]

Electromyography and nerve conduction studies are the main diagnostic methods for scapular winging investigation, assessing the involvement of specific muscles, the extent of denervation and the degree of reinnervation.[5] Additionally, as indicated in our case, high-resolution MRN can provide detailed visualisation of the long thoracic nerve, which is often challenging to be assessed with conventional imaging modalities. The diffuse hyperintense signal on T2-weighted STIR sequences indicated an underlying neuropathic process, while the gadolinium enhancement absence ruled out active inflammation or neoplastic infiltration.[9]

Most patients with isolated serratus anterior palsy respond well to conservative management (e.g. prevention of overuse, pain relief, and physical therapy) and complete symptom resolution has been described within 1-24 months.[3] Tendon transfer surgery could be considered for those patients with persistent symptomatic after 24 months.[3] Early recognition and prompt appropriate treatment initiation, including targeted physiotherapy, could lead to favourable functional outcome.

In summary, this case highlights the clinical utility of high-resolution MRN as a promising and versatile technique for detecting isolated long thoracic nerve palsy in patients presenting with scapular winging. MRN offers a non-invasive assessment of peripheral nerves, aiding in the differential diagnosis of neuropathic processes from other potential causes of scapular dysfunction.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

FUNDING INFORMATION

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None.

ETHICAL APPROVAL

The approval for the study protocol was not necessary because our institutional review board does not require approval for case reports.

INFORMED CONSENT

Informed consent was obtained from the patient in the study.

DATA AVAILABILITY

All data needed to evaluate the conclusions in the paper are present in the paper. Additional data related to this paper may be requested from the corresponding author, upon reasonable request.

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A BIOPSY-VERIFIED CASE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT OF MYCOSIS FUNGOIDES WITH POSITIVE RT-QUIC ASSAY

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ABSTRACT

Introduction: We report a rare case of positive RT-QuIC assay in CNS involvement of mycosis fungoides. **Case presentation:** A 73-year-old man presented with decreased consciousness and generalised convulsions. He had been formerly diagnosed with mycosis fungoides, by that time in full remission. Clinical examination revealed profound cognitive deficits with fluctuating level of alertness during admission. An MRI of the brain showed multiple contrast-enhancing lesions in both hemispheres, while lumbar puncture indicated lymphocytic pleocytosis with elevated CSF protein. The rapidly progressive cognitive decline prompted investigations for Creutzfeldt-Jakob disease (CJD) with 14-3-3 and RT-QuIC assay, both of which came back positive. Meanwhile, flow cytometry analysis reported increased T-cell population, suggestive of CNS lymphoma. Despite the high specificity of the RT- QuIC assay for CJD, the diagnosis was not further supported by imaging or EEG findings. A brain biopsy was performed, reporting brain infiltration by a highly malignant T-cell lymphoma, believed to represent large cell transformation of mycosis fungoides with CD30 expression. Treatment with pulsed steroids had some effect on the level of consciousness, although a degree of memory impairment remained. **Conclusion:** Positive RT-QuIC assay has been strongly linked to CJD, with specificity reaching 99%. This case highlights the possibility of positive RT-QuIC results associated with CNS lymphoma.

Keywords: mycosis fungoides, Creutzfeldt-Jakob syndrome, status epilepticus, T-cell lymphoma

ΜΙΑ ΠΕΡΙΠΤΩΣΗ ΙΣΤΟΛΟΓΙΚΑ ΕΠΙΒΕΒΑΙΩΜΕΝΗΣ ΠΡΟΣΒΟΛΗΣ ΤΟΥ ΚΕΝΤΡΙΚΟΥ ΝΕΥΡΙΚΟΥ ΣΥΣΤΗΜΑΤΟΣ ΑΠΟ ΣΠΟΓΓΟΕΙΔΗ ΜΥΚΗΤΙΑΣΗ ΜΕ ΘΕΤΙΚΗ ΔΟΚΙΜΑΣΙΑ RT-QUIC

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Παρουσιάζουμε σπάνια περίπτωση θετικής ανάλυσης RT-QuIC σε ασθενή με προσβολή του κεντρικού νευρικού συστήματος από σπογγοειδή μυκητίαση. **Παρουσίαση του περιστατικού:** Άνδρας 73 ετών μεταφέρθηκε σε ληθαργική κατάσταση στο Τμήμα Επειγόντων μετά από γενικευμένους τονικοκλονικούς σπασμούς. Κατά το παρελθόν είχε διαγνωστεί με σπογγοειδή μυκητίαση, σε πλήρη ύφεση πλέον. Κατά την νοσηλεία παρουσίαζε κυμαινόμενο επίπεδο συνείδησης και νοητική έκπτωση. Η μαγνητική τομογραφία εγκεφάλου έδειξε πολλαπλές βλάβες με σκιαγραφική ενίσχυση και στα δύο ημισφαίρια, ενώ στην οσφυονωτιαία παρακέντηση διαπιστώθηκε λεμφοκυτταρική πλειοκύτωση με αυξημένο λεύκωμα. Λόγω της ταχέως εξελισσόμενης ανοϊκής συνδρομής χαρακτηριζόμενης από διαταραχές μνήμης, προσανατολισμού σε τόπο και χρόνο, συγχυτικοδιεργετικά επεισόδια και ΗΕΓφική εικόνα βαρείας εγκεφαλοπάθειας, προγραμματίστηκε διερεύνηση για τη νόσο Creutzfeldt-Jakob (CJD) με αναζήτηση πρωτεΐνης 14-3-3 και

RT-QuIC assay,οι οποίες ήταν εντόνως θετικές. Στην ανάλυση κυτταρομετρίας ροής του εγκεφαλονωτιαίου υγρού ανευρέθη αυξημένος πληθυσμός Τ-κυττάρων, ενδεικτικός για λέμφωμα του ΚΝΣ. Πραγματοποιήθηκε βιοψία εγκεφάλου, η οποία ανέδειξε διήθηση του εγκεφάλου από ένα κακοήθες Τ-κυτταρικό λέμφωμα, πιθανώς στα πλαίσια μετατροπής μεγάλων κυττάρων της σπογγοειδούς μυκητίασης με έκφραση CD30. Από νευρολογικής πλευράς η θεραπεία με ώσεις στεροειδών έδρασε αρχικά θετικά στην αφύπνιση και την αποδρομή των συγχυτικών επεισοδίων.Ακολούθησε ογκολογική αντιμετώπιση. **Συμπέρασμα:** Η θετική δοκιμασία RT-QuIC συνδέεται στενά με τη CJD, με ειδικότητα που φθάνει το 99%. Στην βιβλιογραφία είναι σπάνια τα περιστατικά θετικοποίησης της δοκιμασίας σε άλλα αίτια όπως στο λέμφωμα του ΚΝΣ, γεγονός που προσδίδει ενδιαφέρον στην προσέγγιση των υποξέων εγκεφαλοπαθειών.

Λέξεις-κλειδιά: σπογγοειδής μυκητίαση, RT-QuIC, λέμφωμα Τ-κυττάρων

INTRODUCTION

Sporadic Creutzfeldt-Jakob disease (sCJD), characterised by rapidly progressive neurodegeneration, represents the most common form of human prion disease, with mean survival ranging from 4 to 12 months.[1] Early clinical manifestations include cognitive impairment with cerebellar signs, constitutional symptoms, behavioural disturbance, and less commonly corticospinal and extrapyramidal signs, which can resemble those of other non-prion diseases.[2] Seizures and acute onset of consciousness disturbance are reported, but infrequent. Typical MRI findings comprise of cortical ribboning in at least two cortical regions and basal ganglia signal changes, whilst EEG can range from non-specific findings such as diffuse slowing in early stages to typical periodic sharp wave complexes later in the course of the disease.[1,3]

Diagnosis of CJD encompasses clinical signs, neuroimaging and EEG changes, and is usually validated by CSF analysis.[4] The real-time quaking-induced conversion (RT-QuIC) assay detects prion-seeded amyloid fibril formation by recombinant prion protein. Recent research has substantiated the high sensitivity (85%) and specificity (99%) of RT-QuIC in CSF for the diagnosis of prion diseases.[4,5] While a small number of cases with potential false-positive outcomes have been documented, these reports lack comprehensive pathological information.[6]

In this context, we hereby present a rare case of CNS involvement in mycosis fungoides, a type of cutaneous T-cell lymphoma, with large cell transformation with positive RT-QuIC assay result. This case underscores the significance of conducting a comprehensive evaluation and confirming the diagnosis through pathological analysis when interpreting RT-QuIC results in patients with suspected prion diseases.

CASE PRESENTATION

A 73-year-old, previously independent, Caucasian man presented to the ER with status epilepticus. Despite immediate medical management, he required emergency intubation with ventilatory support and observation in ICU. The patient had a past medical history of mycosis fungoides, which had been diagnosed three years previously and managed with PUVA therapy. During follow-up there was no systemic involvement of the disease detected. There was no remarkable family history of neurological diseases and there were no previous neurological symptoms reported.

The patient underwent a CT scan of the head right after intubation, which reported some non-specific white matter hypodensities bilaterally. A lumbar puncture was then performed, which revealed lymphocytic pleocytosis and increased CSF protein levels. The patient was empirically treated with intravenous acyclovir, since viral encephalitis was the principal differential diagnosis. The negative antiviral PCR panel in CSF analysis prompted exploration of other possible differential diagnoses, such as autoimmune encephalitides. A course of intravenous steroids was therefore initiated. The patient was successfully extubated ten days later. Over the course of the following days, he exhibited a fluctuating level of consciousness along with cognitive deficits in the form of memory impairment and disorientation. Subsequently, an MR scan of the brain was performed, which revealed multiple hyperintense lesions in the right frontotemporal region, bilateral insula and right anterior corona radiata, some of which demonstrated contrast enhancement (**Figure 1**). CSF flow cytometry reported increased number of T-lymphocytes with CD7 and CD117 single positivity.

After steroid therapy tapering and subsequent withdrawal, new focal epileptic seizures were observed. A further lumbar puncture was performed. The CSF was acellular with negative paraneoplastic and autoimmune markers. The patient received a second course of pulsed intravenous methylprednisolone. Paraneoplastic and autoimmune encephalitis antibodies in the CSF and serum were negative, however, CSF analysis reported positive results for 14-3-3 protein and RT-QuIC.

Clinical improvement was achieved after steroid therapy in context of the level of consciousness, but continued to exhibit cognitive impairment. On se-

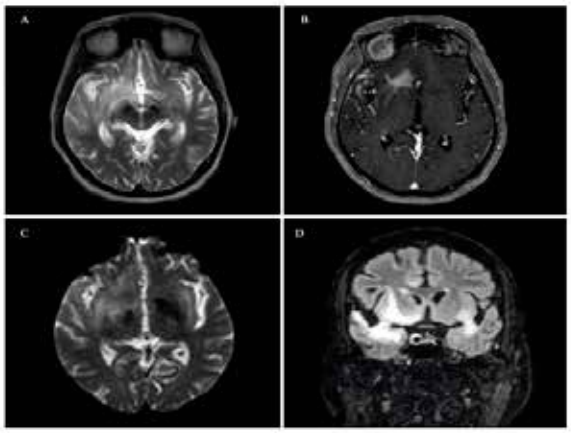

Figure 1. Initial MRI scans of the brain. (a) Axial T2 showing high signal in the right temporal lobe. (b) Axial post-contrast scan, demonstrating an area of contrast enhancement in the right temporal lobe. (c) Axial DWI, depicting a similar area of high signal in the right temporal lobe. (d) Coronal FLAIR with high signal in both temporal lobes and extending to basal ganglia bilaterally.

rial MR scans of the brain, the hyperintense lesions were found slightly decreased in size, but continued to exhibit contrast enhancement. A bone marrow biopsy was carried out in view of the positive immunophenotyping results, but did not detect lymphoma infiltration. On serial EEGs, there was evidence of encephalopathic changes, but no epileptiform activity was observed.

The positive 14-3-3 and RT-QuIC results, in conjunction with the rapid cognitive decline and encephalopathy would support the diagnosis of CJD. The patient fulfilled the CDC diagnostic criteria for probable prion disease.[1] However, there was absence of other neurological signs pointing towards this diagnosis, such as akinetic mutism, cerebellar signs or myoclonus, as well as absence of periodic sharp-wave complexes in serial EEGs, considered typical for the disease or typical neuroimaging findings. A subsequent lumbar puncture performed during steroid therapy revealed decreased levels of 14-3-3, positive RT-QuIC and negative flow cytometry for lymphoma. Due to differential diagnosis ambivalence, a brain biopsy was considered. The latter revealed infiltration of brain tissue by a highly malignant T-cell lymphoma of T-cell origin with intense CD30 expression most likely in the context of large cell transformation spongiform mycosis with CD30 expression (**Figure 2**). The patient was treated for invasive CNS lymphoma with 2 cycles of methotrexate, then cytarabine and brentuximab, but did not sufficiently respond to the treatment and passed away a few months later.

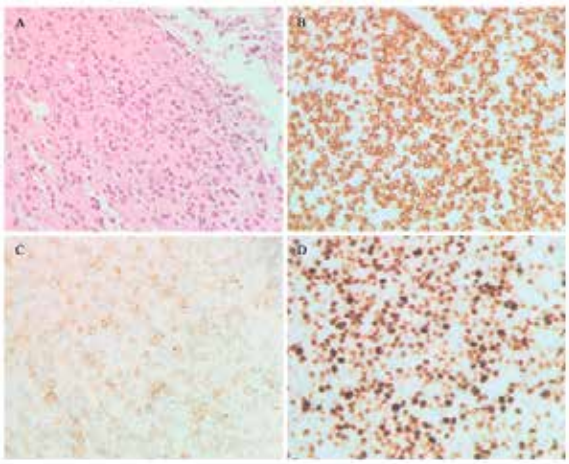

Figure 2. Histological images from the patient's brain biopsy. **(a)** Infiltration of brain parenchyma by medium-sized lymphocytes with dark chromatin and irregular nuclear membrane (Haematoxylin and eosin x400 magnification). **(b)** CD3 expression in medium-sized lymphocytes (IHC x400 magnification). **(c)** CD30 expression in most lymphocytes (IHC x200 magnification). **(d)** Ki-67 expression in the majority of neoplastic lymphocytes (IHC x400 magnification).
IHC: immunochemistry.

DISCUSSION

RT-QuIC assay has been relatively recently added to the diagnostic tests for CJD. Its high sensitivity and specificity render it invaluable for prion disease detection; it has now been added as a component of the diagnostic criteria for CJD.[1] It is able to accurately detect the pathogenic agent (PrP^{Sc}), identified to be responsible for CJD occurrence.[4] The high specificity of RT-QuIC for prion detection is achieved through a lengthy process in which the binding of PrP^{Sc} in the CSF to a mixture of recombinant PrP and thioflavin T is tracked in real time, as the presence of PrP^{Sc} causes fluorescence of the agglomerates formed.[7] RT-QuIC assay appears to be more sensitive and more specific compared to 14-3-3 protein detection, the latter yielding a false-positive rate of 0.098 according to a meta-analysis of 2500 patients, and known to give a false-positive result in cases of neurodegeneration and possibly neuroinflammation.[8] The same meta-analysis reported no false-positive results for RT-QuIC assay.[8] Thus far, there have only been a few cases of RT-QuIC false-positive results reported in literature, in the context of unrelated to prion neurodegeneration and none related to CNS malignant processes.[6] As is the case with all diagnostic immunological assays, RT-QuIC should be interpreted carefully, taking into account the broader clinical presentation, and serving as an adjunct to the clinical signs, examination and other investigations. It would have been of benefit to determine if RT-QuIC and 14-3-3 results turned negative after chemotherapy, but the poor medical state and subsequent death of the patient precluded further investigations. It has been disputed that high white cell count in CSF as well as

high levels of total protein might account for a false positive RT-QuIC response,[7] although infrequently CJD patients demonstrate the above findings.[9] In our case, RT-QuIC remained positive even after an acellular lumbar puncture.

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma.[10] CNS involvement in mycosis fungoides is uncommon, with case-series reporting less than 2% of total patients studied experiencing CNS attack.[11] However, it has been suggested that subclinical involvement rates are higher, as shown in older post-mortem studies. It is estimated that spread of the disease to the CNS might occur within a median time of 5.4 years from diagnosis.[12] Disease with CNS involvement carries a poor prognosis, with a few months of predicted survival time in treated or untreated cases.[11,12] Clinical presentation can largely vary, depending heavily on the location of the injury. Although meningeal disease with leptomeningeal enhancement on post-contrast MRI is more common, cases of contrast-enhancing parenchymal lesions have been reported.[12] Treatment options include various combinations of chemotherapy medications and temozolamide.[12] More recently, radiotherapy has been used with some promising results, although more research has to be conducted on this field.[13]

CONCLUSION

We would hereby like to underline the rare likelihood of positive RT-QuIC assay results on a patient with a biopsy-verified CNS T-cell lymphoma, as demonstrated in two separate CSF samples. The role of RT-QuIC as a laboratory tool of CNS lymphoma diagnosis is at present unchallenged. However, the possibility of coexistence of subclinical CJD has not been excluded. In literature, there has only been one case of coexistence of a brain tumour, a vestibular schwannoma and CJD.[14] This case highlights the significance of pathological confirmation, including western-blot analysis, particularly in complex diagnostic cases where multiple potential aetiologies need to be considered.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Το περιοδικό *ΑΡΧΕΙΑ ΚΛΙΝΙΚΗΣ ΝΕΥΡΟΛΟΓΙΑΣ* κυκλοφορεί κάθε δύο μήνες και αποτελεί το επίσημο όργανο της Ελληνικής Νευρολογικής Εταιρείας. Με την Υπουργική Απόφαση ΔΥ2α/Γ.Π.οικ. 66198/1/6/2006, που δημοσιεύθηκε στο Φ.Ε.Κ. 1034/Β/1-08-2006, προστέθηκε στον κατάλογο των περιοδικών με Εθνική Αναγνώριση.

Ύλη του Περιοδικού

1. Ανασκοπικά Άρθρα: Η έκτασή τους δεν πρέπει να υπερβαίνει τις 6.000 λέξεις.
2. Εργασίες: Κλινικές ή εργαστηριακές μελέτες. Δεν πρέπει να υπερβαίνουν τις 4.000 λέξεις (συμπεριλαμβανομένων έως 6 πινάκων και εικόνων). Δεν πρέπει να έχει προηγηθεί δημοσίευσή τους σε άλλο έντυπο. Περιλαμβάνουν σελίδα τίτλου, δομημένη περίληψη, εισαγωγή, μέθοδο, αποτελέσματα, συζήτηση και βιβλιογραφία.
3. Σύντομες ανακοινώσεις και Γράμματα προς τη σύνταξη: Σχόλια για εργασίες που έχουν δημοσιευθεί ή σύντομες αναφορές σε ένα θέμα. Δεν πρέπει να υπερβαίνουν τις 1.500 λέξεις και περιλαμβάνουν έως 2 πίνακες ή εικόνες.
4. Ενδιαφέροντα περιστατικά: Όριο λέξεων 1.500, με τη σελίδα τίτλου, περίληψη και τις βιβλιογραφικές αναφορές. Επιτρέπονται μέχρι 2 εικόνες ή πίνακες.
5. Νευρολογικές Εικόνες με εκπαιδευτικό ενδιαφέρον: Όριο 4 εικόνες για το ίδιο θέμα και 200 λέξεις.
6. Επιλογές και σχολιασμός της βιβλιογραφίας.
7. Νευρολογικά Νέα - Ειδήσεις - Ενημερωτικές Σελίδες, όπως νέα της Ελληνικής Νευρολογικής Εταιρείας και συγγενών εταιρειών, ανακοινώσει συνεδρίων και άλλων εκπαιδευτικών δραστηριοτήτων.

Δομή της ύλης

Γίνονται δεκτές εργασίες στα ελληνικά ή αγγλικά.
Υποβάλλεται πάντοτε ο τίτλος, τα ονόματα των συγγραφέων και η περίληψη και στα αγγλικά.
Τα κείμενα θα πρέπει να αποστέλλονται σε μορφή Microsoft Word document.
Σελίδα τίτλου: Περιέχει τον τίτλο, τα πλήρη ονόματα των συγγραφέων, το ίδρυμα προέλευσης, τη διεύθυνση και το τηλέφωνο του υπευθύνου για την αλληλογραφία και τον καταμετρημένο αριθμό λέξεων.
Περίληψη: Παρουσιάζει τα κυριότερα σημεία της εργασίας. Δεν πρέπει να υπερβαίνει τις 250 λέξεις. Στο τέλος της παρατίθενται 3-10 λέξεις ευρετηρίου.
Αγγλική περίληψη: Παρουσιάζει σε συντομία την εργασία. Η έκτασή της είναι ως 400 λέξεις. Στην αρχή της γράφονται τα ονόματα των συγγραφέων και ο τίτλος της εργασίας στα αγγλικά.
Λέξεις-κλειδιά: έως 6 λέξεις κλειδιά.
Βιβλιογραφία: Οι βιβλιογραφικές παραπομπές αριθμούνται με αύξοντα αριθμό ανάλογα με τη σειρά εμφάνισής τους στο κείμενο (Vancouver). Όλες οι βιβλιογραφικές παραπομπές να αναφέρονται μέσα σε αγκύλες. Π.χ. Ο Smith [1] ανέφερε ότι ... και τα ευρήματα αυτά επιβεβαιώθηκαν από τον Adams και συν [2]. Αναγράφονται έως και οι 6 πρώτοι συγγραφείς. Στον πίνακα της βιβλιογραφίας περιλαμβάνονται μόνο εκείνες οι βιβλιογραφικές παραπομπές που αναφέρονται στο κείμενο και ο πίνακας συντάσσεται με αύξοντα αριθμό που αντιστοιχεί στη σειρά εμφάνισης των βιβλιογραφικών παραπομπών στο κείμενο π.χ.
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Εικόνες: Αποστέλλονται τα πρωτότυπα σχέδια ή φωτογραφίες καλής ποιότητας. Να υποβάλλονται σαν αρχεία εικόνας ξεχωριστά από το κείμενο του MS Word. Αριθμούνται με τη σειρά εμφάνισης στο κείμενο. Στο κείμενο θα πρέπει να υπάρχει σαφής παραπομπή στον τίτλο των ηλεκτρονικών αρχείων. Σε ξεχωριστή σελίδα αναγράφονται οι τίτλοι των εικόνων και οι τυχόν επεξηγήσεις.
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Συνοδευτικό έντυπο υποβαλλόμενης εργασίας

Θα πρέπει να συμπληρωθούν ΟΛΑ τα σημεία του εντύπου. Άλλη συνοδευτική επιστολή δεν είναι απαραίτητη.

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Επιβεβαιώστε την πληρότητα της υποβολής του χειρογράφου σας, σημειώνοντας ΟΛΑ τα παρακάτω σημεία

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Δηλώνω υπεύθυνα ότι:

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3. Δηλώνω υπεύθυνα ότι δεν υπάρχει θέμα υποκλοπής πνευματικής ιδιοκτησίας (σε περίπτωση εικόνων, πινάκων ή υλικού από άλλες δημοσιεύσει έχει ζητηθεί και ληφθεί η νόμιμη άδεια η οποία και συνυποβάλλεται).
4. Δεν υπάρχουν θέματα σύγκρουσης συμφερόντων – σε περίπτωση εξωτερικής χρηματοδότησης αυτό θα πρέπει να αναφέρεται στο τέλος της εργασίας.

Ο υπεύθυνος για την αλληλογραφία συγγραφέας

(υπογραφή)