Acta Clin Croat 2021; 60:496-509
doi: 10.20471/acc.2021.60.03.21

Review

TREATMENT OF MYASTHENIA GRAVIS PATIENTS WITH COVID-19: REVIEW OF THE LITERATURE

Sven Županić[1,2], Ines Lazibat[1,2], Maja Rubinić Majdak[2] and Mia Jeličić[3]

[1]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;
[2]Dubrava University Hospital, Zagreb, Croatia;
[3]Dr Fran Mihaljević University Hospital for Infectious Diseases, Zagreb, Croatia

SUMMARY – Coronavirus disease 2019 (COVID-19), caused by the late 2019 outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a respiratory disease which could put myasthenia gravis (MG) patients at a greater risk of developing severe disease course, since infections and some drugs are a well-recognized trigger of symptom exacerbation in MG patients. Out of ten most commonly used past and present drugs used in COVID-19 treatment, two (quinolone derivatives and azithromycin) are known to worsen MG symptoms, whereas another two (tocilizumab and eculizumab) might have positive effect on MG symptoms. Colchicine, remdesivir, lopinavir, ritonavir and favipiravir seem to be safe to use, while data are insufficient for bamlanivimab, although it is also probably safe to use. Considering MG treatment options in patients infected with SARS-CoV-2, acetylcholine esterase inhibitors are generally safe to use with some preliminary studies even demonstrating therapeutic properties in regard to COVID-19. Corticosteroids are in general safe to use, even recommended in specific circumstances, whereas other immunosuppressive medications (mycophenolate mofetil, azathioprine, cyclosporine, methotrexate) are probably safe to use. The only exception is rituximab since the resulting B cell depletion can lead to more severe COVID-19 disease. Concerning plasmapheresis and intravenous immunoglobulins, both can be used in COVID-19 while taking into consideration thromboembolic properties of the former and hemodynamic disturbances of the latter. As current data suggest, all known COVID-19 vaccines are safe to use in MG patients.

Key words: *Myasthenia gravis; COVID-19; Immunosuppression; COVID-19 vaccine; Neuromuscular disorders*

Introduction

Coronavirus disease 2019 (COVID-19), caused by the late 2019 outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a respiratory disease with a wide spectrum of disease severity that ranges from mild or almost no upper respiratory symptoms to severe acute respiratory distress syndrome, pneumonia, multiorgan failure, and death[1]. Higher morbidity and mortality rates are seen among the elderly and those with underlying comorbidities and immune deficiencies[2].

Treatment of myasthenia gravis (MG) can be challenging in these conditions for a number of reasons. Patients with neuromuscular disorders, especially patients with autoimmune MG, might be at a higher risk of worse outcomes than otherwise healthy people because of the immunocompromised state related to immunotherapy and possible respiratory and bulbar muscular weakness[3]. However, cessation of immunotherapy in neuroinflammatory disorders has severe risks as well[4]. Moreover, infections and some drugs are a well-recognized trigger of symptom exacerbation in MG patients[5]. In this paper, we will review the existing lit-

Correspondence to: *Sven Županić, MD*, Dubrava University Hospital, Av. Gojka Šuška 6, HR-10000 Zagreb, Croatia
E-mail: szupanic1@kbd.hr
Received February 8, 2021, accepted March 22, 2021

Table 1. COVID-19 treatment options with comments on MG patients

Drug treatment option	Recommendation for use in MG patients
Chloroquine, hydroxychloroquine	Avoid; could worsen MG
Azithromycin	Avoid; could worsen MG
Colchicine	Probably safe to use; no effect on MG, myopathy develops rarely
Remdesivir	Safe to use; no known effects on MG
Lopinavir	Safe to use; no known effects on MG
Ritonavir	Safe to use; no known effects on MG
Favipiravir	Safe to use; no known effects on MG
Bamlanivimab	No data on effects on MG
Tocilizumab	Safe to use; potentially positive effects on MG
Eculizumab	Safe to use; positive effect on MG

COVID-19 = coronavirus disease 2019; MG = myasthenia gravis

erature on the potential problems and pitfalls that can be encountered during treatment of MG patients with COVID-19.

Treatment Options for COVID-19 in Myasthenia Gravis Patients

At the time of writing this article, no single COVID-19 drug treatment option has proven to be hugely successful, although several drug treatment options have proven some degree of success. Although most treatment options have in general proven to be relatively safe when administered to general population, treating COVID-19 in MG patients with some medications can cause worsening of MG symptoms. In this review, we decided to focus on the administration of past and present COVID-19 medications in MG patients. Table 1 summarizes data on COVID-19 drug treatment options in MG patients with COVID-19.

Chloroquine (CQ) or hydroxychloroquine (HCQ) was the first drug to be used in the treatment of COVID-19. The rationale for the use of CQ or HCQ was based on the *in vitro* proven antiviral effects against SARS-CoV-2 virus[6-8], a small and early interim analysis of 100 patients with COVID-19 in China[9], and a small non-randomized study in 20 patients from France[10]. These findings led clinicians worldwide to use them indiscriminately and to include them in their institutional protocols and guidelines for the treatment of COVID-19 as monotherapy or in combination with azithromycin[11]. However, further larger studies including randomized controlled trials (RCT) and meta-analysis disapproved these findings and found, with a moderate level of certainty, that HCQ monotherapy lacks efficacy in reducing short-term mortality in hospitalized patients with COVID-19 or in reducing the risk of hospitalization in outpatients with COVID-19, as well as that the use of HCQ in combination with azithromycin is probably associated with increased short-term mortality among hospitalized patients with COVID-19[11,12]. Since then, HCQ and CQ are no longer used in COVID-19 treatment. Quinolone derivatives in general, which HCQ and CQ are members of, adversely affect both presynaptic and postsynaptic aspects of neuromuscular transmission, and may worsen or provoke disorders of neuromuscular transmission[13]. It is therefore advised to use quinolone derivatives with extreme caution in MG[14]. Nevertheless, there are many reports in the literature where CQ and HCQ were used in MG patients with COVID-19. Jallouli *et al.* report on a case series of eight MG patients with COVID-19, where exacerbation of myasthenic symptoms were seen in only one of these eight patients who received HCQ after the diagnosis of MG[15]. Aksoy and Oztutgan report on excellent recovery of MG patients with COVID-19 despite HCQ administration[16], whereas Anand *et al.* used HCQ in three out of five patients from their case series; two of those three patients were discharged from the hospital, whereas one patient remained hospitalized requiring ongoing mechanical ventilation at the time of writing the article[17]. In summary, CQ and HCQ are generally contraindicated for use in MG pa-

tients with COVID-19, not only due to the negative effects on MG symptoms, but also because of inefficiency in treating COVID-19.

Although the preponderance of evidence indicates that there is no benefit of HCQ in the treatment of COVID-19, fewer studies evaluated azithromycin, a broad-spectrum macrolide antibiotic that has anti-inflammatory properties[18]. Azithromycin is commonly used for bacterial respiratory infections[18], could potentially treat or prevent co-infection with SARS-CoV-2, and could have antiviral activity against some RNA viruses[19,20]. However, despite azithromycin being a promising therapy, there is a paucity of data on its use in COVID-19[21,22]. This macrolide has mostly been administered with HCQ, which has been shown not to provide benefits in the treatment of SARS-CoV-2 pneumonia[21]. The largest clinical trial published to date on the use of azithromycin in hospitalized COVID-19 patients did not demonstrate superiority over usual care alone[22]. Consequently, azithromycin use in patients hospitalized with COVID-19 should be restricted to patients where there is a clear antimicrobial indication[22]. In the context of MG, macrolide antibiotics including azithromycin can cause severe exacerbation of MG[23], most likely due to presynaptic effects[24]. We were able to identify three case series where azithromycin was used in MG patients with COVID-19; in a case series reported by Anand *et al.*, azithromycin was administered to three out of five patients, two of whom were discharged from the hospital, while one patient remained hospitalized requiring ongoing mechanical ventilation at the time of writing the article[17]; in a case series by Hübers *et al.*, one patient administered azithromycin among other antibiotics had positive disease outcome, albeit with prolonged intubation period[25]; and in a case series reported by Camelo-Filho *et al.*, ten patients were treated with azithromycin, and three of them died, one was discharged from the hospital in a clinically worse condition, while the others were discharged from the hospital with unchanged MG status[26]. Therefore, although it seems that macrolide antibiotics could be used with extreme caution in MG patients, it is generally not recommended, especially in the light of the findings of its ineffectiveness in COVID-19 treatment.

Colchicine is an anti-inflammatory drug commonly used in the treatment of acute gouty flares and familial Mediterranean fever[27]. Since colchicine demonstrates inhibitory effects on neutrophil activity, cytokine generation and the inflammation/thrombosis interface, together with an overall lack of evidence for systemic immunosuppression, it was postulated that colchicine might be a potential treatment for COVID-19[28]. So far, two RCTs have demonstrated the superiority of colchicine over standard COVID-19 medical treatment regarding higher survival rate[29] and improved time to clinical deterioration[30]. No results from the two largest studies, COLCORONA and RECOVERY, on colchicine in COVID-19 have yet been officially published. Tardif *et al.* in the COLCORONA trial demonstrated the superiority of colchicine over standard-of-care in 4488 non-hospitalized patients, thus making it the first COVID-19 treatment with proven efficacy for non-hospitalized patients[31]. However, it should be noted that at the time of writing this article, these results have not yet been certified by peer-review. The RECOVERY trial has already randomized more than 6,500 hospitalized patients to colchicine *versus* usual care as one of the arms of the platform trial, but to this day no results have been published. Although colchicine is safe to use in MG patients, the drug does have neuromuscular side effects[32]. Autophagic, vacuolar myopathy is a rare complication of treatment with colchicine[33]. Although colchicine-induced myopathy typically includes features of slowly progressive painless proximal myopathy that develops after prolonged treatment with colchicine[32,34], it can also present with rapidly progressing myopathy and rhabdomyolysis[35]. Physicians treating MG patients with COVID-19 should therefore take every precaution not to misdiagnose newly developing myopathy as MG exacerbation in patients treated with colchicine. Accordingly, we feel that colchicine might be considered as a treatment option for MG patients with COVID-19.

Remdesivir is a nucleotide analog initially developed for the treatment of Ebola and Marburg viruses[36], which also has proven efficacy in MERS-CoV2 treatment[37,38]. Remdesivir was shown to have *in vitro* antiviral activity against SARS-CoV-2[7], and, in a cohort of patients with severe COVID-19 treated with remdesivir, the majority showed clinical improvement[39]. So far, there is no evidence that remdesivir causes any negative effects on MG, therefore there should be no hindrance to its use.

After the emergence of SARS in 2003, screening of approved drugs identified lopinavir, a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, as having *in vitro* inhibitory activity against SARS-CoV, the virus that causes SARS in humans[40-42]. Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450[43]. However, the result on SARS-CoV-2 virus was discouraging with two large RCTs not supporting the use of lopinavir-ritonavir for the treatment of hospitalized patients with COVID-19[43,44]. Concerning the use of lopinavir-ritonavir in MG patients, there have been case reports on MG symptom worsening after induction of ritonavir, albeit in human immunodeficiency virus patients[45]. In general, however, this class of drugs has shown few neuromuscular side effects[46], therefore, these drugs could be used in MG patients.

Favipiravir is an antiviral prodrug with active metabolite favipiravir ribofuranosyl-5′-triphosphate that inhibits viral replication by arresting RNA polymerase triphosphate[47]. In some countries, favipiravir is already approved for influenza virus[48], which led researchers to believe that the drug might exhibit antiviral properties on SARS-CoV-2[49]. Although most studies on the usefulness of favipiravir as COVID-19 treatment are still underway[50], at least one study has already demonstrated promising effectiveness of favipiravir for treating patients with COVID-19[51]. No known neuromuscular side effects have been reported for the drug, therefore favipiravir could be used in MG patients. We identified one MG patient with COVID-19 in the published literature, who was treated with favipiravir and HCQ for the first five days, leading to complete clinical recovery[16].

Bamlanivimab is a human immunoglobulin G1 (IgG1) kappa monoclonal antibody directed against the SARS-CoV-2 virus[52], which resulted in reduction of viral replication in the upper and lower respiratory tract in the experimental model of rhesus macaque monkey[53]. Several clinical trials on human subjects are currently underway[53]. So far, there are no data on the safety of bamlanivimab in MG patients, although it is also probably safe to use as judging by its mechanism of action.

Tocilizumab is a monoclonal antibody the clinical effects of which are explained by targeting interleukin-6 receptor, inhibiting signal transduction, and thus counteracting the effects of proinflammatory interleukin-6, which was shown to be involved in inflammatory storms in severe COVID-19[54]. Results of studies of tocilizumab on patients with COVID-19 are, however, mixed; three RCTs showed no difference in mortality compared to standard care and no benefit on disease progression or death prevention[55-57], whereas one, the newest RCT demonstrated that in hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival[58]. The observational, multicenter cohort study conducted by Gupta *et al*. demonstrated that among critically ill patients with COVID-19 in this cohort study, the risk of in-hospital mortality was lower in patients treated with tocilizumab in the first two days of intensive care unit (ICU) admission compared with patients whose treatment did not include early use of tocilizumab[59]. Although evidence for the use of tocilizumab in MG is extremely scarce, it seems that tocilizumab could have therapeutic capabilities. A case series by Jonsson *et al*. demonstrated positive effects on MG symptoms in two female MG patients with high titers of serum acetylcholine receptor (AChR) antibodies and insufficient response to rituximab. Therefore, the use of tocilizumab in MG patients with COVID-19 is most probably safe and could potentially be recommended if the efficacy in COVID-19 be proven in further studies.

The possible use of eculizumab in COVID-19 was also suggested, owing to eculizumab effect of inhibiting C5 complement, which is postulated to be increased in COVID-19, as suggested in MERS-CoV2[60]. Preliminary results in COVID-19 patients with severe pneumonia or acute respiratory distress syndrome (ARDS) show positive results; all four patients in the study successfully recovered after treatment with eculizumab[61]. The study of eculizumab (Soliris®) in COVID-19 infected patients (SOLID-C19) is currently underway, which could confirm initial positive results[62]. On the other hand, eculizumab is the first targeted complement inhibitor to be approved for use in anti-AChR antibody-positive adults with generalized MG or refractory generalized MG[63]. Eculizumab was generally well tolerated, with a tolerability profile generally similar to that reported previously for other indications[63]. Therefore, according to pub-

Table 2. MG treatment options with comments on COVID-19

Drug treatment option	Recommendation for use in COVID-19
Acetylcholine esterase inhibitors	Continue treatment; potentially positive effects on COVID-19
Corticosteroids	Continue existing treatment with dose escalation in severe or critically ill patients with COVID-19; positive effect seen on severe or critically ill COVID-19
Mycophenolate mofetil	Probably safe to use; data insufficient
Azathioprine	Probably safe to use; data insufficient
Cyclosporine	Probably safe to use; data insufficient
Methotrexate	Probably safe to use; data insufficient
Rituximab	Results in more severe COVID-19 disease; if possible, delay initiation until the peak of the outbreak is over; consider extending dosing intervals

COVID-19 = coronavirus disease 2019; MG = myasthenia gravis

lished data, eculizumab can most certainly be administered to MG patients with COVID-19.

Treatment Options for Myasthenia Gravis Patients with COVID-19

Medical therapies are used in MG patients for either direct alleviation of symptoms, or as immunomodulatory drugs with the aim of dampening the underlying immunopathology causing the disease with the aim of inducing remission or minimal manifestations[64]. Table 2 summarizes data on MG drug treatment options in MG patients with COVID-19.

Acetylcholine esterase inhibitors (AChEI) are the first-line treatment for all forms of MG[65]. Pyridostigmine is the most commonly used AChEI for symptomatic treatment of MG symptoms. It is used for symptom management alone in purely ocular and mild generalized cases, or in combination with immunosuppressants in more severe cases[66]. Cholinergic side effects are most common, which include abdominal cramps, diarrhea, and excessive lacrimation[66]. AChEI are used by 99% of MG patients[67]. There is no scientific evidence to suggest that symptomatic therapies such as pyridostigmine or 3,4-diaminopyridine increase the risk of infection and should not be discontinued unless there are other clinical reasons to do so[68]. Moreover, acetylcholine (ACh) modulates the acute inflammatory response, a neuro-immune mechanism known as the inflammatory reflex, and since according to recent evidence, electrical and chemical stimulation of the inflammatory reflex may reduce the burden of inflammation in chronic inflammatory diseases, it is postulated that pyridostigmine, by increasing the half-life of endogenous ACh, mimics the inflammatory reflex[69]. This could lead to prevention of development of severe systemic inflammatory response, pulmonary damage, and even ARDS in patients with COVID-19[69]. A parallel-group, multicenter randomized, double-blinded, placebo-controlled, phase 2/3 clinical trial to test the efficacy of pyridostigmine bromide at low doses to reduce mortality or invasive mechanical ventilation in adults with severe SARS-CoV-2 infection is currently underway[69]. There are events when pyridostigmine should be withheld. Since pyridostigmine as AChEI may lead to excessive bronchial secretions, in the event of excessive bronchial secretions due to COVID-19 disease, the dose of pyridostigmine could be adjusted or pyridostigmine could be withheld entirely in order to prevent further complications during hospital stay[70]. This should be performed with extreme caution since withdrawal of AChEI can lead to MG worsening.

Despite AChEI treatment, 54% of MG patients require corticosteroids[67]. Eighty percent or more patients show signs of either medical remission or marked improvement upon the introduction of corticosteroids[71]. Although evidence from RCTs remain limited and side effects pose significant challenges in clinical use, corticosteroids are considered as the most effective oral immunosuppressive agents and are widely recommended as the first-line agent for use in MG patients[72-75]. The systemic side effects of long-term corticosteroid therapy are numerous and can be highly

impactful[76]. The most concerning side effects of corticosteroids during COVID-19 pandemic are their effects on immune suppression. Although strong data are still lacking, immunosuppressed patients are plausibly at a higher risk of a more severe COVID-19 course[77]. Data on the subject derive from study results of higher odds of hospitalization of patients with rheumatic disease exposed to ≥10 mg/day glucocorticoids[78]. There are no data on MG patients. Data from a meta-analysis have, however, also confirmed a beneficial effect of corticosteroids on short-term mortality and reduction in the need for mechanical ventilation in hospitalized patients with COVID-19[79], while newer studies also demonstrated that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving not only invasive mechanical ventilation but also oxygen therapy alone[80]. Corticosteroids have beneficial effects in overcoming both hyperinflammation and ARDS[80]. Consequently, patients are advised to continue existing therapies unless there are clinical reasons to change it, since reduction or discontinuation poses the risk of MG worsening[68]. It should be noted that most COVID-19 glucocorticoid trials were examining dexamethasone. Prednisone, which is used in most MG patients, was not examined as COVID-19 treatment. Methylprednisolone (MP), a drug formulation most similar to prednisone[81], was examined as COVID-19 treatment in fewer trials; a RCT by Jeronimo *et al*. failed to demonstrate clinical benefit of MP in hospitalized patients with COVID-19[82]; a study by Nelson *et al*. demonstrated increased ventilator-free days and higher probability of extubation in a propensity-score matched cohort of mechanically ventilated patients with ARDS due to COVID-19 with MP use[83]; a study by Corral-Gudino *et al*. demonstrated that a short course of MP had a beneficial effect on the clinical outcome of severe COVID-19 pneumonia[84]; and a retrospective study by Wang *et al*. demonstrated worse outcome associated with MP therapy in patients with non-severe COVID-19 pneumonia[85]. In spite of the relatively conflicting evidence, most guidelines recommend the use of prednisone, methylprednisolone or hydrocortisone if dexamethasone is not available for severe and critically ill patients with COVID-19[86]. We have positive clinical experience with increasing the dose of prednisone to 40 to 50 mg in hospitalized MG patients with COVID-19 if the patient is already on prednisone therapy, or induction of dexamethasone if the patient was corticosteroid free.

Mycophenolate mofetil, azathioprine and cyclosporine, a monophosphate dehydrogenase inhibitor, a purine analog and calcineurin inhibitor, respectively, are other immunosuppressive medications occasionally used in difficult-to-treat MG. Although data on the risk of developing COVID-19 on these medications are scarce, patients are advised to continue existing therapies unless there are clinical reasons to change it, since reduction or discontinuation poses the risk of MG worsening[68]. In case of developing COVID-19, standard immunosuppressive agents (azathioprine, mycophenolate) should probably be continued, since the effects of dosing are longer lasting, drug wash-out takes longer, and rebuilding of the effects takes several months[68]. A handful of *in vitro* studies have established that mycophenolic acid, calcineurin inhibitors and thiopurine analogs inhibit the proteolytic activity or replication of SARS-CoV-2, SARS-CoV and/or MERS-CoV[87]. So far, only one small retrospective cohort study of 51 patients on the use of mycophenolate mofetil in hospitalized patients with MERS-CoV was performed with positive results[88]. Interestingly, in the largest case study on MG patients with COVID-19 to date, all patients that did not require mechanical ventilation were using prednisone plus a second immunosuppressive drug[26]. Previous small reports on MG patients with COVID-19 also demonstrated a favorable course in the patients using prednisone plus a second immunosuppressive drug at baseline[17,25,89,90], although there also are reports on patients requiring mechanical ventilation despite having been treated with prednisone plus a second immunosuppressive drug[17,70]. Briefly, although there is a lack of studies of mycophenolate mofetil, azathioprine and cyclosporine use in COVID-19, given the known pharmacological and pathophysiological properties of the said drugs, the continuation of treatment in MG patients with COVID-19 infection is probably considered safe-profile treatment.

Methotrexate is a folic acid antagonist most commonly indicated for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis[91]. Its use in MG remains controversial. Most recent RCTs of methotrexate for patients with generalized MG found no steroid-sparing benefit of methotrexate in MG over 12 months of treatment, despite being well-tolerated[92].

Data on the safety of methotrexate during COVID-19 pandemic, however, seem reassuring. A recently published study on 32,076 patients with COVID-19 found that patients with recent tumor necrosis factor inhibitors (TNFi) and/or methotrexate exposure did not have increased hospitalization or mortality compared to patients with COVID-19 without recent TNFi and/or methotrexate exposure[93]. Consequently, methotrexate treatment can probably be continued in MG patients in case of COVID-19 infection.

Rituximab is a genetically engineered chimeric mouse/human IgG1-kappa anti-CD20 monoclonal immunoglobulin[94] most commonly used as targeted therapy for the treatment of non-Hodgkin's B-cell lymphoma, rheumatoid arthritis, Wegener granulomatosis and microangiopathic vasculitis[95,96]. Recently, rituximab is being increasingly used for a number of neurologic diseases including MG[97]. A 2017 systemic review article by Tandan *et al*. reviewed the efficacy and safety of rituximab in 169 MG patients from case reports and series, concluding that rituximab is an effective treatment for AChR- and muscle-specific tyrosine kinase (MuSK)-antibody-positive MG patients, typically in most patients with moderate to severe refractory disease already being treated with several immune-based therapies[95]. The main concern regarding the use of rituximab during COVID-19 arises due to the drug property to cause B cell depletion that can be associated with decreased antibody production[98]. Studies indicate that patients treated with rituximab might develop more severe COVID-19 disease[99]. Consequently, the International MG/COVID-19 Working Group advises to delay initiation of cell depleting therapies until the peak of the outbreak is over in their region while taking into consideration the fact that the risk of not starting cell depleting therapy in occasional patients may outweigh the risk of severe COVID-19 infection[68]. Some alternative strategies regarding rituximab use have been recommended in other autoimmune diseases. For example, some authors have suggested extending the dosing intervals of rituximab in multiple sclerosis patients[100]. Whether this strategy can be safely executed in MG patients is unknown. We were able to identify only one hospitalized MG patient with COVID-19 in published literature; the patient was successfully treated with five plasmapheresis (PLEX) sessions and discharged home after 28-day hospital stay with clinically unchanged MG status[26].

Rescue Therapy for Worsening or Crisis in Myasthenia Gravis Patients with COVID-19

Since infections in general have been the leading cause of exacerbation of MG and myasthenic crisis in retrospective studies[101], it is presumed that COVID-19 might be the cause of acute MG exacerbations, although there are still no definitive data on the issue. Intervention therapies are applied for the prevention and therapy of myasthenic crisis and in special situations such as unstable MG during pregnancy and distinct single cases of therapy resistant MG with severely disabling symptoms[102]. Intervention therapies in MG include intravenous immunoglobulins (IVIG) and plasma exchange (PLEX). Both have similar clinical effect, and a similar responder rate[103].

Intravenous immunoglobulins consist of pooled polyclonal immunoglobulins derived from several thousand healthy donors. The precise mechanism by which IVIG suppress autoimmune inflammation has not been definitely established but it is likely to involve a plethora of molecular effects *via* their Fab- or Fc-fragments[104-106]. Advantages of IVIG consist of slightly longer lasting therapeutic effects and ease of use in comparison to PLEX[107]. The International MG/COVID-19 Working Group recommends IVIG use in patients with acute MG exacerbations since currently there is no evidence to suggest that IVIG carry any additional risk of contracting COVID-19[68]. Moreover, although the mechanism of action is still largely unknown, Xie *et al*. have reported a statistically significant reduction in 28-day mortality in patients receiving IVIG for COVID-19 pneumonia within 48 hours of admission compared to those who received IVIG after 48 hours of admission[108]. Several RCTs evaluating the efficacy of IVIG therapy in severe COVID-19 are underway[109]. Theoretical concerns on the use of IVIG in MG patients with COVID-19, however, exist regarding thromboembolic events. According to the study by Marie *et al*., IVIG-related thrombotic complications occur in 13% of patients receiving IVIG for various medical conditions, half of which were pulmonary embolisms[110]. COVID-19 studies, on the other hand, have reported various thromboembolic events in 15% to 86% of hospitalized patients, depending on disease severity, 17% to 81% of which were pulmonary embolism[111]. Therefore, MG COVID-19 patients could potentially be at a higher risk of thromboem-

bolic complications. The most appropriate dose of anticoagulant therapy in these patients has not been established. We identified eight MG patients with COVID-19 in published case series and case reports who received IVIG, seven of whom recovered and were discharged home, while one remained on mechanical ventilation[17,25,26,90,112,113]. No thromboembolic complications were reported in any of these patients.

Plasmapheresis is the extracorporeal technique performed *via* an apheresis device where patient plasma is separated from whole blood and removed, while the cellular blood components are returned to the patient together with a replacement fluid[114,115]. PLEX mechanism of action in MG is assumed to be the result of removal of plasma-soluble factors, including pathogenic autoantibodies and cytokines[116]. In comparison to IVIG, PLEX has faster treatment response[107]. Some evidence exists that PLEX may be more effective than IVIG in the treatment of myasthenic crisis[117]. Just as for IVIG, the International MG/COVID-19 Working Group recommends PLEX use in patients with acute exacerbation since currently no evidence has been found to suggest that PLEX carries any additional risk of contracting COVID-19[68]. PLEX causes more side effects in comparison to IVIG[118] and is more difficult to administer, especially in COVID-19 conditions. Hemodynamic instability in the form of severe hypotension, although rare, does occur in approximately 1% of cases, while mild and moderate hypotension occurs commonly[119]. Hypotension could theoretically pose a problem in MG patients with COVID-19 since hemodynamic complications seem to be common in COVID-19, although they probably occur only in critically ill patients admitted to the ICU[120]. Around 1% of patients receiving PLEX develop mild bronchospasm[119], which also poses a challenge in patients with COVID-19. PLEX has also been suggested as a treatment option for fulminant COVID-19, although randomized trials need to be designed to investigate this further[121].

COVID-19 Vaccine in Myasthenia Gravis Patients

Worldwide, at the time of writing this article, at least 90 preclinical vaccines are under active investigation in animals, 68 vaccines in humans, 20 have reached the final stages of testing, 3 have been approved in various countries, with 10 in early, limited or emergency use in various countries[122]. Although there are no data on the effects of SARS-CoV-2 vaccination in MG patients, vaccinations are generally recommended for MG patients[5]. Data presented here are based on research data on other vaccines. Three studies that analyzed the safety of influenza vaccination for MG patients found no significant association between seasonal influenza vaccination and MG symptom severity, concluding that influenza vaccine is safe for MG patients[123-125]. Caution should be exercised, however, with vaccination with live-attenuated vaccines, which should preferentially be undertaken before initiation of immunosuppressive therapy[126]. Since none of the vaccines currently in development is a live-attenuated vaccine, MG as such is not a contraindication for COVID-19 vaccination; therefore, all MG patients should be counseled to vaccinate if possible[127]. Patients on immunosuppressive therapy should also be vaccinated[127], although special considerations should be taken about patients receiving anti-CD20-depleting therapy. Based on trial data, protective neutralizing antibody and vaccination responses are predicted to be blunted until naive B cells repopulate, based on B cell repopulation kinetics and vaccination responses[128]. Consequently, although B-cell depletion should not necessarily expose people to severe SARS-CoV-2-related issues, it may inhibit or blunt the protective immunity following infection and vaccination[128,129]. Ideally, vaccination should be undertaken at least 4 weeks before rituximab therapy[130], or, if the patient is already on rituximab therapy, it is recommended to postpone vaccination for at least 6 months after rituximab infusion[129]. It should be noted that all data on rituximab vaccination presented here come from data on patients with rheumatologic conditions. Therefore, timing of COVID vaccination of MG patients should be discussed individually.

Conclusion

Although treatment of MG in the time of COVID-19 pandemic can be challenging, rapidly emerging evidence is continually clarifying the best pharmacological treatment options for this population of patients. Despite the epidemic reaching global proportions with close to 100 million cases worldwide, at the time of writing this article only a handful of case series

reports on MG patients with COVID-19 have been published. Studies with a larger number of participants are needed to provide better understanding on the best treatment strategy in MG patients with COVID-19.

References

1. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. J Med Virol. 2020 May;92(5): 479-90. http://dx.doi.org/10.1002/jmv.25707.
2. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020 Apr;87(4):281-6. http://dx.doi.org/10.1007/s12098-020-03263-6.
3. Muppidi S, Guptill JT, Jacob S, Li Y, Farrugia ME, Guidon AC, *et al*. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). Lancet Neurol. 2020 Dec;19(12): 970-1. http://dx.doi.org/10.1016/S1474-4422(20)30413-0.
4. Korsukewitz C, Reddel SW, Bar-Or A, Wiendl H. Neurological immunotherapy in the era of COVID-19 9 – looking for consensus in the literature. Nat Rev Neurol. 2020 Sep;16(9): 493-505. http://dx.doi.org/10.1038/s41582-020-0385-8.
5. Beloor Suresh A, Asuncion RMD. Myasthenia gravis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 15]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559331/
6. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, *et al*. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Jul 28;71(15):732-9. http://dx.doi.org/10.1093/cid/ciaa237.
7. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res. 2020 Mar; 30(3):269-71. http://dx.doi.org/10.1038/s41422-020-0282-0.
8. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*. Cell Discov. 2020 Dec;6(1):16. http://dx.doi.org/10.1038/s41421-020-0156-0.
9. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020 Mar 16;14(1):72-3. http://dx.doi.org/10.5582/bst.2020.01047.
10. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul;56(1):105949. http://dx.doi.org/10.1016/j.ijantimicag.2020.105949.
11. Kashour Z, Riaz M, Garbati MA, AlDosary O, Tlayjeh H, Gerberi D, *et al*. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. J Antimicrob Chemother. 2021 Jan 1;76(1):30-42. http://dx.doi.org/10.1093/jac/dkaa403.
12. The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020 Nov 19;383(21):2030-40. http://dx.doi.org/10.1056/NEJMoa2022926.
13. Sieb JP, Milone M, Engel AG. Effects of the quinoline derivatives quinine, quinidine, and chloroquine on neuromuscular transmission. Brain Res. 1996 Mar;712(2):179-89. http://dx.doi.org/10.1016/0006-8993(95)01349-0.
14. Gisselmann G, Alisch D, Welbers-Joop B, Hatt H. Effects of quinine, quinidine and chloroquine on human muscle nicotinic acetylcholine receptors. Front Pharmacol. 2018 Nov 20;9:1339. http://dx.doi.org/10.3389/fphar.2018.01339.
15. Jallouli M, Saadoun D, Eymard B, Leroux G, Haroche J, Thi Huong D, *et al*. The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. J Neurol. 2012 Jul;259(7):1290-7. http://dx.doi.org/10.1007/s00415-011-6335-z.
16. Aksoy E, Oztutgan T. COVID-19 presentation in association with myasthenia gravis: a case report and review of the literature. Case Rep Infect Dis. 2020 Aug 18;2020:1-4. http://dx.doi.org/10.1155/2020/8845844.
17. Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, *et al*. COVID -19 in patients with myasthenia gravis. Muscle Nerve. 2020 Aug;62(2):254-8. http://dx.doi.org/10.1002/mus.26918.
18. Oldenburg CE, Doan T. Azithromycin for severe COVID-19. Lancet. 2020 Oct;396(10256):936-7. http://dx.doi.org/10.1016/S0140-6736(20)31863-8.
19. Retallack H, Di Lullo E, Arias C, Knopp KA, Laurie MT, Sandoval-Espinosa C, *et al*. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci. 2016 Dec 13;113(50):14408-13. http://dx.doi.org/10.1073/pnas.1618029113.
20. Schögler A, Kopf BS, Edwards MR, Johnston SL, Casaulta C, Kieninger E, *et al*. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. Eur Respir J. 2015 Feb;45 (2):428-39. http://dx.doi.org/10.1183/09031936.00102014.
21. Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, De-Antonio Cuscó M, Ferrández O, Horcajada JP, *et al*. Azithromycin in the treatment of COVID-19: a review. Expert Rev Anti Infect Ther. 2020 Oct 6;1-17. http://dx.doi.org/10.1080/14787210.2020.1813024.
22. Horby PW, Roddick A, Spata E, Staplin N, Emberson JR, Pessoa-Amorim G, *et al*. Azithromycin in hospitalised patients with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Dec [cited 2021 Jan 27]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.12.10.20245944. http://dx.doi.org/10.1101/2020.12.10.20245944
23. Cadisch R, Streit E, Hartmann K. [Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax)]. Schweiz Med Wochenschr. 1996 Feb 24;126(8):308-10. (in German)

24. Herishanu Y, Taustein I. The electromyographic changes by antibiotics. A preliminary study. Confin Neurol. 1971;33(1):41-5.

25. Hübers A, Lascano AM, Lalive PH. Management of patients with generalised myasthenia gravis and COVID-19: four case reports. J Neurol Neurosurg Psychiatry. 2020 Oct;91(10):1124-5. http://dx.doi.org/10.1136/jnnp-2020-323565.

26. Camelo-Filho AE, Silva AMS, Estephan EP, Zambon AA, Mendonça RH, Souza PVS, *et al*. Myasthenia gravis and COVID-19: clinical characteristics and outcomes. Front Neurol. 2020 Sep 11;11:1053. http://dx.doi.org/10.3389/fneur.2020.01053.

27. Sadiq NM, Robinson KJ, Terrell JM. Colchicine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK431102/

28. Reyes AZ, Hu KA, Teperman J, Wampler Muskardin TL, Tardif J-C, Shah B, *et al*. Anti-inflammatory therapy for COVID-19 infection: the case for colchicine. Ann Rheum Dis. 2020 Dec 8;annrheumdis-2020-219174. http://dx.doi.org/10.1136/annrheumdis-2020-219174.

29. Scarsi M, Piantoni S, Colombo E, Airó P, Richini D, Miclini M, *et al*. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis. 2020 Oct;79(10):1286-9. http://dx.doi.org/10.1136/annrheumdis-2020-217712.

30. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, *et al*. Effect of colchicine *vs* standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. JAMA Netw Open. 2020 Jun 24;3(6):e2013136. http://dx.doi.org/10.1001/jamanetworkopen.2020.13136.

31. Tardif J-C, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, *et al*. Efficacy of colchicine in non-hospitalized patients with COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jan [cited 2021 Jan 28]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.01.26.21250494. http://dx.doi.org/10.1101/2021.01.26.21250494.

32. Gupta M, Nikolic A, Ng D, Martens K, Ebadi H, Chhibber S, *et al*. Colchicine myopathy: a case series including muscle MRI and ABCB1 polymorphism data. Front Neurol. 2019 May 24;10:553. http://dx.doi.org/10.3389/fneur.2019.00553.

33. Kuncl RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M. Colchicine myopathy and neuropathy. N Engl J Med. 1987 Jun 18;316(25):1562-8. http://dx.doi.org/10.1056/NEJM198706183162502.

34. Tapal MF. Colchicine myopathy. Scand J Rheumatol. 1996 Jan;25(2):105-6. http://dx.doi.org/10.3109/03009749609069217.

35. Fernández-Cuadros ME, Goizueta-San-Martin G, Varas-de-Dios B, Casique-Bocanegra LO, Manrique-de-Lara-Cadiñanos P, Albaladejo-Florin MJ, *et al*. Colchicine-induced rhabdomyolysis: clinical, biochemical, and neurophysiological features and review of the literature. Clin Med Insights Arthritis Musculoskelet Disord. 2019 Jan;12:117954411984988. http://dx.doi.org/10.1177/1179544119849883.

36. Costamagna G, Abati E, Bresolin N, Comi GP, Corti S. Management of patients with neuromuscular disorders at the time of the SARS-CoV-2 pandemic. J Neurol [Internet]. 2020 Aug 17 [cited 2021 Jan 8]; Available from: http://link.springer.com/10.1007/s00415-020-10149-2. http://dx.doi.org/10.1007/s00415-020-10149-2.

37. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, *et al*. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020 Dec;11(1):222. http://dx.doi.org/10.1038/s41467-019-13940-6.

38. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, *et al*. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. Subbarao K, editor. mBio. 2018 Mar 6;9(2):e00221-18, /mbio/9/2/mBio.00221-18.atom. http://dx.doi.org/10.1128/mBio.00221-18.

39. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al*. Remdesivir for the treatment of COVID-19 – final report. N Engl J Med. 2020 Nov 5;383(19):1813-26. http://dx.doi.org/10.1056/NEJMoa2007764.

40. Chu CM. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004 Mar 1;59(3):252-6. http://dx.doi.org/10.1136/thorax.2003.012658.

41. Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, Fan KW, *et al*. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004 Sep;31(1):69-75. http://dx.doi.org/10.1016/j.jcv.2004.03.003.

42. Wu C-Y, Jan J-T, Ma S-H, Kuo C-J, Juan H-F, Cheng Y-SE, *et al*. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci. 2004 Jul 6;101(27):10012-7. http://dx.doi.org/10.1073/pnas.0403596101.

43. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al*. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020 May 7;382(19):1787-99. http://dx.doi.org/10.1056/NEJMoa2001282.

44. Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, *et al*. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020 Oct;396(10259):1345-52. http://dx.doi.org/10.1016/S0140-6736(20)32013-4.

45. Suthar R, Sankhyan N, Goswami JN, Suri D, Gupta A, Singhi P. Myasthenia gravis in HIV positive girl. Indian J Pediatr. 2018 Jul;85(7):578-9. http://dx.doi.org/10.1007/s12098-017-2593-9.

46. Vermaak J-R, Dave JA, Levitt N, Heckmann JM. Sensory neuropathy and metabolic risk factors in human immune deficiency virus infected South Africans receiving protease inhibitors. AIDS Res Ther. 2015 Dec;12(1):30. http://dx.doi.org/10.1186/s12981-015-0073-8. eCollection 2015.

47. Kaur RJ, Charan J, Dutta S, Sharma P, Bhardwaj P, Sharma P, *et al*. Favipiravir use in COVID-19: analysis of suspected ad-

verse drug events reported in the WHO database. Infect Drug Resist. 2020 Dec;13:4427-38. http://dx.doi.org/10.2147/IDR.S287934.

48. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B. 2017;93(7):449-63. http://dx.doi.org/10.2183/pjab.93.027.
49. Agrawal U, Raju R, Udwadia ZF. Favipiravir: a new and emerging antiviral option in COVID-19. Med J Armed Forces India. 2020 Oct;76(4):370-6. http://dx.doi.org/10.1016/j.mjafi.2020.08.004.
50. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, *et al*. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021 Jan;102:501-8. http://dx.doi.org/10.1016/j.ijid.2020.10.069.
51. Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K, Palavutitotai N, Saiyarin J. Real-world experience with favipiravir for treatment of COVID-19 in Thailand: results from a multicenter observational study [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Jul [cited 2021 Jan 28]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.06.24.20133249. http://dx.doi.org/10.1101/2020.06.24.20133249.
52. Bamlanivimab. In: Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006 [cited 2021 Jan 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK564281/
53. Jones BE, Brown-Augsburger PL, Corbett KS, Westendorf K, Davies J, Cujec TP, *et al*. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection [Internet]. Immunology. 2020 Oct [cited 2021 Jan 28]. Available from: http://biorxiv.org/lookup/doi/10.1101/2020.09.30.318972. http://dx.doi.org/10.1101/2020.09.30.318972.
54. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020 Jun;19(6):102537. http://dx.doi.org/10.1016/j.autrev.2020.102537.
55. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, *et al*. Effect of tocilizumab *vs* usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med. 2021 Jan 1;181(1):32. http://dx.doi.org/10.1001/jamainternmed.2020.6820.
56. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, *et al*. Effect of tocilizumab *vs* standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med. 2021 Jan 1;181(1):24. http://dx.doi.org/10.1001/jamainternmed.2020.6615.
57. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, *et al*. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med. 2020 Dec 10;383(24):2333-44. http://dx.doi.org/10.1056/NEJMoa2028836.
58. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, *et al*. Tocilizumab in patients hospitalized with COVID-19 pneumonia. N Engl J Med. 2021 Jan 7;384(1):20-30. http://dx.doi.org/10.1056/NEJMoa2030340.
59. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, *et al*. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med. 2021 Jan 1;181(1):41. http://dx.doi.org/10.1001/jamainternmed.2020.6252.
60. Jiang Y, Zhao G, Song N, Li P, Chen Y, Guo Y, *et al*. Blockade of the C5a-C5aR axis alleviates lung damage in *hDPP4* -transgenic mice infected with MERS-CoV. Emerg Microbes Infect. 2018 Dec 1;7(1):1-12. http://dx.doi.org/10.1038/s41426-018-0063-8.
61. Diurno F, Numis FG, Porta G, Cirillo F, Maddaluno S, Ragozzino A, *et al*. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. Eur Rev Med Pharmacol Sci. 2020 Apr;24(7):4040-7. http://dx.doi.org/10.26355/eurrev_202004_20875.
62. https://clinicaltrials.gov/. ClinicalTrials.gov Identifier: NCT04288713.
63. Dhillon S. Eculizumab: a review in generalized myasthenia gravis. Drugs. 2018 Mar;78(3):367-76. http://dx.doi.org/10.1007/s40265-018-0875-9.
64. Farrugia ME, Goodfellow JA. A practical approach to managing patients with myasthenia gravis – opinions and a review of the literature. Front Neurol. 2020;11:604. http://dx.doi.org/10.3389/fneur.2020.00604.
65. Maggi L, Mantegazza R. Treatment of myasthenia gravis: focus on pyridostigmine. Clin Drug Investig. 2011 Oct;31(10):691-701. http://dx.doi.org/10.2165/11593300-000000000-00000.
66. Ciafaloni E. Myasthenia gravis and congenital myasthenic syndromes. Contin Lifelong Learn Neurol. 2019 Dec;25(6):1767-84. http://dx.doi.org/10.1212/CON.0000000000000800.
67. Mantegazza R, Beghi E, Pareyson D, Antozzi C, Peluchetti D, Sghirlanzoni A, *et al*. A multicentre follow-up study of 1152 patients with myasthenia gravis in Italy. J Neurol. 1990 Oct;237(6):339-44. http://dx.doi.org/10.1007/BF00315656.
68. Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, Howard JF, *et al*. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci. 2020 May;412:116803. http://dx.doi.org/10.1016/j.jns.2020.116803.
69. Fragoso-Saavedra S, Iruegas-Nunez DA, Quintero-Villegas A, García-González HB, Nuñez I, Carbajal-Morelos SL, *et al*. A parallel-group, multicenter randomized, double-blinded, placebo-controlled, phase 2/3, clinical trial to test the efficacy of pyridostigmine bromide at low doses to reduce mortality or invasive mechanical ventilation in adults with severe SARS-CoV-2 infection: the Pyridostigmine In Severe COvid-19 (PISCO) trial protocol. BMC Infect Dis. 2020 Dec;20(1):765. http://dx.doi.org/10.1186/s12879-020-05485-7.
70. Singh S, Govindarajan R. COVID-19 and generalized myasthenia gravis exacerbation: a case report. Clin Neurol Neurosurg. 2020 Sep;196:106045. http://dx.doi.org/10.1016/j.clineuro.2020.106045.

71. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol. 1984 Mar;15(3):291-8. http://dx.doi.org/10.1002/ana.410150316.

72. Benatar M, Mcdermott MP, Sanders DB, Wolfe GI, Barohn RJ, Nowak RJ, *et al*. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): a randomized, controlled trial: Steroids for Ocular Myasthenia. Muscle Nerve. 2016 Mar;53(3):363-9. http://dx.doi.org/10.1002/mus.24769.

73. Lindberg C, Andersen O, Lefvert AK. Treatment of myasthenia gravis with methylprednisolone pulse: a double blind study. Acta Neurol Scand. 1998 Jun;97(6):370-3. http://dx.doi.org/10.1111/j.1600-0404.1998.tb05968.x.

74. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, *et al*. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016 Jul 26;87(4):419-25. http://dx.doi.org/10.1212/WNL.0000000000002790.

75. Gilhus NE. Myasthenia Gravis. Longo DL, editor. N Engl J Med. 2016 Dec 29;375(26):2570-81. http://dx.doi.org/10.1056/NEJMra1602678.

76. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of myasthenia gravis. Neurol Clin. 2018 May;36(2):311-37. http://dx.doi.org/10.1016/j.ncl.2018.01.011.

77. Valencia-Sanchez C, Wingerchuk DM. A fine balance: immunosuppression and immunotherapy in a patient with multiple sclerosis and COVID-19. Mult Scler Relat Disord. 2020 Jul;42:102182. http://dx.doi.org/10.1016/j.msard.2020.102182.

78. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, *et al*. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020 Jul;79(7):859-66. http://dx.doi.org/10.1136/annrheumdis-2020-2178.

79. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020 Dec;24(1):696. http://dx.doi.org/10.1186/s13054-020-03400-9.

80. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 – preliminary report. N Engl J Med. 2020 Jul 17;NEJMoa2021436. http://dx.doi.org/10.1056/NEJMoa2021436

81. Szefler SJ, Ebling WF, Georgitis JW, Jusko WJ. Methylprednisolone *versus* prednisolone pharmacokinetics in relation to dose in adults. Eur J Clin Pharmacol. 1986;30(3):323-9. http://dx.doi.org/10.1007/BF00541537.

82. Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, *et al*. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis. 2020 Aug 12;ciaa1177. http://dx.doi.org/10.1093/cid/ciaa1177.

83. Nelson BC, Laracy J, Shoucri S, Dietz D, Zucker J, Patel N, *et al*. Clinical outcomes associated with methylprednisolone in mechanically ventilated patients with COVID-19. Clin Infect Dis. 2020 Aug 9;ciaa1163. http://dx.doi.org/10.1093/cid/ciaa1163.

84. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, *et al*. GLUCOCOVID: a controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Jun [cited 2021 Jan 11]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.06.17.20133579. http://dx.doi.org/10.1101/2020.06.17.20133579.

85. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, *et al*. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther. 2020 Dec;5(1):57. http://dx.doi.org/10.1038/s41392-020-0158-2.

86. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed.

87. Schoot TS, Kerckhoffs APM, Hilbrands LB, van Marum RJ. Immunosuppressive drugs and COVID-19: a review. Front Pharmacol. 2020 Aug 28;11:1333. http://dx.doi.org/10.3389/fphar.2020.01333.

88. Al Ghamdi M, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, *et al*. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. BMC Infect Dis. 2016 Dec;16(1):174. http://dx.doi.org/10.1186/s12879-016-1492-4.

89. Ramaswamy SB, Govindarajan R. COVID-19 in refractory myasthenia gravis – a case report of successful outcome. J Neuromuscul Dis. 2020 Jun 2;7(3):361-4. http://dx.doi.org/10.3233/JND-200520.

90. Rein N, Haham N, Orenbuch-Harroch E, Romain M, Argov Z, Vaknin-Dembinsky A, *et al*. Description of 3 patients with myasthenia gravis and COVID-19. J Neurol Sci. 2020 Oct;417:117053. http://dx.doi.org/10.1016/j.jns.2020.117053.

91. Hannoodee M, Mittal M. Methotrexate. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2021 Jan 12]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK556114/

92. Pasnoor M, He J, Herbelin L, Burns TM, Nations S, Bril V, *et al*. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. Neurology. 2016 Jul 5;87(1):57-64. http://dx.doi.org/10.1212/WNL.0000000000002795.

93. Yousaf A, Gayam S, Feldman S, Zinn Z, Kolodney M. Clinical outcomes of COVID-19 in patients taking tumor necrosis factor inhibitors or methotrexate: a multicenter research network study. J Am Acad Dermatol. 2021 Jan;84(1):70-5. http://dx.doi.org/10.1016/j.jaad.2020.09.009.

94. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. Am J Transplant. 2006 May;6(5p1):859-66. http://dx.doi.org/10.1111/j.1600-6143.2006.01288.x.

95. Tandan R, Hehir MK, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review: rituximab in myasthenia gravis. Muscle Nerve. 2017 Aug;56 (2):185-96. http://dx.doi.org/10.1002/mus.25597.

96. Milunović V. Rituximab maintenance strategy in advanced follicular lymphoma: facts and controversies. Acta Clin Croat. 2017;56:143-55. http://dx.doi.org/10.20471/acc.2017.56.01.20.

97. Whittam DH, Tallantyre EC, Jolles S, Huda S, Moots RJ, Kim HJ, *et al*. Rituximab in neurological disease: principles, evidence and practice. Pract Neurol. 2019 Feb;19(1):5-20. http://dx.doi.org/10.1136/practneurol-2018-001899.

98. Kow CS, Hasan SS. Use of rituximab and the risk of adverse clinical outcomes in COVID-19 patients with systemic rheumatic disease. Rheumatol Int. 2020 Dec;40(12):2117-8. http://dx.doi.org/10.1007/s00296-020-04715-0.

99. Loarce-Martos J, García-Fernández A, López-Gutiérrez F, García-García V, Calvo-Sanz L, del Bosque-Granero I, *et al*. High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study. Rheumatol Int. 2020 Dec;40(12): 2015-21. http://dx.doi.org/10.1007/s00296-020-04699-x.

100. Maarouf A, Rico A, Boutiere C, Perriguey M, Demortiere S, Pelletier J, *et al*. Extending rituximab dosing intervals in patients with MS during the COVID-19 pandemic and beyond? Neurol Neuroimmunol Neuroinflamm. 2020 Sep;7(5): e825. http://dx.doi.org/10.1212/NXI.0000000000000825.

101. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. Muscle Nerve. 2019 Dec;60(6):693-9. http://dx.doi.org/10.1002/mus.26689.

102. Melzer N, Ruck T, Fuhr P, Gold R, Hohlfeld R, Marx A, *et al*. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol. 2016 Aug;263(8):1473-94. http://dx.doi.org/10.1007/s00415-016-8045-z.

103. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2008 [cited 2021 Jan 14]. p. CD002277.pub3. Available from: http://doi.wiley.com/10.1002/14651858.CD002277.pub3. http://dx.doi.org/10.1002/14651858.CD002277.pub3.

104. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med. 2012 Nov 22;367 (21):2015-25. http://dx.doi.org/10.1056/NEJMra1009433.

105. Ballow M. Mechanisms of immune regulation by IVIG. Curr Opin Allergy Clin Immunol. 2014 Dec;14(6):509-15. http://dx.doi.org/10.1097/ACI.0000000000000116.

106. Bašić-Kes V, Kes P, Zavoreo I, Lisak M, Zadro L, Ćorić L, *et al*. Guidelines for the use of intravenous immunoglobulin in the treatment of neurologic diseases. Acta Clin Croat. 2012; 51(4):673-83.

107. Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist. 2011 Jan;1(1):16-22. http://dx.doi.org/10.1177/1941875210382918.

108. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, *et al*. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020 Aug;81(2):318-56. http://dx.doi.org/10.1016/j.jinf.2020.03.044.

109. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs. 2020 Sep;80(13):1267-92. http://dx.doi.org/10.1007/s40265-020-01367-z.

110. Marie I, Maurey G, Hervé F, Hellot M-F, Levesque H. Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature: IvIg-related thrombotic complications. Br J Dermatol. 2006 Oct;155(4):714-21. http://dx.doi.org/10.1111/j.1365-2133.2006.07390.x.

111. Ribes A, Vardon-Bounes F, Mémier V, Poette M, Au-Duong J, Garcia C, *et al*. Thromboembolic events and COVID-19. Adv Biol Regul. 2020 Aug;77:100735. http://dx.doi.org/10.1016/j.jbior.2020.100735.

112. Kushlaf H. COVID-19 in muscle-specific kinase myasthenia gravis: a case report. Muscle Nerve [Internet]. 2020 Oct [cited 2021 Jan 6];62(4). Available from: https://onlinelibrary.wiley.com/doi/10.1002/mus.27020. http://dx.doi.org/10.1002/mus.27020

113. Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. Ann Intern Med. 2020 Dec 15;173(12):1027-8. http://dx.doi.org/10.7326/L20-0845.

114. Fernández-Zarzoso M, Gómez-Seguí I, de la Rubia J. Therapeutic plasma exchange: review of current indications. Transfus Apher Sci. 2019 Jun;58(3):247-53. http://dx.doi.org/10.1016/j.transci.2019.04.007.

115. Roman-Filip C. Therapeutic plasma exchange and double filtration plasmapheresis in severe neuroimmune disorders. Acta Clin Croat [Internet]. 2019 [cited 2021 Mar 11];58. Available from: https://hrcak.srce.hr/index.php?show=clanak&id_clanak_jezik=341723. http://dx.doi.org/10.20471/acc.2019.58.04.08.

116. Yeh J-H, Wang S-H, Chien P-J, Shih C-M, Chiu H-C. Changes in serum cytokine levels during plasmapheresis in patients with myasthenia gravis: changes in cytokine levels after plasmapheresis. Eur J Neurol. 2009 Dec;16(12):1318-22. http://dx.doi.org/10.1111/j.1468-1331.2009.02729.x.

117. Qureshi AI, Choudhry MA, Akbar MS, Mohammad Y, Chua HC, Yahia AM, *et al*. Plasma exchange *versus* intravenous immunoglobulin treatment in myasthenic crisis. Neurology. 1999 Feb 1;52(3):629-32. http://dx.doi.org/10.1212/wnl.52.3.629.

118. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C, for the Myasthenia Gravis Clinical Study Group. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Ann Neurol. 1997 Jun;41(6):789-96. http://dx.doi.org/10.1002/ana.410410615.

119. Sutton D, Nair R, Rock G. Complications of plasma exchange. Transfusion (Paris). 1989 Feb;29(2):124-7. http://dx.doi.org/10.1046/j.1537-2995.1989.29289146829.x.

120. Xie J, Wu W, Li S, Hu Y, Hu M, Li J, *et al*. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. Intensive Care Med. 2020 Oct;46(10):1863-72. http://dx.doi.org/10.1007/s00134-020-06211-2.

121. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care Lond Engl. 2020 Apr 2;24 (1):128. http://dx.doi.org/10.1186/s13054-020-2836-4.

122. Zimmer C, Corum J, Wee S. Coronavirus vaccine tracker [Internet]. The New York Times; [cited 2021 Jan 15]. Available from: https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

123. Seok HY, Shin HY, Kim JK, Kim BJ, Oh J, Suh BC, *et al*. The impacts of influenza infection and vaccination on exacerbation of myasthenia gravis. J Clin Neurol. 2017;13(4):325. http://dx.doi.org/10.3988/jcn.2017.13.4.325.

124. Auriel E, Regev K, Dori A, Karni A. Safety of influenza and H1N1 vaccinations in patients with myasthenia gravis, and patient compliance: short reports. Muscle Nerve. 2011 Jun; 43(6):893-4. http://dx.doi.org/10.1002/mus.22077.

125. Zinman L, Thoma J, Kwong JC, Kopp A, Stukel TA, Juurlink DN. Safety of influenza vaccination in patients with myasthenia gravis: a population-based study. Muscle Nerve. 2009 Dec;40(6):947-51. http://dx.doi.org/10.1002/mus.21440.

126. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. J Neurol. 2018 Jun;265(6):1251-8. http://dx.doi.org/10.1007/s00415-018-8751-9.

127. National Center for Immunization and Respiratory Diseases. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States [Internet]. Available from: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

128. Baker D, Roberts CAK, Pryce G, Kang AS, Marta M, Reyes S, *et al*. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin Exp Immunol. 2020 Nov;202(2):149-61. http://dx.doi.org/10.1111/cei.13495.

129. van Assen S, Holvast A, Benne CA, Posthumus MD, van Leeuwen MA, Voskuyl AE, *et al*. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum. 2010 Jan;62(1):75-81. http://dx.doi.org/10.1002/art.25033.

130. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T, *et al*. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 Jun;70(6):909-20. http://dx.doi.org/10.1136/ard.2010.144998.

Sažetak

LIJEČENJE BOLESNIKA OBOLJELIH OD MIJASTENIJE GRAVIS S COVID-19: PREGLED LITERATURE

S. Županić, I. Lazibat, M. Rubinić Majdak i *M. Jeličić*

Koronavirusna bolest 2019 (COVID-19) uzrokovana širenjem virusa SARS-CoV-2 izaziva respiracijsku bolest koja potencijalno može dodatno ugroziti pacijente koji boluju od mijastenije gravis. Uz infekcije, egzacerbaciju simptoma mijastenije gravis mogu uzrokovati i neki lijekovi. Od deset najčešće primjenjivanih skupina lijekova za liječenje COVID-19, dvije skupine lijekova (kinoloni i azitromicin) mogu uzrokovati pogoršanje simptoma mijastenije gravis, a dvije skupine lijekova (tocilizumab i ekulizumab) imaju pozitivne učinke na simptome mijastenije gravis. Kolhicin, remdesivir, lopinavir, ritonavir i favipiravir nemaju učinka na simptome mijastenije gravis, dok su podatci za bamlanivimab nedostatni, no isti je vjerojatno siguran za upotrebu u bolesnika s mijastenijom gravis. Što se tiče primjene lijekova za mijasteniju gravis kod bolesnika zaraženih virusom SARS-CoV-2, inhibitori acetilkolinestaraze su u pravilu sigurni za primjenu; neke studije su čak dokazale i terapijske mogućnosti navedenih lijekova u liječenju COVID-19. Kortikosteroidi su uglavnom sigurni za primjenu, a čak se i preporučaju u određenim okolnostima, dok su ostali imunosupresivi (mikofenolat mofetil, azatioprin, ciklosporin i metotreksat) sigurni za primjenu. Jedina iznimka je rituksimab učinak kojega na B-staničnu imunost može rezultirati težom kliničkom slikom bolesti COVID-19. Plazmafereza i intravenski imunoglobulini, dvije najčešće primjenjivane terapijske opcije liječenja akutnih egzacerbacija mijastenije gravis, mogu se primijeniti kod bolesnika s COVID-19 uzimajući u obzir tromboembolijske učinke intravenskih imunoglobulina, odnosno hemodinamske učinke plazmafereze. Sva cjepiva COVID-19, koliko je poznato, sigurna su za primjenu u bolesnika s mijastenijom gravis.

Ključne riječi: *Mijastenija gravis; COVID-19; Imunosupresija; Cjepivo COVID-19; Neuromišićne bolesti*