INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease that leads to fatigable skeletal muscle weakness. Antibodies targeting acetylcholine receptors, or functionally related molecules such as muscle-specific kinase or lipoprotein receptor-related receptor 4, in the postsynaptic membrane of the neuromuscular junction result in failure of neuromuscular transmission.1 The ensuing weakness can vary from day to day and over the course of the day. It can be generalized or localized and is often associated with repetitive muscle use (ie, fatigability). Immunosuppressive agents, including but not limited to corticosteroids, antimetabolites, and calcineurin inhibitors, are effective for the treatment of MG.1,2

The immunosuppressive agents utilized for MG treatment may put these patients at higher risk of contracting severe acute respiratory syndrome coronavirus 2 and exhibiting more severe manifestations of the novel coronavirus disease 2019 (COVID-19). Multiple agents have been studied for the management of the COVID-19, including remdesivir. To date, no published reports have evaluated the utilization of the antiviral remdesivir in patients with myasthenia gravis. We describe the first reported clinical course of three patients with myasthenia gravis who safely received remdesivir in combination with dexamethasone for the management of COVID-19.

CASES

2.1 Case 1

A 71-year-old male with MG was treated at baseline with mycophenolic acid monotherapy (Table 1). His comorbidities included type 2 diabetes mellitus, hyperlipidemia, hypertension, and a prior stroke. The patient was a poor historian, and information regarding past MG exacerbations was limited. He was brought to an outside hospital emergency department after being found down at his assisted living facility. He was noted to be hypoxic and febrile, with hazy bilateral opacities on chest x-ray. Nasopharynx real-time reverse transcription polymerase chain reaction (RT-PCR) was positive for SARS-CoV-2. He was given 200 mg of intravenous (IV) remdesivir and 6 mg of IV dexamethasone and was transferred to our institution’s intensive care unit (ICU) for management of hypoxic respiratory failure. In our hospital, he received 10 total days of dexamethasone 6 mg/day and 4 additional days of IV remdesivir 100 mg/day. In addition to these therapies, the patient qualified for a clinical trial and received lenzilumab 600 mg every 8 h for 3 doses or placebo as per the study protocol. He continued his maintenance mycophenolic acid...
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regimen for MG. He required continuous positive airway pressure (CPAP) and high-flow nasal cannula (HFNC) to maintain oxygenation, but did not have evidence of significant hypercapnia (arterial blood gas with pH of 7.43, partial pressure of carbon dioxide of 45 mmHg, and partial pressure of oxygen 56 mmHg). Due to progressively worsening hypoxemic respiratory failure, Neurology was consulted to ensure neuromuscular weakness was not contributing to his declining respiratory status. Neurologic examination was notable for absence of accessory respiratory muscle use and lack of paradoxical breathing pattern. He had preserved strength overall with no ptosis with sustained upward gaze and no evidence of bulbar weakness. Thus, MG was not felt to be contributing to his respiratory failure and he was ultimately diagnosed with an acute pulmonary embolism. After further goals of care discussions, the patient was transitioned to comfort-focused care measures and passed away in the hospital.

2.2 | Case 2

A 41-year-old female had been diagnosed with MG in 1995. She had undergone thymectomy and was treated with mycophenolate mofetil, prednisone, and pyridostigmine at baseline. Comorbidities included...
anxiety and morbid obesity. She had no known prior MG exacerbations. She initially presented to an outside hospital emergency department with shortness of breath, fever, and delirium in the setting of multiple family members with known SARS-CoV-2 infection. At the outside emergency department, her chest x-ray revealed diffuse bilateral infiltrates consistent with COVID-19 pneumonia. Her nasopharynx RT-PCR was positive for SARS-CoV-2. She was placed on 6 L/min nasal cannula (NC) for hypoxia and transferred to our institution's ICU with worsening respiratory distress. Upon arrival at our institution, she was placed on HFNC for hypoxia and was later transitioned to bi-level positive airway pressure (BiPAP). A one-time remdesivir 200 mg IV dose was given followed by 100 mg IV daily for 4 additional days. She was also started on dexamethasone 6 mg IV daily and completed a 10-day course. After completing the dexamethasone regimen, she was transitioned to her baseline prednisone 5 mg daily. The patient continued her baseline MG regimen of mycophenolate mofetil 1000 mg in the morning and 1500 mg in the evening along with pyridostigmine 60 mg every 2 h while awake. There was no evidence of ocular or muscle weakness noted on physical examination. The patient never required mechanical ventilation and ultimately improved and was transferred out of the ICU.

2.3 | Case 3

A 59-year-old male had a recent diagnosis of MG in May 2020. Comorbidities include type 2 diabetes mellitus, sleep apnea, obesity, and asthma. Baseline MG therapy included azathioprine, pyridostigmine, monthly infusions of intravenous immune globulin (IVIG), and prednisone. He had a recent MG exacerbation 1 month prior to admission while prednisone was being tapered and after missing an IVIG infusion. After receiving IVIG, his MG symptoms resolved. He presented to an outside hospital emergency department with hypoxic respiratory failure requiring intubation and mechanical ventilation and was transferred to our ICU. A chest x-ray showed bilateral patchy opacities consistent with COVID-19 pneumonia, and nasopharyngeal RT-PCR was positive for SARS-CoV-2. Due to ventilator dysynchrony, he was sedated and paralyzed with atracurium. He received remdesivir 200 mg IV once followed by 100 mg IV daily for 4 additional doses. He received one dose of dexamethasone 6 mg IV and then continued on his baseline prednisone 60 mg per day. He also continued his baseline azathioprine 100 mg in the morning and 50 mg in the evening and pyridostigmine 60 mg every 8 h. He was ultimately extubated and transitioned to supplemental oxygen via NC and discharged from the hospital. He was followed by Neurology during his hospitalization and had transient ptoxis and diplopia which resolved with no evidence of MG crisis.

3 | DISCUSSION

Little is known about the use of remdesivir in patients with MG and COVID-19. In this case series, we describe the clinical course and outcomes of three patients with MG and COVID-19 pneumonia with hypoxic respiratory failure who were treated with remdesivir in combination with dexamethasone. None of the patients experienced significant clinical worsening of MG after treatment with remdesivir.

There is a concern that MG and the associated pharmacologic management options, including immunosuppressive agents, could place these patients at higher risk of contracting SARS-CoV-2 and exhibiting more severe manifestations of COVID-19. Current guidance documents from the International MG/COVID-19 Working Group and the FILNEMUS COVID-19 study group acknowledged the potential utilization of various COVID-19 therapeutic agents in patients with MG but did not make any recommendations to guide use of these agents based on a lack of supporting evidence.3,4 Since these guidance documents were published in March and April of 2020, respectively, there has been new evidence regarding therapeutic options for COVID-19.

Remdesivir, an antiviral, was studied in a double-blind, randomized, placebo-controlled clinical trial (ACTT-1) and was found to be superior to placebo in shortening the time to recovery in hospitalized adults with COVID-19 and lower respiratory tract infection.8 Although there is additional conflicting evidence regarding use of remdesivir in COVID-19, it is currently approved by the United States Food and Drug Administration for the treatment of COVID-19 in appropriate hospitalized patients requiring supplemental oxygen but are not requiring mechanical ventilation.7,9,10 Remdesivir is an adenosine nucleotide prodrug that is rapidly converted to two initial metabolites (alanine metabolite and nucleoside monophosphate metabolite).7,11 The monophosphate metabolite is further phosphorylated to the active remdesivir triphosphate. The remdesivir triphosphate inhibits viral replication by competing with endogenous nucleotides for incorporation into viral RNA. The parent remdesivir compound has a plasma half-life of approximately 1 h. The monophosphate metabolite has a plasma half-life of approximately 25 h, and the remdesivir triphosphate has a peripheral blood mononuclear cell intracellular half-life of approximately 40 h. These long half-lives result in prolonged exposure beyond the completion of the dosing regimen.

Since some antivirals and other classes of medications can worsen MG, we had initial hesitancy to prescribe remdesivir in these critically ill patients with SARS-CoV-2 infection. We reviewed the prescribing information and the mechanism of action which did not seem to be related to alterations of acetylcholine or the associated receptors and decided to proceed with remdesivir treatment.5,7,8,11,12 All three patients were monitored for worsening neuromuscular weakness and respiratory failure for more than 10 days after receiving the first dose of remdesivir. According to reported half-lives, the monophosphate metabolite would reach plasma steady state by day 8 and the triphosphate intracellular steady state by day 10. Thus, we anticipate that any neurologic or respiratory worsening would have occurred by day 10. None of the patients developed significant worsening of MG symptoms suggestive of an exacerbation or crisis after treatment with remdesivir. It should also be noted that all three of the patients in our case series received dexamethasone...
in addition to remdesivir and the 2 surviving patients resumed their baseline steroids which obscures the ability to assess the effect of remdesivir in isolation.13,14 Yet, corticosteroids are part of the MG treatment algorithm and the COVID-19 dosing of 6 mg per day of dexamethasone (~40 mg/day prednisone equivalent) is equivalent to or higher than standard MG prednisone equivalents utilized for maintenance dosing.2 Considering the current practice of co-administering dexamethasone and remdesivir in COVID-19 patients requiring supplemental oxygen, we believe our findings suggest that remdesivir used in combination with dexamethasone is not associated with significant clinical worsening of MG.

It is well known that infections can precipitate MG exacerbations and crises, and there are multiple reports of COVID-19 being associated with worsening MG symptoms, some resulting in exacerbations and crises.15-22 Prior case reports in patients with MG and COVID-19 reported use of alternative medications, such as hydroxychloroquine, azithromycin, tocilizumab, lopinavir, and ritonavir. Some of these medications, such as hydroxychloroquine and azithromycin, have notably been associated with MG exacerbations.22-25 Considering that COVID-19 can precipitate MG symptoms, our finding of minimal ocular to no symptom worsening in three patients who received remdesivir suggests that remdesivir does not significantly worsen MG. Most importantly, remdesivir did not clinically precipitate a myasthenic respiratory crisis. To our knowledge, this is the first reported description of remdesivir use in patients with MG and COVID-19.

4 CONCLUSION

In this case series, we describe three patients with MG and active SARS-CoV-2 infections who received remdesivir. In these critically ill patients with MG and COVID-19 pneumonia, the use of the antiviral remdesivir in combination with dexamethasone did not precipitate a MG exacerbation or crisis.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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*How to cite this article:* Peters BJ, Rabinstein AA, DuBrock HM. Use of Remdesivir in Myasthenia gravis and COVID-19. *Pharmacotherapy*. 2021;41:546–550. https://doi.org/10.1002/phar.2524