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Research Article

Challenges of Antiviral Therapy on Clinical Outcomes and 30-Day Survival Benefits in Hospitalized Multiple Sclerosis Patients with COVID-19

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Abstract

Background: This study aimed to evaluate the efficacy and safety concerns of remdesivir and type 1 interferons (INFs) on the clinical outcomes of multiple sclerosis (MS) patients who were hospitalized with COVID-19.

Methods: Using electronic health records systems, this is a cross-sectional study of two years of hospital admissions in terms of COVID-19 in Iran from March 2019 to August 2021. The severities of COVID-19 outcomes were ICU admission, hospitalization days, and 30-day mortality rates.

Results: Nine hundred ninety-nine hospitalized MS patients with a definite diagnosis of COVID-19 based on PCR were recorded in the electronic health systems. Almost half of the patients were under treatment with an anti-CD-20 agent (rituximab or ocrelizumab) at the time of hospital admission (50.3%), with higher mortality rates, needing ICU admission, and longer hospitalization ($p < 0.05$).

There was a significant association between taking IFN alone (adjusted IRR = 1.21, 95% CI 1.32 to 1.42) or in combination with RDV (adjusted IRR = 1.30, 95% CI 1.18 to 1.5042) and longer hospitalization.

There were no significant associations between antiviral treatment (RDV alone, IFNβ1 alone, and IFNβ1 plus RDV) and ICU admission ($p > 0.2$), in-hospital mortality rate ($p > 0.2$), or 30-day survival rate ($p > 0.2$). The results were similar in patients who did or did not receive anti-CD-20 agents.

Conclusion: Our data reveal that RDV, IFN, or a combination of IFN and RDV administration has no benefit in the treatment of hospitalized MS patients with COVID-19.

Keywords: Multiple Sclerosis; COVID-19; Remdesivir; Interferon; Survival

Introduction

Antiviral therapeutic drugs target specific parts of a virus to stop it from replicating in living cells, helping the body to prevent serious diseases and decrease the mortality rate. Since the global outbreak of the SARS-CoV-2 virus, several antiviral medications have been used to treat COVID-19. Not all of them have *Food and Drug Administration (FDA) approval for the treatment of* COVID-19 in patients who are at risk of severe illness [1].

In *hospitalized COVID-19 patients* who are immunocompromised, such as those with multiple sclerosis (MS), there is insufficient evidence to guide clinicians in using antiviral medicines for COVID-19 management [2,3]. Most clinicians prescribe antiviral therapies to patients who have immunocompromising conditions at a dose and duration similar to the guidelines of the general population. In our current study, hospitalized patients with COVID-19 who also had multiple sclerosis and were on immunosuppressive disease-modifying therapies had severe outcomes in terms of hospitalization duration (adjusted OR = 2.06, 95% CI: 1.48, 2.86) and mortality rate (adjusted OR = 2.05, 95% CI: 1.52, 6.29) [4].

Case reports suggest that antiviral drugs can suppress viral replication in this population, but they do not always eliminate it [5-7]. Recent studies have evaluated the efficacy and safety of antiviral agents, including remdesivir (RDV), hydroxychloroquine, lopinavir, and interferon β-1a, in treating COVID-19 [1,8,9]. However, the evidence is insufficient to recommend their use in immunocompromised patients.

RDV, a prodrug derived from nucleoside analogs, possesses the ability to hinder the RNA polymerase activity of numerous viruses. It has exhibited antiviral properties against SARS-CoV-2 in both laboratory tests and animal studies [10]. Exogenous interferons are potent antiviral and immune-modulating substances that play a crucial role in responding to viral infections and shaping the subsequent immune response to infection [11]. They are the favored drugs to treat multiple sclerosis [12].

This study aimed to evaluate the efficacy and safety concerns of exogenously administered remdesivir (RDV) and type 1 interferons β-1 (INFs) on the clinical outcomes and 30-day survival probability of hospitalized MS patients with COVID-19.

Methods

Study design and data source

The data have been described previously [4]. Briefly, this study is a cross-sectional study on COVID-19-related hospital admissions in Iran, spanning from March 2019 to August 2021. The research was conducted using electronic health record systems known as the Medical Care Monitoring Center (MCMC) and Hospitals' Information System (HIS). The MCMC collected data on COVID-19 patients admitted to the hospital, while the HIS recorded information such as demographics, admission, and discharge dates, initial and final diagnoses, hospital inpatient services, including medications, wards (ICU, isolation, and others), procedures (mechanical ventilation), comorbidities, and hospital mortality. The International Classification of Diseases 10 (ICD-10) was used to assign diagnostic codes for COVID-19, specifically U07.1 and U07.2.

For quality control purposes, all patients with MS were recalled, and a questionnaire was completed to gather relevant data. The questionnaire included information on their MS diagnosis date, the MS medications they were taking at the time of COVID-19 admission, any history of other chronic illnesses, smoking history at the time of COVID-19 admission, and height and weight measurements.

The MS medications included fingolimod, azathioprine, interferons, glatiramer acetate, dimethyl fumarate, teriflunomide, natalizumab, azathioprine, and ocrelizumab/rituximab.

Chronic disorders include hypertension, diabetes, heart disorders, malignancy, chronic kidney disease, lung disorders, asthma, and immunodeficiency.

The available data on the Expanded Disability Status Scale (EDSS) of MS patients were obtained from their electronic medical records. This information was collected from patients who had visited a neurologist within the three months before their hospital admission.

Ethical approval and consent to participate

The study was conducted based on the Declaration of Helsinki, and the Ethical Committee of Neuroscience Institute of Tehran University of Medical Sciences approved human experiments (IR.

TUMS.NI.REC.1400.007). Informed consent was obtained from all patients or their close relatives of those who died.

COVID/19 treatment

Based on the national guidelines [13], the three regimes were as follows

- **Regimen 1:** "Remdesivir was administered intravenously as a 200 mg loading dose on day 1, followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death."
- **Regimen 2:** "IFNs (1a or 1b) were administered intravenously daily for 5-7 days or until hospital discharge or death (for IFN-1a: 44 mcg, for IFN-1b: 250 mcg)."

During admission, all patients received supportive care according to the standards of the COVID-19 committee of the Iran Ministry of Health guidelines.

Disease severity at the time of admission

Patients were considered to have severe disease at the time of admission if the oxygen saturation as measured by pulse oximetry (Spo_2) was 93% or lower or had affected lung(s) based on CT results.

The disease outcomes

- **Primary outcome:** The primary outcome was the need for oxygen therapy defined according to the ordinal scale. Patients were defined by a score of 1 if they did not require supplemental oxygen, 2 if they required any supplemental oxygen, and 3 if they required invasive mechanical ventilation.
- **Secondary outcomes:** The length of hospitalization, need for ICU admission, overall in-hospital mortality, and 30-day survival probability were defined as late secondary outcomes.

Statistical analysis

To consider the effectiveness of antiviral therapies, multivariate regression models were used: ordinal regression model for needing oxygen therapy, Poisson regression model for hospitalization length, logistic regression model for needing ICU admission, and Cox regression models for 30-day survival analysis. Clinical outcomes were added as a dependent variable in the model, and antivirals (RDV, IFNs, and IFNs plus RDV) were added as fixed variables. Adjusting covariates were selected based on the parameters associated with severe COVID-19 outcomes, including 1. demographic characteristics (age, sex, body mass index (BMI), living in populated cities, smoking status), 2. comorbidity, 3. COVID-19 status (disease severity, use of corticosteroids, use of immunosuppressive agents (azathioprine, hydroxychloroquine) or other antivirals (tocilizumab, baricitinib, and favipiravir) from the time of admission), 4. MS disease course (MS duration, MS type (relapsing-remitting MS vs. progressive MS), EDSS (Expanded Disability Status Scale) score ≥ 5, and MS medications at the time of admission (anti-CD-20 agents)). If the P value was less than 0.2 (P value <0.2), it was adjusted in multivariable regression analyses.

The data were analyzed by STATA statistical software. All tests were two-sided, and a P value of less than 0.05 was defined as statistically significant.

Results

Study population

Among 1634 patients diagnosed with COVID-19 based on PCR, data related to hospital services, including drug treatment, were available for 993 patients. The mean age of 993 patients was 43 ± 10 years, and approximately 2 out of three were women (Table 1).

	N*	Total (993)
Demographic characteristics		
Age, year	993	43±10
Sex, Female	993	70.2% (697)
BMI, kg/m^2	488	26.1±4.6
Smoking status	486	18.5% (90)
MS-duration, year	985	7(9)
MS type	936	
RRMS		72.0% (674)
Progressive MS		28% (262)
History of chronic disorders (at least one)	993	29.7% (295)
Coronavirus vaccination before hospital admission	993	2.9% (29)
EDSS score≥5	619	25.5% (158)

Table 1: Baseline clinical and demographic characteristics of patients.

Continuous variables are presented as the mean ± standard deviation or median (interquartile range), and categorical variables are presented as percentages (number).

Abbreviations: BMI: Body Mass Index; EDSS: Expanded Disability Status Scale, MS: Multiple Sclerosis; RRMS; relapsing remitting MS

*N: Number, available data

In total, 29.7% (n = 295) of MS patients with SARS-CoV-2 infection had at least a history of one chronic disorder. In this study, 94.4% received disease-modifying therapies (DMTs) at the time of hospital admission (Figure 1). Almost half of the patients were receiving anti-CD20 antibody agents (ocrelizumab or rituximab) (50.3%).

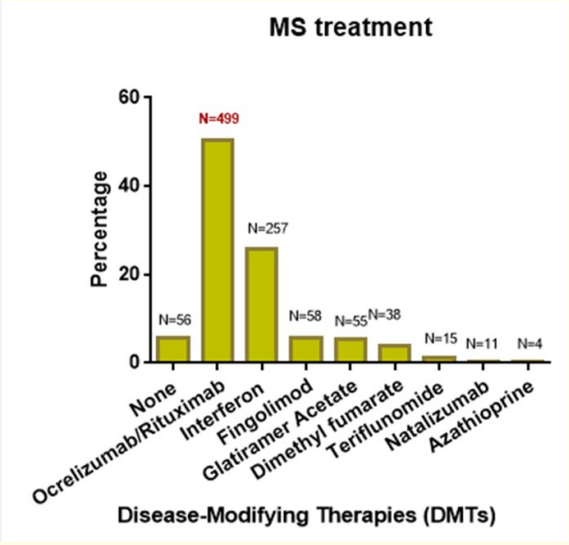

Figure 1: The distribution of disease-modifying therapies (DMTs) at the time of admission in the study population

At the time of hospital admission, 54% of patients had O2 saturation less than 93%, and 74% had affected lungs based on CT results.

In cases of needing oxygen therapy, 37.8% (375) did not require supplemental oxygen, 54.8% (544) required supplemental oxygen (mask, nasal, reserve bag, ambo, or EBOT), and 7.5% (74) required a mechanical ventilator. Among the study population, the median length of hospitalization was 6 days, and 38% of patients were hospitalized for one week or more. In addition, 13.2% of patients needed ICU admission, and the hospital mortality rate was 10.6%.

Antiviral therapies

In the study population, RDV and/or IFNs (IFNβ1a and IFNβ1b) were used in 54% of cases, with 25.6% (254) receiving RDV, 16.5% (164) receiving IFNs (14.4% IFN1a, 2.1% IFN1b), and 12.3% (122) receiving RDV plus IFN1a or 1b. Other antivirals were used as follows: 12.1% (120) lopinavir/ritonavir, 7.5% (74) favipiravir, 1.8% (18) oseltamivir, 3.1% (31) atazanavir, and 0.5% (5) daclatasvir. Among patients who received RDV and/or IFN therapy, 20.7% received other antivirals, 7.2% received disease-modifying antirheumatic drugs (hydroxychloroquine, azathioprine), and 60.7% received hydrocortisone. Our findings showed that RVD and/or IFN therapy was prescribed more frequently in patients with O2 saturation ≤ 93% at the time of admission (61.5% vs. 45.9%, p=0.0001). To evaluate the efficacy of antiviral therapies in the MS population, we subclassified the data based on prescribing RVD, IFNs, or a combination of IFNs and RVD. Table 2 shows the comparison of clinical outcomes in MS patients who were on RVD alone, IFNs alone, or IFNs plus RDV, and those who were not on RVD or IFN therapy (as a reference group).

COVID-19 clinical outcomes based on treatment with three antiviral regimes

Primary outcome

Oxygen therapy requirement during hospitalization

Needing noninvasive supplemental O2 (67.4% vs. 53.9%, p = 0.000) and invasive oxygen supplementation (9.3% vs. 5.3%, p = 0.018) were more common in patients who were treated with RDV, IFNs, or IFN plus RDV compared to those not receiving them (table 2). In the ordinal logistic regression model, after adjusting for confounding factors, using each of the antiviral regimes had a significant direct association with the severity of oxygen therapy ($p < 0.007$).

The odds of severity of oxygen therapy were found to be 1.70 (95% CI, 1.11 to 2.59), 1.81 (95% CI, 1.25 to 2.63), and 1.71 (95% CI, 1.24 to 2.37) times higher in patients who were on IFNs in combination with RDV, INFs alone, and RDV alone, respectively, compared to the reference group after adjusting for confounding factors.

Secondary outcomes

Hospitalization length

Patients who were on IFN alone or IFN plus RDV in their treatment regimen had significantly longer hospitalization compared to the reference group (Median (IQR): 6(7), 7(6) vs. 5(5), $p < 0.001$). The RDV regimen had a significant benefit on shorter hospitalization length compared to IFNs or IFN plus RDM (median (IQR): 6(7), 7(6) vs. 5(5), $p < 0.001$) but not the reference group (5(3) vs. 5(5), p = 0.4).

In the Poisson regression, after adjusting for confounding factors, hospitalization length did not have a significant association with taking RDV alone on their treatment regimen (adjusted IRR = 1.01, 95% CI 0.94, 1.10). However, there was a significant association between taking IFN alone (adjusted IRR = 1.21, 95% CI 1.32 to 1.42) or in combination with RDV (adjusted IRR = 1.30, 95% CI 1.18 to 1.50) in their treatment regimen and longer hospitalization length. The model also found a significant association between taking anti-CD20 at the time of admission and longer hospitalization length (adjusted IRR = 1.18, 95% CI 1.12 to 1.23) (Table S1).

			Univariate Cox regression		Multivariate Cox Regression	
Cofactors	**N***	**Classified**	**HR (CI %)**	**P-value**	**HR (CI %)**	**P-value**
Age (years)	993	---	1.04 (1.02, 1.06)	0.0001	1.04 (1.02, 1.06)	0.0001
Sex	993	Male	Ref	---		
		Female	1.13 (0.74, 1.70)	0.57		
smoking	486	Non-smoker				
		smoker	.70 (.31, 1.55)	0.37		
BMI (kg/m^2)		---	.98 (0.92, 1.04)	0.45		
MS type	936	Relapsing re-mitting	Ref	---		
		progressive	1.41(0.95, 2.09)	0.09	1.06 (0.71, 1.59)	0.76
MS duration (years)	985	---	1.01 (0.98, 1.04)	0.48		
Anti-CD20 antibodies	993	No	Ref			
		Yes	1.15 (0.78, 1.67)	0.44		
Lung(s) status at admission time	993	Non- affected	Ref	---		
		affected	0.96 (0.63, 1.45)	0.83		
O2 saturation	993	>93%	Ref	---		
		≤93%	2.94 (1.90, 4.56)	0.0001	2.54 (1.61, 4.00)	0.0001
Comorbidity	993	No	Ref			
		Yes	2.23 (1.54, 3.22)	0.0001	1.83 (1.25, 2.69)	0.002
Antiviral Therapy	993	None	Ref			
		RDV	1.01 (0.61, 1.65)	0.97	0.94 (0.57, 1.55)	
		IFNs	1.40 (0.84, 2.34)	0.19	1.23 (0.73, 2.09)	
		IFN plus RDV	1.80 (1.07, 3.03)	0.03	1.35 (0.79, 2.30)	
Taking other antivirals	993	No	Ref	---		
		yes	1.26 (0.83, 1.91)	0.28		
Taking DMAR	993	No	Ref	---		
		yes	1.09 (0.65, 1.82)	0.75		
Taking corticosteroids	993	No	Ref	---		
		yes	1.95 (1.31, 2.93)	0.001	1.84 (1.21, 2.79)	0.004

Table S-1: The efficacy of remdesivir, type 1 interferon β, or remdesivir plus type 1 interferon β on 30-day survival.

To consider the 30-day survival probability, Cox univariate and multivariate regression models were used. Adjusting covariates were selected based on the parameters associated with severe COVID-19 outcomes including age, sex, BMI, smoking status, comorbidity, O2 saturation at the time of admission, affected lung(s) at the time of admission, and using corticosteroids, immunosuppressive agents, DMARDs (azathioprine, hydroxychloroquine) or other antivirals (tocilizumab, baricitinib, and favipiravir) from the time of admission. In addition, MS disease course (MS duration, MS type (RRMS vs. progressive), and EDSS score ≥ 5 and MS medications at the time of admission (rituximab or ocrelizumab) were added to the model as cofactors. If the P-value was less than 0.2 (P-value <0.2), it was adjusted in multivariable regression analyses.

Among confounding factors, there was a high correlation between MS type and EDSS. EDSS was removed from the multivariate analysis because of the high missing variable and MS type was added in the model.

Abbreviations: anti-CD20: Anti-Cluster of Differentiate 20; BMI: Body Mass Index; IFNs: Type 1- Interferon Beta-1a or -1b; DMARDs: Disease-Modifying Antirheumatic Drugs; EDSS: The Expanded Disability Status Scale; MS: Multiple Sclerosis; RRMS: Relapsing Remitting MS; RVD: Remdesivir

*N=Number, Available Data

To consider the role of anti-CD20 as a treatment strategy for multiple sclerosis and the efficacy of antivirals, we split the data based on whether patients were taking anti-CD20 at the time of admission and used less than one week of hospitalization as a short hospitalization.

In patients who were not on an anti-CD20 antibody, there was a significant association between taking RDV and being discharged earlier than 1 week (adjusted OR = 0.55, 95% CI 0.29 to 0.94). Prescribing RDV did not have a benefit in patients who were on an anti-CD20 antibody at the time of hospital admission (adjusted OR = 1.06, 95% CI 0.65 to 1.73).

In MS patients who were on an anti-CD20 antibody, there was a significant association between taking IFN and longer hospitalization (1 week or more) (adjusted OR = 2.01, 95% CI 1.15 to 3.50) but not in patients who were not on an anti-CD20 antibody (adjusted OR = 1.31, 95% CI 0.86 to 1.98).

ICU admission

In the multivariable logistic regression model, after adjusting for confounding factors, there was no significant association between taking antiviral RDV (adjusted OR = 1.03, 95% CI 0.62 to 1.70), IFNs (adjusted OR = 1.39, 95% CI 0.82 to 2.34), or IFN plus RDV (adjusted OR = 1.27, 95% CI 0.70 to 2.30) and the need for ICU admission.

30-day survival rate

The mortality rate was higher in patients who were treated with IFNs alone (14.6%) and a combination of IFNs and RDV (17.2%) compared to the reference group (10.8%) and those taking RDV (10.6%) (Table 2). To address the benefit of taking antivirals on survival, we considered the 30-day survival probability.

	None	Antiviral therapy		
	Reference group (N = 453)	**RDV (N = 254)**	**IFNs (N = 164)**	**RDV plus INF (N = 122)**
O2 saturation≤93%	45.9%[a]	61.0% (155)[a]	61.6% (101)[a]	62.3% (76)[a]
Lung (s) affected	67.8%	79.1% (201)	79.9% (131)	78.7% (96)
Primary outcome				
Supplemental O2				
The need for supplemental O2	49.4% (224)[a]	61.0% (155)[a]	57.3% (94)[a]	58.2% (71)[a]
The need for mechanical ventilation	5.3% (24)[a]	7.5% (19)[a]	11.6% (19)[a]	9.8% (12)
Secondary outcomes				
Hospitalization days*	5 (5)	5 (3)	6 (7)	7 (6)
Hospitalization length≥1 week	34.9% (152)[a]	28.3% (71)[b]	49.1% (79)[ab]	54.1% (66)[ab]
Needing ICU admission	11.5% (52)[a]	12.2% (31)	17.1% (28)[a]	16.4% (20)
Mortality rate	10.8% (49)[a]	10.6% (27)	14.6% (24)[c]	18.9% (23)[ac]

Table 2: Severity and clinical outcomes of COVID-19 based on antiviral regimes.

Numerical variables are expressed as medians (IQRs). Categorical variables are presented as percentages.

Pearson's x^2 test was used for categorical variables.

2x2 comparison statistical significance (p-value < 0.05): (a) comparison between normal and other subgroups, (b) comparison between RDV and IFN alone or in combination with RDV, and (3) comparison between IFN alone and IFN plus RDV

Abbreviations: RDV: Remdesivir; IFN: type 1 Interferon Beta (1-a or 1b)

*Median (IQR)

Figure 2 presents the 30-day survival curve in MS patients with different types of antiviral therapy: RDV alone, IFNs alone, INFs plus RDV, and reference group (none of them). Regarding Kaplan–Meier survival analysis, all three antiviral regimes had the same distribution curve at a 30-day survival period ($p > 0.2$).

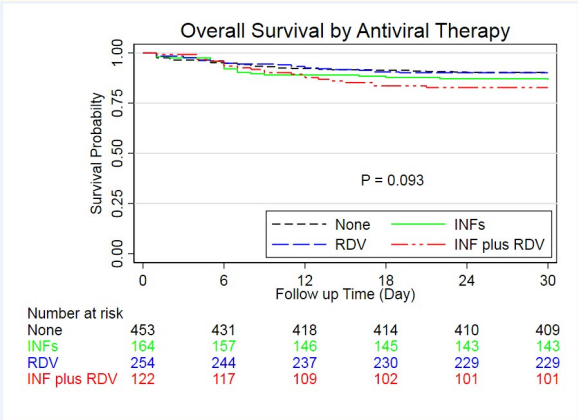

Figure 2: The 30-day survival rate distribution in multiple sclerosis (MS) patients with COVID-19 according to antiviral therapies.

Kaplan-Meier curves showed that there was no significant association between taking IFNs, type 1 interferon beta (1-a or 1b), RDV, remdesivir, or IFNs plus RDV and overall 30-day survival in MS patients with COVID-19.

The multivariable extended Cox model was used to determine the factors that affected the survival of COVID-19 patients. The data showed no association between taking any type of antiviral therapy and the survival of MS patients who were admitted with COVID-19 ($p>0.2$). In the model, age, comorbidity, O2 saturation ≤93% and corticosteroid use were the most important factors affecting the survival of COVID-19 patients at the time of admission (Table S1).

Discussion

In this study, we evaluated the efficacy of three antiviral regimes, namely, remdesivir (RDV), type 1 interferon β (IFNβ-1a or -1b), and RDV plus IFNs, in hospitalized MS patients admitted with COVID-19 on an electronic data set.

Our findings showed that RDV was associated with short hospitalization (less than one week), but this effect was observed only in patients who were not on anti-CD-20 agents. Taking IFNβ alone or in combination with RDV increased the hospitalization length by one week or more. However, this effect was seen specifically in patients who were already on anti-CD-20 agents. These findings suggest that the effectiveness of RDV in reducing hospitalization length may be influenced by the presence of anti-CD-20 agents, while the use of IFNβ in combination with anti-CD-20 agents may lead to longer hospital stays.

Rituximab or ocrelizumab is a monoclonal antibody that specifically targets the surface molecule CD20 [14] and is widely used to treat autoimmune diseases such as MS [15]. In our study, approximately half of MS patients admitted with COVID-19 were receiving rituximab at the time of hospital admission. Demonstrated studies show that rituximab effectively reduces inflammatory activity, the occurrence of relapses, and the formation of new brain lesions in patients with relapsing–remitting MS (RRMS) [9].

Rituximab specifically binds to CD20-positive B-lymphocytes, triggers cell-mediated apoptosis, and selectively depletes CD20+ B-cell activation [9,16]. B cells serve various roles, such as differentiating into plasma cells to produce antibodies and facilitating the activation of T cells through antigen presentation [17], the production of soluble neurotoxic factors [18], and the switch to memory cells [19]. Memory B cells (MBCs) are essential for long-term immunity, as they generate new antibody-secreting cells with enhanced specificity upon encountering the same antigen again. However, rituximab treatment leads to complete depletion of B cells within 72 hours, and it takes approximately 6-9 months for B-cell recovery after the treatment is finished [20,21]. Prolonged B-cell depletion hinders the adaptive immune response and the capacity to produce neutralizing antibodies, resulting in severe manifestations and a prolonged duration of COVID-19 infection [9,22,23]. In addition, the decreased immunoglobulin G levels in MS patients due to B-cell depletion [24] may result in persistent SARS-CoV-2 infection. Therefore, rituximab can reduce the host immune response, suppress viral replication, and increase the risk of prolonged viral shedding and infection [25].

It is important to consider the risks and benefits of rituximab treatment in patients with COVID-19, particularly those who are immunocompromised.

In the case of other clinical outcomes, our data did not demonstrate the benefit of prescribing RDV or IFNs in reducing the risk of in-hospital mortality or needing ICU admission. Of note, in our study population, therapies with IFNs and/or RDV were not related to 30-day survival.

During the pandemic, clinicians prescribe therapies for the treatment of COVID-19, which can limit the availability of medicines. Although there are no clinical trials specifically evaluating the efficacy and safety of RDV in patients with multiple sclerosis, it is the only antiviral agent that has received FDA approval for treating patients with mild to moderate COVID-19.

In trials conducted on the general population of COVID-19 patients, there is a lack of consensus on the clinical effectiveness of RDV. At present, the guidelines for the use of RDV against COVID-19 vary, leading to inconsistent recommendations, and the World Health Organization acknowledges the uncertainty surrounding its optimal role [9]. In a clinical trial conducted by Spinner., *et al*. [26], the administration of RDV for 5 days in patients with COVID-19 pneumonia did not show any clinical benefit in moderate to severe cases of COVID-19. The results of the WHO Solidarity Trial Consortium, 2020, support the notion that RDV is not considered an essential drug for COVID-19-specific treatment [9], as suggested by the latest clinical guidelines (CDC, 2020; Ministry of Health and Labor, 2021; World Health Organization, 2021).

Our results showed that the administration of IFN-β alone or along with RDV was roughly one in three of our study population. Using IFN alone or in combination with RDV did not provide clinical benefits for MS patients in terms of reducing the mortality rate, reducing hospitalization, and reducing the need for ICU admission. These findings suggest that the use of IFN-β alone or in combination with RDV may not be effective for MS patients in terms of the outcomes mentioned.

Discussion

According to observations in the course of virus infections such as SARS and MERS [27], the early use of interferon β, before starting a cytokine storm, appears to be safe and effective in treating COVID-19. Using IFN-β leads to alleviating symptoms, shortening viral shedding, and consequently reducing the need for respiratory support and duration of hospitalization through the acceleration of serum antibody onset against SARS-CoV-2."

Multiple clinical trials have evaluated the efficacy and safety of interferon β-1a in treating severe COVID-19 [12,28,29]. A randomized controlled trial evaluating the efficacy of IFN-β1a in patients with severe COVID-19 showed a significantly lower 28-day mortality rate [12,30]. Another study revealed that the combination of interferon β-1a with RDV did not show superiority over using RDV alone in hospitalized patients with COVID-19 pneumonia [28]. The WHO Solidarity Trial did not show any additional advantages of using interferons in conjunction with supportive care [13]. A more recent study also did not find any additional advantages of using interferon β-1a in combination with RDV [23]. Both studies were constrained by delayed treatment initiation after symptom onset and the absence of a viral load profile. It is important to note that while interferon β has shown promise in treating COVID-19, its effectiveness in treating other diseases, such as MS, may differ. A review of the literature on interferon β in MS found that it has wide immunomodulatory effects, resulting in its efficacy in treating MS [12,31]. However, it is unclear whether interferon β alone or in combination with other drugs is effective in treating MS patients with COVID-19.

Based on our findings, RVD and/or IFN therapy was administered more frequently in patients with affected lung (s) or in patients with O2 saturation less than 93% at the time of admission compared to those with mild COVID-19. Our data showed that taking antiviral agents had a significant association with needing oxygen therapy during hospitalization. It seems that ordering IFNs, RDV, or IFNs plus RDV is more common in patients with severe disease. To address their efficacy, the severity of the disease was adjusted in multivariable regression models.

It is worth noting that the efficacy of antiviral therapy may be associated with the number of days after symptom onset, but we did not have access to this data. However, the variability of the time interval between symptom onset and treatment initiation, which is a crucial factor for evaluating antiviral drugs, remains a limitation. Regarding the need for oxygen supplements, we did not have access to the start date of oxygen therapy or invasive oxygen therapy in our data.

Conclusion

There is insufficient evidence to guide clinical recommendations on using antiviral agents in multiple sclerosis patients for the

treatment of COVID-19. Our data showed that taking IFNs alone or in combination with RDV was associated with a longer hospitalization length in patients. Patients who were on anti-CD20 agents and received INF alone or in combination with RDV were discharged later, one week or more, compared with patients who were not on an anti-CD20 agent. In the case of RDV, administration of the drug alone can reduce the length of hospitalization in patients who were not on an anti-CD20 antibody. However, there were no other clinical benefits for MS patients with COVID-19. Patients with multiple sclerosis may have a higher risk of prolonged viral shedding and infection due to reduced immune responses that suppress viral replication. Based on recent findings, clinicians should consider adjusting the doses of DMTs or shifting to other medications, if possible, to improve the patient's immune response to the infection. It is important to identify safe, affordable, and easily accessible generic repurposed medications for the treatment and prevention of COVID-19 in immunocompromised patients. However, it is recommended to consult with healthcare professionals or refer to authoritative sources such as guidelines from reputable organizations for the most up-to-date and evidence-based recommendations on the use of antiviral agents in MS patients with COVID-19.

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