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REVIEW

MYASTHENIA GRAVIS AND COVID-19: A SYSTEMATIC REVIEW OF CASE REPORTS AND CASE SERIES

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease involving neuromuscular transmission and possible respiratory failure when concomitant with COVID-19. The aim of this study was to analyze the need for ventilatory support (VS), length of hospital stay (LOS) and mortality in patients diagnosed with MG and COVID-19. In this systematic review, PubMed, SciELO, LILACS, MEDLINE and IBECS databases were searched for primary studies published from January 2010 to March 2021, with no language restrictions. Fourteen eligible studies were identified. The main factor associated with the need for VS was the use of antibiotics other than azithromycin (AZM) for the treatment of COVID-19 (RR 1.60; 95% CI 1.20–2.91; p = 0.009). Patients who used hydroxychloroquine (HCQ) and AZM had almost twice the risk of needing invasive ventilatory support (IVS) (RR 1.94; 95% CI 1.07-3.52; p = 0.16). There were non-significant trends towards less need for IVS in patients who used intravenous immunoglobulin (IVIg) and corticosteroid therapy (RR 0.54; 95% CI 0.09–3.26; p = 0.60). There was a trend towards shorter LOS in patients who received therapy with IVIg and corticosteroid therapy [8 (5 - 8) vs 19 (12.2–23.7); p = 0.007]. 10.3% (n = 4/39) died and 100% did not use IVIg or IVIg and prednisone. There was a non-significant trend towards higher mortality in patients who used AZM (RR 2.55; 95% CI 0.26–30.02; p = 0.60). IVIg and corticotherapy presented themselves as a favorable alternative in relation to the outcomes.

KEY WORDS: Coronavirus infections; length of stay; Myasthenia gravis; Respiratory insufficiency.

INTRODUCTION

COVID-19, a pandemic disease in 2020, is a respiratory infection generated by the SARS-CoV-2 virus, causing a severe acute respiratory syndrome. In March, according to Johns Hopkins University & Medicine (2021), the

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mortality rate for Sars-Cov-2 ranged from 0% (Singapore) to 21.0% (Yemen), depending on the location. According to Ioannidis (2020), the global mortality rate was at 0.23%, with a higher prevalence among the elderly patients with underlying comorbidities, and presenting immunological deficiencies (Aksoy & Oztutgan, 2020; Keller et al., 2020).

Coronavirus 2 generates a massive inflammatory response, with lesions in skeletal and cerebrovascular muscles, in addition to neurological impairment. Symptoms may include fever, cough, diarrhea, dyspnea, hypoxia, hyposmia, myalgia, fatigue, headache, dysphagia, rhinorrhea, arthralgia, confusion, and hemoptysis. Severe cases may evolve to respiratory failure, requiring invasive (IVS) or non-invasive ventilatory support (NIVS) (Anand et al., 2020; Singh & Govindarajan, 2020).

Myasthenia gravis (MG) is an autoimmune disease characterized by variable muscle weakness, fluctuating character, and potentially deleterious symptoms, such as respiratory failure. Neuromuscular transmission is compromised by autoantibodies linked to acetylcholine receptors or functional molecules, at the neuromuscular junction, affecting ocular, respiratory, bulbar and limb muscles. Treatment may include cholinesterase inhibitory drugs, such as pyridostigmine, immunosuppressants, such as prednisone and azathioprine, and immunomodulators, such as mycophenolate mofetil (MMF) (Hübers et al., 2020; Ruiter et al., 2020).

Symptoms of MG can worsen quickly and may be triggered by infectious conditions. This exacerbation may progress to restrictive respiratory failure, characterizing a myasthenic crisis. Plasmapheresis (PLEX) and intravenous immunoglobulin (IVIg) are essential for successful treatment during myasthenic crises or respiratory complications on worsening or life risk are detected (Jaretzki et al., 2000; Conitec, 2020; Ramaswamy & Govindarajan, 2020).

The use of hydroxychloroquine (HCQ) and chloroquine (CQ) can cause myasthenia gravis, as has been known since 1981 (Schumm et al., 1981). Likewise, AZM may trigger myasthenic crises (Anand et al., 2020). Such drugs are still prescribed indiscriminately by doctors who judge the benefits to be greater than the harms. In both MG and COVID-19, drug suppression in immune and inflammatory processes can be simultaneous (Ruiter et al., 2020).

There is no high-quality scientific evidence to guide the care management of patients with MG infected by Sars-Cov-2, according to their risks and particularities, despite the existence of expert opinions. With regard to public health relevance, the determination of risk factors that may aggravate underlying diseases is urgent. These may be MG, leading to unnecessary longer hospitalization, since the cure of the most serious cases is related to availability of resources in the health field, such as workforce, beds in intensive care units (ICUs) and mechanical ventilators (Emanuel et al., 2020; Remuzzi & Remuzzi, 2020).

This study aims to analyze scientific evidence on the management, evolution, and prognosis of patients with MG and COVID-19, to clarify and fill the knowledge gaps in the presentation of both diseases. The PICO strategy (Patient, Intervention, Comparison and Outcomes) (Santos et al., 2007) was used to elaborate the guiding question: "Do patients with myasthenia gravis infected by Sars-Cov-2, have a greater chance of hospitalization, need for ventilatory support and mortality if treated with azithromycin and/or hydroxychloroquine compared to intravenous immunoglobulin and prednisone?"

METHODS

The eligibility criteria were primary studies on human beings, published from January 2010 to March 2021, with no language restrictions. Inclusion criteria were patients previously diagnosed with myasthenia gravis, with no restriction of genre, age group or location, and infected with Sars-Cov-2. The exclusion criteria were studies on patients who had hydroxychloroquine-induced or diagnosed myasthenia gravis after Sars-Cov-2 infection.

The search strategy used was: ("Myasthenia gravis" or "Myasthenia serious") and ("COVID"). Case series, case reports (non-comparative observational studies) and retrospective cross-sectional studies were included through PubMed (64 articles) and SciELO (1 article) databases. The articles were initially selected by title and abstract, and then added to the review after applying inclusion and exclusion criteria.

The variables analyzed were gender (as a biological factor), age, treatment with IVIg and prednisone without HCQ and AZM, use of AZM and use of HCQ. The analyzed outcomes were need for ventilatory support (VS), mean hospital stay (LOS) and mortality. Two independent researchers evaluated the methodological quality, risk of bias and level of evidence of this systematic review, using the AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews 2), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) recommendation and GRADE (Grading of Recommendations Assessment, Development and Evaluation). This systematic review was registered in PROSPERO under number CRD42021241404.

Statistical analysis

Categorical variables were described as frequencies and percentages and tested using the chi-square test or Fisher's exact test. The relationships between categorical variables were described using the relative risk (RR) as a measure of association, with 95% confidence intervals (95% CI). Continuous variables with normal distribution were described as mean and standard deviation (SD), and non-normal variables as median and interquartile range (IIQ). Normal

continuous variables were tested with the Student's t test for independent samples, and non-normal continuous variables with the Mann-Whitney U test. $p < 0.05$ was considered statistically significant. The analysis were performed using the statistical program Statistical Package for the Social Sciences (SPSS version 20.0).

RESULTS

The search identified 65 articles, of which 14 were selected for the final sample, according to the following eligibility criteria: non-comparative observational studies and myasthenia gravis not caused by Sars-Cov-2 and hydroxychloroquine (Figure 1). As Camelo-Filho et al. (2020) did not determine the gender and age of its participants, this study was not considered for the final calculation of the percentage of these variables.

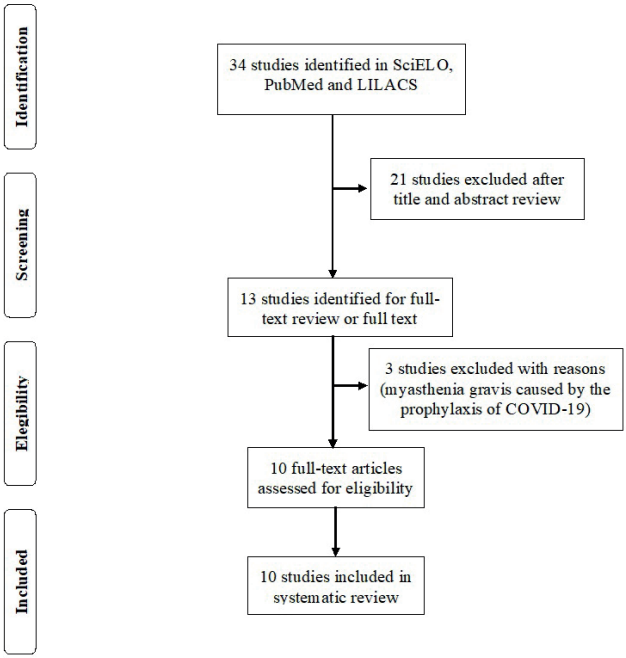

Figure. Study selection.

Ventilatory support was performed in 26 patients (66%) in the sample with 18 (46%) needing IVS. The main factor associated with the need for SV was the use of antibiotics other than AZM for the treatment of COVID-19 (RR 1.60; 95% CI 1.20–2.91; p = 0.009), and there was also a non-significant trend towards greater IVS (RR 1.34; 95% CI 0.66–2.73; p = 0.39). Patients who used HCQ and AZM had almost twice the risk of needing invasive ventilatory support (IVS) (RR 1.94; 95% CI 1.07-3.52; p = 0.16). In addition, we highlight the non-significant trends for lower need for IVS in patients who underwent therapy with IVIg (RR 0.86; 95% CI 0.19–3.03; p = 0.62) and in patients who used IVIg associated with corticosteroid therapy (RR 0.57; 95% CI 0.16 –1.93; p = 0.60).

Most of the cases found required hospitalization (79%, n = 31/39), with an average hospital stay of 15 days (IIQ 9-22.5). The main factors associated with the length of hospital stay are shown in Table 1. The use of other antibiotics in addition to azithromycin for the treatment of COVID-19 was associated with an increase in LOS [20 days (9.5-32) vs 10 days (9-14); p = 0.01]. The main factor associated with reduced hospital stay was use of IVIg associated with corticosteroid therapy [8 (5-8) vs 19 (12.2 –23.7); p = 0.007]. In addition, there was a statistically non-significant trend towards shorter hospital stays in patients who used only IVIg [9 (6.5-40) vs 19 (13.75–21.75); p = 0.12].

In the sample of cases found in this review, 4 deaths were reported in patients with myasthenia gravis infected with SARS-CoV-2, resulting in a mortality rate of 10.3% (n= 4/39). Although no factor was associated in a statistically significant way with mortality, there was a non-significant trend towards higher mortality in patients who used AZM (RR 2.55; 95% CI 0.26–30.02; p = 0.60), and in patients who used antibiotics other than azithromycin (RR 2.5; 95% CI 0.23–26.6; p = 0.61). In addition, all patients who died did not use IVIg or IVIg associated with prednisone (Table 2).

The treatment variables for MG and COVID-19, in addition to the analyzed outcomes of the total sample, are shown in Table 3. The sample was coded in increasing numerical order, according to the authors' alphabetical order. The variables and results analyzed for the thirty-nine patients are shown in Tables 1, 2, 4 and 5. The analysis of authors, year of publication, funding and location of the studies included in this review are shown in Table 6.

The AMSTAR-2 consists of 16 items evaluated as "yes", "no" or "partial yes", which measure the quality of the systematic review in "high," "moderate", "low" or "critically low" (Shea et al., 2017). This study received "moderate" quality. Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation), the articles included in this systematic review are classified as low quality of evidence because they are non-comparative observational studies, difficult to reproduce in experimental studies.

Table 1. Factors associated with length of hospital stay.

Variables	Length of hospital stay (days)	p value
Sex, median (IIQ)		
Masculine	14 (9 - 63)	0.21[a]
Feminine	10 (5 - 17)	
HCQ use, median (IIQ)		
Yes	17 (11 – 20.75)	0.61[a]
No	13.5 (8.75 - 25)	
AZM use, median (IIQ)		
Yes	14 (9 - 27)	0.96[a]
No	16.5 (9 – 21.25)	
HCQ + AZM use, median (IIQ)		
Yes	17 (11 – 305)	0.66[a]
No	14 (9 – 22.5)	
Use of other antibiotics for COVID-19, median (IIQ)		
Yes	20 (9.5 - 32)	0.01[a]
No	10 (9 – 14)	
IV Immunoglobulins use (without HCQ or AZM), median (IIQ) (n=13)		
Yes	9 (6.5 - 40)	0.12[a]
No	19 (13.75 – 21.75)	
IV Immunoglobulins and corticotherapy use (without HCQ or AZM), median (IIQ) (n=13)		
Yes	8 (5.0 – 8.0)	0.007[a]
No	19 (12.2 – 23.7)	

[a]Mann Whitney U Test. Legend: AZM = azithromycin, HCQ = hydroxychloroquine, IV = intravenous.

Table 2. Factors associated with mortality in patients with myasthenia gravis infected by SARS-CoV-2.

Variables	Death, yes (n=4)	Death, no (n=33)	RR (CI 95%)	P Value
HCQ use, n (%)				
Yes	0 (0)	8 (100)	-	0.55[a]
No	4 (13.8)	25 (86.2)		
AZM use, n (%)				
Yes	3 (15)	17 (85)	2.55 (0.26 – 30.02)	0.60[a]
No	1 (5.9)	16 (94.1)	1	
HQC + AZM use, n (%)				
Yes	0 (0)	4 (100)	-	1.0[a]
No	4 (12.1)	29 (87.9)		
Use of other antibiotics for COVID-19, n (%)				
Yes	3 (14.3)	18 (85.7)	2.5 (0.23 – 26.6)	0.61[a]
No	1 (6.2)	15 (93.8)		
No treatment for COVID-19, n (%)				
Yes	0 (0)	9 (100)	-	0.55[a]
No	4 (14.3)	24 (85.7)		
IV Immunoglobulins use (without HCQ or AZM), n (%) (n=16)				
Yes	0 (0)	7 (100)	-	1.00[a]
No	1 (11.1)	8 (88.9)		
IV Immunoglobulins and corticotherapy use (without HCQ or AZM), n (%) (n=16)				
Yes	0 (0)	4 (100)	-	1.00[a]
No	1 (8.3)	11 (91.7)		

[a]Fisher's Exact Test. Legend: AZM = azithromycin, HCQ = hydroxychloroquine, IV = intravenous.

Table 3. Ventilatory support outcomes analyzed, length of hospital stay and mortality.

	Sample	Gender/ Age	Treatment for COVID-19	Treatment for MG	Evolution and LOS
Aksoy & Oztutgan (2020)	1	F/42 years	Favipiravir, meropenem, oseltamivir, HCQ (400 mg twice daily on the first day, then 200mg twice daily) and subcutaneous low molecular weight heparin. HCQ stopped on day 5.	Pyridostigmine 240 mg daily. Methylprednisolone 40 mg daily, added on day 5.	Received VS after immediate healing with PLEX. Discharged on 22nd day.
Anand et al. (2020)	2	F/ 42 years	No treatment for COVID-19.	Prednisone 20 mg every day and IVIg 2 g/kg.	Patient did not need VS. She was discharged on the 5th day.
	3	F/ 64 years	No treatment for COVID-19.	MMF 750 mg twice daily, prednisone 15 mg every day. MMF was discontinued 1 week after discharge.	Patient did not need VS and she was discharged on the 9th day of hospitalization.
	4	F/ 90 years	HCQ 400 mg twice daily for 1 day, and 200 mg twice daily for 4 days; AZM 500 mg for 5 days and ceftriaxone 1g for 5 days.	MMF discontinued; prednisone 25 mg for 6 days, then daily; IVIg continued.	The patient received VS from the 10th to the 17th day. She stayed in the ICU for 17 days and then She was referred to the ward.
	5	M/ 57 years	HCQ 400 mg twice daily for 1 day, 200 mg twice daily after day 1; AZM 500 mg. AZA 50 mg daily.	AZA 50 mg daily.	Patient received IV. Discharged on the 9th day after using tocilizumab 300 mg in a single dose.
	6	M/ 64 years	HCQ 400 mg; AZM on the first day, followed by 250 mg daily for 4 days; ceftriaxone 2g for 2 days, and 1g three times a day for 3 days.	MMF discontinued, resumed on the 11th day of hospitalization. Prednisone 10mg for 9 days, then by 5mg every day. The patient was intubated on the first day of hospitalization and remained on mechanical ventilation after 35th day. There was no further data in the article.	The patient was intubated on the first day of hospitalization and remained on mechanical ventilation after 35th day. There was no further data in the article on the patient's evolution.

Camelo-Filho et al. (2020)	7	NA	AZM, cefuroxime; oseltamivir, amikacin, and teicoplanin.	Prednisone 20 mg.	Patient received IVS. He died after 13 days in hospital.
	8	NA	Piperacilline/ tazobactame, ceftriaxone, and AZM.	Prednisone 30 mg.	Patient died after 9 days in hospital.
	9	NA	Ceftriaxone.	Prednisone and AZA continued, IVIg 2 g/kg added.	The Patient was hospitalized for 8 days and did not require mechanical ventilation.
	10	NA	Ceftriaxone.	Adding prednisone dose to 40 mg/day, methotrexate was maintained.	18 days hospital stay. Patient remained hospitalized.
	11	NA	Ceftriaxone, oseltamivir, meropenem, colistin, and linezolid.	Prednisone was maintained; discontinuation of methotrexate.	Patient received IVS, and after 29 days of hospitalization, remained hospitalized at the end of the study.
	12	NA	Clarithromycin, ceftriaxone, AZM, and oseltamivir.	None reported.	7 days of hospitalization with IVS. Died.
	13	NA	Ceftriaxone, AZM, piperacilline/ tazobactame, and meropenem.	Up the prednisone, 5 PLEX sessions added; cyclosporine suspended.	Patient was hospitalized for 42 days and needed IVS.
	14	NA	Piperacilline/ tazobactame, ceftrixone, and AZM.	Up prednisone, 4 PLEX sessions added; AZA suspended.	Patient needed IVS. 24 days hospitalized.
	15	NA	Ceftriaxone.	Prednisone continued, 5 PLEX sessions added and AZA suspended.	Patient needed IVS. 20 days hospitalized.
	16	NA	Ceftriaxone and AZM.	Held 5 PLEX sessions.	Patient remained hospitalized for 28 days, 16 in the ICU. IVS needed.
	17	NA	AZM.	Prednisone 20 mg and AZA 150 mg.	3 days of hospitalization without VS.
	18	NA	Ceftriaxone, clarithromycin, meropenem and vancomycin.	Up Prednisone, dose not reported.	Hospitalized for 16 days, 15 in the ICU. The patient needed VS and died.
	19	NA	Ceftriaxone and AZM.	Prednisone 60 mg and AZA suspended.	Hospital discharge after 8 days, without the need for mechanical ventilation.
	20	NA	AZM, ceftriaxone, meropenem, linezolid, amikacyn, polymyxin B.	Up prednisone, dose not reported.	Hospital discharge after 42 days of total hospitalization (32 days in the ICU) – requiring IVS.
	21	NA	Ceftriaxone.	Increased prednisone, dose not reported.	Hospital discharge after 22 days of total hospitalization (17 days in the ICU) – requiring IVS.

Delly et al. (2020)	22	F/ 56 years	Vancomycin, cefepime, AZM initially. Antibiotics were discontinued and HCQ 200 mg per day was started.	Prednisone 40 mg twice daily, on day 3, pyridostigmine and IVIg started 400 mg/ kg for 5 days.	Patient needed IVS. She healed after 17 days of hospitalization. She was waiting for a subacute rehabilitation facility.
Hofstadt-van Oy et al. (2021)	23	M/ 62 years	Dexamethasone, heparin, piperacilline/ tazobactame.	30 g intravenous immunoglobulins (IVIg) for five days and pyridostigmine. PLEX (6 cycles 3 times weekly), rituximab 1000 mg and eculizumab (900 mg weekly for 4 weeks, followed by 1200 mg every 2 weeks).	Patient needed IVS. Tracheostomy was removed after the second dose of eculizumab. Bulbar symptoms were completely resolved 10 weeks after the start of eculizumab.
Hübers et al. (2020)	24	F/ 36 years	No treatment for COVID-19.	IVIg for 5 days after worsening of MG symptoms; break from using AZA 50 mg and pyridostigmine 60 mg.	10 days of hospitalization; without VS.
	25	F/ 36 years	No treatment for COVID-19.	Pyridostigmine 60 mg four to five times a day, prednisone 25 mg per day and subcutaneous immunoglobulins 12 g every 4 days.	Patient received IVS. Intubated on the second day and extubated on the 7th; hospitalized for 9 days.
	26	M/ 25 years	AZM and piperacillin/ tazobactam.	Pyridostigmine 60 mg three times a day.	Patient received IVS. Tracheostomy removed after 9 weeks.
	27	M/ 55 years	No treatment for COVID-19.	Chronic drugs.	Hospitalized for 13 days, without receiving VS.
Kushlaf (2020)	28	F/ 66 years	HCQ for 5 days; AZM avoided; AZA dose adjusted according to the patient`s renal status.	IVIg 1g/kg daily for 2 consecutive days, and tocilizumab.	IVS. Extubated after 17 days and discharged for hospital rehabilitation.
Octaviana et al. (2021)	29	F/ 25 years	Vitamin, NAC, ceftriaxone, AZM were discontinued.	Pyridostigmine.	The patient needed VS and healed after 5 days of hospitalization.
	30	F/ 42 years	HCQ and NAC.	MMF and pyridostigmine.	14 days of hospitalization without VS.
	31	M/ 49 years	AZM 500 mg daily for 5 consecutive days, vitamin C 3000 mg once daily and paracetamol 1500 mg once daily.	Pyridostigmine 180 mg every day and AZA 100 mg once daily.	The patient needed VS and healed after 14 days of hospitalization.

Phillip & Prerana (2020)	32	M/ 70 years	Hydrocortisone sodium succinate 100 mg.	PLEX.	Patient received IVS. Extubated after steroid therapy and PLEX on 5th day.
Ramaswamy & Govindarajan (2020)	33	F/ 42 years	No treatment for COVID-19.	Pyridostigmine 30 mg three times a day.	Quarantine at home for 14 days. She did not need VS.
Rein et al. (2020)	34	F/ 38 years	HCQ 600 mg twice daily, after 200 mg three times daily for additional 9 days; lopinavir 400 mg twice daily and ritonavir 100 mg twice daily for 10 days. AZM was avoided.	IVIg, prednisone 25 mg once daily and pyridostigmine 60 mg 5 times daily. After exacerbation, she received IVIg 2g/kg for 5 days and the prednisone dosage was titrated up to 60 mg per day.	Patient received VS. After 10 days of hospitalization, and was discharged with minimal residual symptoms of myasthenia.
	35	F/ 42 years	No treatment for COVID-19.	IVIg monthly, prednisone 10 mg once daily, and pyridostigmine.	Home recovery without VS.
	36	M/ 66 years	No treatment for COVID-19.	Prednisone and PLEX was replaced by IVIg	Patient did not receive VS. The symptoms of COVID 19 solved in 2 days.
Salik et al. (2020)	37	M/ 80 years	AZM for 4 days and HCQ for 7 days. AZA performed. HCQ was removed after patient`s reintubation.	Pyridostigmine, then 5 days of daily IVIg, after myasthenic crisis and reintubation.	Patient received IVIg for 6 days reintubed after aspiration. HCQ discontinued. He underwent an open surgical tracheostomy on the 20th day.
Singh & Govindarajan (2020)	38	F/ 36 years	No treatment for COVID-19.	Stopped pyridostigmine and oral prednisone; MMF continuity. PLEX performed, 5 changes every two days during the 14 days of intubation.	She remained in the hospital for another 7 days after extubation and was discharged, resuming the home dose of prednisone (25 mg daily) and MMF (1000mg twice daily).
Sriwastava et al (2020)	39	F/ 65 years	Ceftriaxone, AZM, 1-unit convalescent plasma, she was placed in the prone position for 1 h at a time for 4 days, received intravenous dexamethasone 6 mg and 4 doses of intravenous dexamethasone.	Pyridostigmine 60 mg every 6 h and after pyridostigmine dosage was reduced to 60 mg every 8 h.	Patient received VS. After 10 days of hospitalization, she was discharged with minimal residual symptoms of myasthenia ocular and COVID-19.

AZA = azathioprine. AZM = azithromycin. F = female gender. HCQ = hydroxychloroquine. ICU = intensive care unit. IVIg = intravenous immunoglobulin. IVS = invasive ventilatory support. M = male gender. MMF = mycophenolate mofetil. NAC = N-acetylcysteine. NA = not applicable. VS = ventilatory support. LOS = length of hospital stay.

Table 4. Factors associated with the necessity of ventilatory support in patients with myasthenia gravis infected by SARS-CoV-2

Variables	Ventilatory Support Yes (n=26)	Ventilatory Support No (n=11)	RR (CI 95%)	p value
Sex, n (%)				
Masculine	7 (77.8)	2 (22.2)	1.9 (0.75 – 2.22)	0.65[a]
Feminine	9 (60)	6 (40)	1	
HCQ use, n (%)				
Yes	8 (88.9)	1 (11.1)	1.38 (0.96 – 1.98)	0.22[a]
No	18 (64.3)	10 (35.7)	1	
AZM use, n (%)				
Yes	17 (85)	3 (15)	1.60 (0.98 – 2.60)	0.33[b]
No	9 (52.9)	8 (47.1)	1	
HCQ + AZM use, n (%)				
Yes	5 (100)	0 (0)	-	0.29[a]
No	21 (65.6)	11 (34.4)		
Use of other Antibiotics, n (%)				
Yes	17 (89.5)	2 (10.5)	1.78 (1.10 – 2.91)	0.009[b]
No	9 (50)	9 (50)	1	
IV immunoglobulins use (without HQC or AZM), n (%) (n=16)				
Yes	2 (28.6)	5 (71.4)	0.42 (0.12 – 1.51)	0.31[a]
No	6 (66.7)	3 (33.3)	1	
IV immunoglobulins and corticotherapy use (without HQC or AZM), n (%) (n=16)				
Yes	1 (25.0)	3 (75.0)	0.43 (0.07 – 2.50)	0.56[a]
No	7 (58.3)	5 (41.7)	1	

[a]Fisher's Exact Test [b]Pearson's chi-squared test. Legend: AZM = azithromycin, HCQ = hydroxychloroquine, IV = intravenous.

Table 5. Factors associated with the need for invasive ventilation.

Variables	Invasive Ventilation Yes (n=18)	Invasive Ventilation No (n=21)	RR (CI 95%)	p value
Sex, n (%)				
Masculine	6 (66.7)	3 (33.3)	2.50 (0.95 – 6.51)	0.09[a]
Feminine	4 (26.7)	11 (73.3)	1	
HCQ use, n (%)				
Yes	5 (55.6)	4 (44.4)	1.63 (0.36 – 7.32)	0.70[a]
No	13 (43.3)	17 (56.7)	1	
AZM use, n (%)				
Yes	10 (47.6)	11 (52.4)	1.13 (0.32 – 4.02)	0.84[b]
No	8 (44.4)	10 (55.6)	1	
HCQ + AZM use, n (%)				
Yes	4 (80)	1 (20)	1.94 (1.07 – 3.52)	0.16[a]
No	14 (41.2)	20 (58.8)	1	
Use of other Antibiotics, n (%)				
Yes	11 (52.4)	10 (47.6)	1.34 (0.66 – 2.73)	0.39[b]
No	7 (38.9)	9 (61.1)	1	
IV immunoglobulins use (without HQC or AZM), n (%) (n=16)				
Yes	2 (28.6)	5 (71.4)	0.57 (0.16 – 2.15)	0.62[a]
No	5 (50)	5 (50)	1	
IV immunoglobulins and corticotherapy use (without HQC or AZM), n (%) (n=17)				
Yes	1 (25.0)	3 (75.0)	0.54 (0.09 – 3.26)	0.60[a]
No	6 (46.2)	7 (53.8)	1	

[a] Fisher's Exact Test; [b]Pearson's chi-squared test. Legend: AZM = azithromycin, HCQ = hydroxychloroquine, IV = intravenous.

Table 6. The analysis of authors, year of publication, funding and location of the studies included in this review.

Authors	Year	Funding	Location
Aksoy & Oztutgan	2020	No financing related	Turkey
00Anand et al.	2020	No financing related	United States of America
Camelo-Filho et al.	2020	No financing related	Brazil
Delly et al.	2020	None	Brazil
Hofstadt-van Oy et al.	2021	None	Germany
Hübers et al.	2020	None	Switzerland
Kushlaf	2020	No financing related	Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, Ohio United States of America
Octaviana et al.	2021	This publication is funded by Universitas Indonesia	Indonesia
Phillip & Prerana	2020	None	United States of America
Ramaswamy & Govindarajan	2020	No financing related	United States of America
Rein et al.	2020	None	Israel
Salik et al.	2020	No financing related	United States of America
Singh & Govindarajan	2020	No financing related	United States of America
Sriwastava et al.	2020	None	India United States of America

DISCUSSION

The concern regarding patients with Sars-Cov-2 and MG infection centers on two aspects: chronic immunological suppression and respiratory failure due to myasthenic exacerbation (Rein et al., 2020). Establishing the etiology of respiratory failure is very difficult, especially in cases of ventilatory support, requiring neurological consultation (Camelo-Filho et al., 2020).

In the present study AZM was associated with mortality, need for IVS and elevated LOS compared to the mean. Patients who used HCQ and AZM had almost twice the risk of needing IVS (RR 1.94; 95% CI 1.07-3.52). The use of other antibiotics in addition to azithromycin for the treatment of COVID-19 was associated with an increase in LOS [20 days (9.5-32) vs 10 days (9-14); p = 0.01]. Patients who used hydroxychloroquine (HCQ) and AZM had almost twice the risk of needing IVS (RR 1.94; 95% CI 1.07-3.52; p = 0.16). In the study by Camelo-Filho et al. (2020) on patients who died, 75% used azithromycin and this medication was associated with the clinical worsening of participants in other studies. (Aksoy & Oztutgan, 2020; Camelo-Filho et al., 2020; Salik et al., 2020).

The use of azithromycin and hydroxychloroquine may exacerbate COVID-19 and trigger myasthenic attacks (Anand et al., 2020; Gilhus et al., 2018; Jallouli et al., 2011). A retrospective study of 127 participants with autoimmune myasthenia gravis demonstrated worsening of the disease after administration of azithromycin (odds ratio: 1.42) (Abicht et al., 2012; Solé et al., 2020). Therefore, health professionals who work in the coronavirus pandemic must be aware of the risks involved in relation to drugs that worsen clinical conditions and cause respiratory failure in patients with MG.

All of these findings confirm the National Institute of Health guideline, which does not recommend the use of hydroxychloroquine alone or in combination with azithromycin for COVID-19 (NIH, 2020; Fiolet et al., 2020). A clinical trial conducted on non-human primates has shown that neither HCQ nor the combination of HCQ with AZM showed any significant effect on the viral load in the analyzed tissues, did not provide protection against COVID-19 infection and were ineffective in pre-exposure prophylactic treatment (Maisonnasse et al., 2020; Mega et al., 2020).

In the present study both chronic corticosteroid therapy and the use of IVIg were associated with less need for ventilation, mortality and length of hospital stay. Regarding IVIg associated prednisone, there were interesting trends, since patients using IVIg and prednisone had almost half the risk of IVS and shorter hospital stays (8 days vs 16.5 days in median). Another important fact is that the mortality rate of 10.3% (n=4/39) was not associated with immunosuppressive treatment, IVIg or PLEX. However, we recognize the need for further studies with larger samples to draw conclusions based on stronger evidence.

It is important to highlight that immunosuppressive therapy in immunosuppressed patients does not uniformly present a higher complication risk. Patients using chronic immunosuppressants to prevent transplant rejection responded positively to COVID-19 infection, despite their immunocompromised status (Jacob et al., 2020). It is therefore essential that physicians be critical when discontinuing immunosuppressive drugs in the midst of the pandemic.

Discontinuity of immunosuppressive therapy should only be considered in a patient with Sars-Cov-2 and MG if the symptoms are severe, such as in hospitalization and bacterial infections/sepsis. Immune depletion agents should be avoided in these situations, while AZA and MMF can be continued, since the dosage effects are more persistent, the elimination of the agent is slower, and the reconstruction of the effects takes months. In addition, it is advisable for patients using medications that cause profound lymphopenia to undergo prophylaxis with antivirals in the post-infusion phase (Jacob et al., 2020).

Depending on the infection stage, corticosteroids, such as prednisone, may have adverse effects, initially causing viremia and impairing viral clearance. Later, however, they inhibit the migration of immune cells and the production of chemokines, reducing the cytokine storm. For this reason, the relationship between chronic corticosteroid therapy, COVID-19 and MG has become essential (Rein et al., 2020).

In the study by Camelo-Filho et al. (2020), all patients who did not require VS used prednisone associated with a second immunosuppressive drug. In addition, Delly et al. (2020) reported that a participant in his study who was in IVS showed improvement in the respiratory function after IVIg, being extubated early.

According to Diez et al. (2020), the intravenous immunoglobulins available on the market proved to react against COVID-19 and other viral antigens in vitro. This is because IVIg preparations contain proteins collected from thousands of donors and ameliorate the course of inflammatory autoimmune diseases by blocking Fc-gamma receptors, neutralizing inflammatory cytokines (Baker et al., 2017).

In cases of severe COVID-19, early administration of high-dose IVIg (25 g/day for 5 days), combined with antivirals and methylprednisolone, allows lymphocytosis, reduction of inflammatory markers, resolution of pulmonary disorders and nasal and negative oropharyngeal smear tests a few days after therapy (Cao et al., 2020; Gasparyan et al., 2020; Paez et al, 2020). Since this medication optimizes passive immunity and modulates the inflammatory response, it has great potential and promising effects when used at the onset of clinical deterioration by coronavirus 2, not when systemic damage has already set in (Cao et al., 2020; Jawhara, 2020; Lin L et al., 2020).

A recent meta-analysis study found that anti-inflammatory agents (corticosteroids, tocilizumab, anakinra and IVIg), convalescent plasma and remdesivir are associated with better prognosis in hospitalized patients with COVID-19. However, there are still no studies with a high level of evidence involving these agents and MG associated with COVID-19 (Kim et al., 2020).

It is important to note that, in relation to plasmapheresis, Aksoy & Oztutgan (2020) report that a participant in their study received PLEX therapy and did not need IVS due to immediate improvement and speedy discharge.

Studies have shown that both plasmapheresis and IVIg prevent worsening of lymphocyte count and should be promptly administered to patients with COVID-19 for more effective and safer treatment. This administration must occur before the 14th day, since early initiation is related to better outcomes (Ramtin et al., 2020).

One participant from Anand et al. (2020) who was in IVS was discharged on the 9th day after using tocilizumab (300 mg in a single dose). According to a retrospective study, carried out with 21 seriously ill patients by COVID-19, after the use of tocilizumab, an interleukin-6 inhibitor (IL-6), the clinical picture and alterations in the tomography improved immediately. This suggests that the drug may be effective for the treatment of Sars-Cov-2, when there are no contraindications (Xu et al., 2020).

Among the limitations in this article is the fact that prospective primary studies were scarce and the lack of information caused difficulties in establishing a causal link between therapeutic measures and medium and long-term outcomes. In addition, there was no analysis to verify whether the unfavorable course of the condition was associated with other variables, such as age, gender, previous pathological history, and secondary bacterial infections; as well as no correlations with the other medication also used during the patient's hospitalization.

FINAL CONSIDERATIONS

The literature review presented in this article leads to the conclusion that there is no consensus on the conduct to be taken in patients with MG infected by Sars-Cov-2, since the clinical course is quite varied, probably related to the general health status of patients and their comorbidities. Despite this, there was an association between the use of hydroxychloroquine and azithromycin with a worse prognosis, in concordance with other articles, which also performed this correlation.

For this reason, it is important that health professionals working on the "frontline" coping with the pandemic do not prescribe drugs, like AZM, HCQ and other antibiotics with harmful effects for MG. In addition, IVIg immunotherapy and corticotherapy are recommended for patients who have respiratory complications, without contraindications to the drug. As demonstrated, basic immunosuppressive therapy was not harmful. In short, as myasthenia gravis is a rare disease, more case reports are needed, with reliable statistical analysis, to better understand the implications between MG, Sars-Cov-2 infection, and drug therapies.

CONFLICT OF INTEREST.

There is no conflict of interest to declare.

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