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

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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 death¹. Higher morbidity and mortality rates are seen among the elderly and those with underlying comorbidities and immune deficiencies². 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 weakness³. However, cessation of immunotherapy in neuroinflammatory disorders has severe risks as well⁴. Moreover, infections and some drugs are a well-recognized trigger of symptom exacerbation in MG patients⁵. In this paper, we will review the existing lit-
Treatment of myasthenia gravis patients with COVID-19

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 virus6-8, a small and early interim analysis of 100 patients with COVID-19 in China9, and a small non-randomized study in 20 patients from France10. 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 azithromycin11. 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-1911,12. 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 transmission13. It is therefore advised to use quinolone derivatives with extreme caution in MG14.

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 MG15. Aksoy and Oztutgan report on excellent recovery of MG patients with COVID-19 despite HCQ administration16, 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 article17. In summary, CQ and HCQ are generally contraindicated for use in MG pa-

| 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
patients 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. Azithromycin is commonly used for bacterial respiratory infections, could potentially treat or prevent co-infection with SARS-CoV-2, and could have antiviral activity against some RNA viruses. However, despite azithromycin being a promising therapy, there is a paucity of data on its use in COVID-19. This macrolide has mostly been administered with HCQ, which has been shown not to provide benefits in the treatment of SARS-CoV-2 pneumonia. 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. Consequently, azithromycin use in patients hospitalized with COVID-19 should be restricted to patients where there is a clear antimicrobial indication. In the context of MG, macrolide antibiotics including azithromycin can cause severe exacerbation of MG, most likely due to presynaptic effects. 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. In a case series by Hübers et al., one patient administered azithromycin among other antibiotics had positive disease outcome, albeit with prolonged intubation period; 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. 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. 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. So far, two RCTs have demonstrated the superiority of colchicine over standard COVID-19 medical treatment regarding higher survival rate and improved time to clinical deterioration. No results from the two largest studies, COLCORONA and RECOVERY, on colchicine in COVID-19 have yet been officially published. Consequently, it seems that macrolide antibiotics could be used with extreme caution in MG patients, the drug does have neuromuscular side effects. Autophagic, vacuolar myopathy is a rare complication of treatment with colchicine. Although colchicine-induced myopathy typically includes features of slowly progressive painless proximal myopathy that develops after prolonged treatment with colchicine, it can also present with rapidly progressing myopathy and rhabdomyolysis. 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, which also has proven efficacy in MERS-CoV2 treatment. Remdesivir was shown to have antiviral activity against SARS-CoV-2, and, in a cohort of patients with severe COVID-19 treated with remdesivir, the majority showed clinical improvement. 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. Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. However, the result of 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. 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. In general, however, this class of drugs has shown few neuromuscular side effects, 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. In some countries, favipiravir is already approved for influenza virus, which led researchers to believe that the drug might exhibit antiviral properties on SARS-CoV-2. Although most studies on the usefulness of favipiravir as COVID-19 treatment are still underway, at least one study has already demonstrated promising effectiveness of favipiravir for treating patients with COVID-19. 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.

Bamlanivimab is a human immunoglobulin G1 (IgG1) kappa monoclonal antibody directed against the SARS-CoV-2 virus, which resulted in reduction of viral replication in the upper and lower respiratory tract in the experimental model of rhesus macaque monkey. Several clinical trials on human subjects are currently underway. 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. 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, 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. 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. 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-CoV. 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. The study of eculizumab in COVID-19 infected patients (SOLID-C19) is currently underway, which could confirm initial positive results. 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. Eculizumab was generally well tolerated, with a tolerability profile generally similar to that reported previously for other indications. Therefore, according to pub-
lished data, eculizumab can most certainly be adminis-
tered to MG patients with COVID-19.

**Treatment Options for Myasthenia Gravis Patients with COVID-19**

Medical therapies are used in MG patients for ei-
ther direct alleviation of symptoms, or as immuno-
modulatory drugs with the aim of dampening the un-
derlying immunopathology causing the disease with
the aim of inducing remission or minimal manifesta-
tions. Table 2 summarizes data on MG drug treat-
ment options in MG patients with COVID-19.

Acetylcholine esterase inhibitors (AChEI) are the
first-line treatment for all forms of MG. Pyridostig-
mine is the most commonly used AChEI for symp-
tomatic treatment of MG symptoms. It is used for
symptom management alone in purely ocular and mild
generalized cases, or in combination with immuno-
suppressants in more severe cases. Cholinergic side
effects are most common, which include abdominal
cramps, diarrhea, and excessive lacrimation. AChEI
are used by 99% of MG patients. There is no scien-
tific evidence to suggest that symptomatic therapies
such as pyridostigmine or 3,4-diaminopyridine in-
crease the risk of infection and should not be discon-
tinued unless there are other clinical reasons to do so.
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 re-
flex. This could lead to prevention of development of
severe systemic inflammatory response, pulmonary
damage, and even ARDS in patients with COVID-
ID-19. 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 infec-
tion is currently underway. There are events when
pyridostigmine should be withheld. Since pyridostig-
mime as AChEI may lead to excessive bronchial secre-
tions, 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 dur-
ing hospital stay. This should be performed with ex-
treme caution since withdrawal of AChEI can lead to
MG worsening.

Despite AChEI treatment, 54% of MG patients
require corticosteroids. Eighty percent or more pa-
tients show signs of either medical remission or
marked improvement upon the introduction of corti-
costeroids. 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 wide-
ly recommended as the first-line agent for use in MG
patients. The systemic side effects of long-term
corticosteroid therapy are numerous and can be highly

| 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
impactful. 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. Data on the subject derive from study results of higher odds of hospitalization of patients with rheumatic disease exposed to ≥10 mg/day glucocorticoids. 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, 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. Corticosteroids have beneficial effects in overcoming both hyperinflammation and ARDS. 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. 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, 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; 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; 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; and a retrospective study by Wang et al. demonstrated worse outcome associated with MP therapy in patients with non-severe COVID-19 pneumonia. 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. 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. 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. 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. 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. 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. 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, although there are also reports on patients requiring mechanical ventilation despite having been treated with prednisone plus a second immunosuppressive drug. 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. 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.

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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. 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 most commonly used as targeted therapy for the treatment of non-Hodgkin’s B-cell lymphoma, rheumatoid arthritis, Wegener granulomatosis and microangiopathic vasculitis. Recently, rituximab is being increasingly used for a number of neurologic diseases including MG. 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. 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. Studies indicate that patients treated with rituximab might develop more severe COVID-19 disease. 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. 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. 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.

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, 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. Intervention therapies in MG include intravenous immunoglobulins (IVIG) and plasma exchange (PLEX). Both have similar clinical effect, and a similar responder rate.

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. Advantages of IVIG consist of slightly longer lasting therapeutic effects and ease of use in comparison to PLEX. 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. 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. Several RCTs evaluating the efficacy of IVIG therapy in severe COVID-19 are underway. 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. 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. Therefore, MG COVID-19 patients could potentially be at a higher risk of thromboemb-
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. 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. PLEX mechanism of action in MG is assumed to be the result of removal of plasma-soluble factors, including pathogenic autoantibodies and cytokines. In comparison to IVIG, PLEX has faster treatment response. Some evidence exists that PLEX may be more effective than IVIG in the treatment of myasthenic crisis. 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. PLEX causes more side effects in comparison to IVIG 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. 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. Around 1% of patients receiving PLEX develop mild bronchospasm, 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.

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. Although there are no data on the effects of SARS-CoV-2 vaccination in MG patients, vaccinations are generally recommended for MG patients. 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. Caution should be exercised, however, with vaccination with live-attenuated vaccines, which should preferentially be undertaken before initiation of immunosuppressive therapy. 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. Patients on immunosuppressive therapy should also be vaccinated, 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. 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. Ideally, vaccination should be undertaken at least 4 weeks before rituximab therapy, or, if the patient is already on rituximab therapy, it is recommended to postpone vaccination for at least 6 months after rituximab infusion. 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.

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Liječenje bolesnika oboljelih od mijastenije gravis s COVID-19: Pregled literature

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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. Kolhıc, 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 i preporučaju se 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 imunosupresiju 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