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Clinical Research Article

Enhancing Clinical Outcomes and Survival in Hospitalized Multiple Sclerosis Patients with COVID-19: Challenges of Antiviral Therapy

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ABSTRACT

Introduction: This study aimed to evaluate the efficacy and safety concerns of remdesivir and type 1 interferons on the clinical outcomes of hospitalized multiple sclerosis patients 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 survival rates.

Results: A total of 993 hospitalized multiple sclerosis patients with a confirmed diagnosis of COVID-19 based on PCR testing were recorded in the electronic health systems. Nearly half of these patients (50.3%) had received treatment with an anti-CD20 agent (rituximab or ocrelizumab) at the hospital admission. This group exhibited higher mortality rates, increased need for ICU admission, and longer hospitalization ($p<0.05$).

There was a significant association between taking interferon-β1 alone (adjusted IRR=1.21, 95% CI 1.32 to 1.42) or in combination with remdesivir (adjusted IRR=1.30, 95% CI 1.18 to 1.5042) and longer hospitalization.

There were no significant associations between antiviral treatment (remdesivir alone, interferon-β1- β1 alone, and interferon-β1plus remdesivir) and ICU admission ($p>0.2$), the 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-CD20 agents. These results were consistent among patients regardless of whether they received anti-CD20 agents.

Conclusion: Our data suggest that remdesivir, interferon-β1, or a combination of both does not benefit hospitalized MS patients with COVID-19.

Keywords:
Multiple sclerosis
COVID-19
Remdesivir
Interferon
Survival
Anti-CD20 agents

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Introduction

Antiviral therapeutic drugs target specific parts of a virus to stop it from replicating in living cells, helping the body prevent serious diseases and decrease mortality. 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 (https://www.covid19treatmentguidelines.nih.gov/).

In *hospitalized COVID-19 patients* who are immunocompromised, such as those with multiple sclerosis (MS), there is insufficient evidence to guide clinicians in the use of antiviral therapies (Hollen and Bernard 2022; Hughes et al., 2021). Most clinicians prescribe antiviral therapies to patients with immunocompromising conditions at a dose and duration similar to the guidelines for the general population. Case reports suggest that antiviral drugs can suppress viral replication in this population, but do not always eliminate it (Baldi et al., 2022; D'Abramo et al., 2021; Kintrilis et al., 2022). Recent studies have evaluated the efficacy and safety of antiviral agents, including remdesivir (RDV), hydroxychloroquine, lopinavir, and interferon β-1a, in treating COVID-19 (Chisari et al., 2022; https://www.covid19treatmentguidelines.nih.gov/ ; Pan et al., 2021). However, the evidence is insufficient to recommend their use in immunocompromised patients (Haddad et al., 2022). 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 (Schreiber 2020). They are the favored drugs to treat MS (Jakimovski et al., 2018).

This study aimed to evaluate the efficacy and safety concerns of exogenously administered RDV and type 1 interferon-β1 (INFs), on the clinical outcomes and 30-day survival probability of hospitalized MS patients with COVID-19.

Material and Methods

Study design and data source:

The data have been described previously (Maghbooli et al., 2022). Briefly, this was a nationwide cross-sectional study on MS patients diagnosed with COVID-19 and administered from March 2019 to August 2021 in Iran. Two national databases, the Medical Care Monitoring Center (MCMC) and the Hospitals' Information System (HIS), were used to collect patient data. The research was conducted using electronic health record systems known as the Medical Care Monitoring Center (MCMC) and the 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. The dates of vaccination for each dose were obtained from the SALAMAT System. Patients who received at least one dose of the COVID-19 vaccine before the date of hospital admission were recorded in the data.

All MS patients were recalled to collect data related to the MS course. A questionnaire was filled out to gather the required data, including MS diagnosis date, MS medications taken at the time of COVID-19 admission, history of other chronic illnesses, smoking history at the time of COVID-19 admission, and height /weight measurements.

In our data, we screened the following MS medications: fingolimod, interferons, glatiramer acetate, dimethyl fumarate, teriflunomide, natalizumab, azathioprine, and ocrelizumab/rituximab.

Screened chronic disorders included 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 three months of their hospital admission with a COVID-19 diagnosis.

Ethical approval and consent to participate

The study was conducted for the Declaration of Helsinki and was approved by the Ethical Committee of Neuroscience Institute of Tehran University of Medical Sciences (IR.TUMS.NI.REC.1403.007). Due to challenges in obtaining written consent in various cities, the participants were informed verbally about the study and

their rights, and gave their voluntary consent.

COVID-19 antiviral treatments

Based on the national guidelines (Hashemi-Meshkini et al., 2022)COVID-19 patients received one of the following two regimens of antiviral treatment:

Regimen 1: RDV 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 (β1a or β1b) 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 upon admission if their oxygen saturation (SpO_2), measured by pulse oximetry, was 93% or lower, or if lung involvement was observed on CT scans.

Primary outcome

The primary outcome of the need for oxygen therapy was defined according to the ordinal scale. Patients were categorized as follows: no need for supplemental oxygen (the score of 1), need for any supplemental oxygen (the score of 2), and need for invasive mechanical ventilation (the score of 3).

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 evaluate the effectiveness of antiviral therapies, multivariate regression models were used: an ordinal regression model for needing oxygen therapy, a poisson regression model for hospitalization length, a logistic regression model for needing ICU admission, and cox regression models for 30-day survival analysis. Clinical outcomes were added as dependent variables in the models, and antivirals (RDV, IFNs, and IFNs plus RDV) were added as independent 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. comorbidities, 3. COVID-19-related factors: vaccination before hospitalization, disease severity, use of corticosteroids, use of immunosuppressive agents (azathioprine, hydroxychloroquine), or other antivirals (tocilizumab, baricitinib, and favipiravir) at the time of admission 4. MS-related factors: MS disease duration, MS type (relapsing-remitting MS vs. progressive MS), EDSS score ≥ 5, and MS medications at the time of admission (including anti-CD20 agents). To ensure the robustness of the models, multicollinearity among the covariates was evaluated using the Variance Inflation Factor (VIF) scores. VIF values ranged from 1.02 to 1.7, indicating minimal multicollinearity.

Covariates with a P value < 0.2 were adjusted for the 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 testing, 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).

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% of the patients were receiving disease-modifying therapies (DMTs) at the time of hospital admission (Figure 1), with nearly half (50.3%) receiving anti-CD20 antibody agents (ocrelizumab or rituximab). Upon admission, 54% of patients had an oxygen saturation of less than 93%, and 74% had affected lungs based on CT results.

Regarding oxygen therapy, 37.8% (375) did not require supplemental oxygen, 54.8% (544) required supplemental oxygen (via mask, nasal cannula, reservoir bag, or ambu bag), and 7.5% (74) required mechanical ventilation. 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%.

TABLE 1: Baseline clinical and demographic characteristics of patients

	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% (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)

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

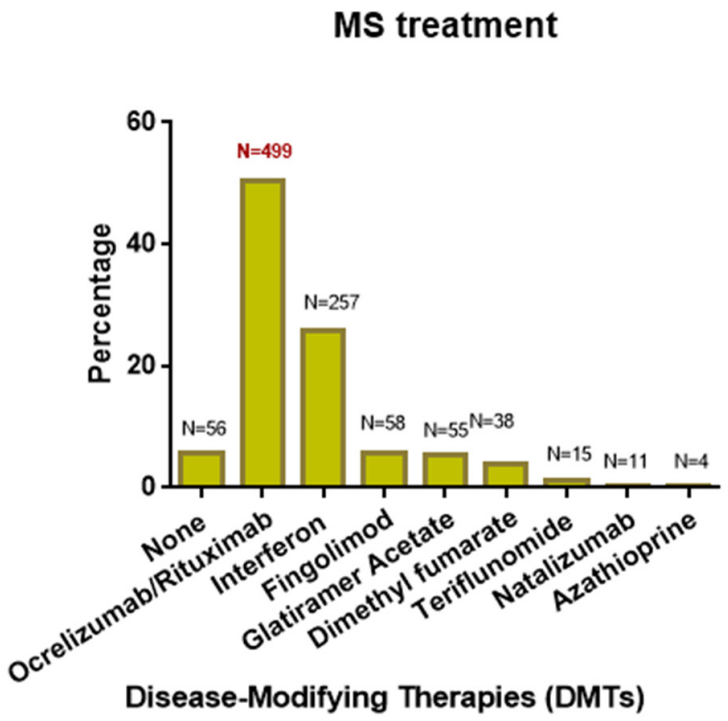

FIGURE 1. The distribution of disease-modifying therapies (DMTs) at the time of admission in the study population. Almost half of the patients received anti-CD20 antibody agents (ocrelizumab or rituximab) (50.3%).

Antiviral therapies

In the study population, RDV and/or IFNs (IFN-β1a and IFN-β1b) were used in 54% of cases, with 25.6% (254) receiving RDV, 16.5% (164) receiving IFNs (14.4% IFN-β1a, 2.1% IFN-β1b), and 12.3% (122) receiving RDV plus IFN-β1a or 1b. Other antivirals were used as follows: 12.1% (120) lopinavir/ritonavir, 7.5% (74) favipiravir, 1.8% (18) oseltamivir, 3.1% (31) ataza-

TABLE 2: Severity and clinical outcomes of COVID-19 based on antiviral regimens

	None	Antiviral therapy		
	Reference group(N=453)	RDV (N=254)	IFNs (N=164)	RDV plus INF (N=122)
O_2 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 O_2				
The need for supplemental O_2	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]

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 reference 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, IFNs; type 1 interferon beta (1-a or 1b)
*median (IQR)

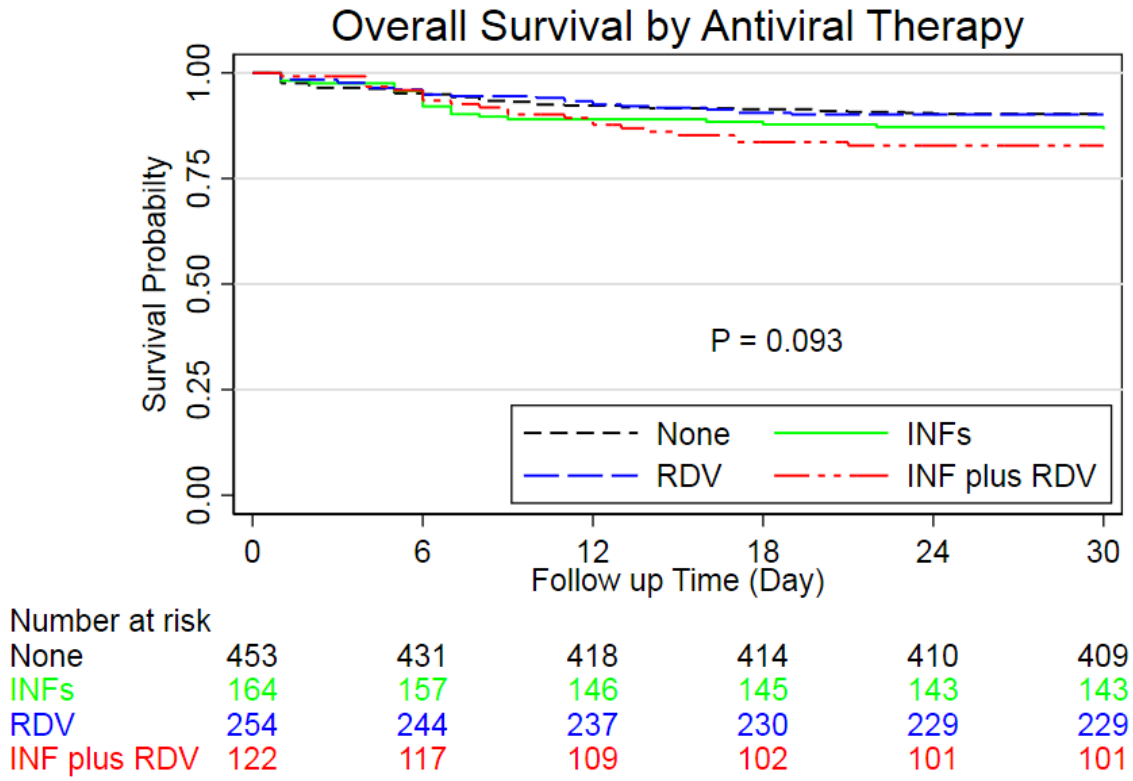

FIGURE 2. The 30-day survival rate distribution in multiple sclerosis (MS) patients with COVID-19 according to antiviral therapies
Kaplan–Meier curves showed no significant association between taking IFNs, RDV, or IFNs plus RDV and overall 30-day survival in MS patients with COVID-19.
Abbreviations: RDV; remdesivir, IFN; type 1 interferon beta (1a or 1b)

TABLE 3: The efficacy of remdesivir, type 1 interferon-β, or remdesivir plus type 1 interferon-β on 30-day survival

			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	Ref			
		smoker	0.70 (.31, 1.55)	0.37		
BMI (kg/m^2)		---	0.98 (0.92, 1.04)	0.45		
MS type	936	Relapsing-remitting	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		
O_2 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

To consider the 30-day survival probability, Cox univariate and multivariate regression models were used.
Abbreviations: anti-CD20; anti-cluster of differentiate 20, BMI; body mass index, HR; hazard ratio, 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, RDV; remdesivir
*N=number, available data

navir, 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 RDV and/or IFN therapy was prescribed more frequently in patients with O_2 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 RDV, IFNs, or a combination of IFNs and RDV. Table 2 compares the clinical outcomes of MS patients receiving RDV alone, IFNs, or a combination of RDV and IFNs, with those not receiving either RDV or IFN therapy

serving as the reference group.

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

Primary outcome

Oxygen therapy requirement during hospitalization:

Needing noninvasive supplemental oxygen (O_2) (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 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, taking at least one of the antiviral regimens was significantly associated 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 receiving 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 receiving 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 RDV (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).

Poisson regression showed no significant association between length of hospital stay and RDV use alone in the treatment regimen after adjusting for confounders (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 anti-CD20 use at the admission time and longer length of hospital stay (adjusted IRR=1.18, 95% CI 1.12 to 1.23).

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 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 benefit patients receiving an anti-CD20 antibody at the hospital admission time (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 the 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.

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

The multivariable extended Cox model was used to determine the factors that affected the survival of COVID-19 patients. The data showed no significant association between receiving any type of antiviral regimen and survival of MS patients admitted with COVID-19 (p>0.2). However, age, comorbidities, O_2 saturation ≤93% and corticosteroid use were the most important factors affecting the survival of COVID-19 patients at the time of admission (Table 3).

Discussion

In this study, we evaluated the efficacy of three antiviral regimens, namely, remdesivir (RDV), type 1 interferon β (IFN-β1a 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 shorter hospitalization (less than one week), but this effect was observed only in patients not receiving anti-CD20 agents. Taking IFNβ alone or in combination with RDV increased the hospitalization length by one week or more. One possible reason for the observed ineffectiveness of RDV and IFN therapies could be related to the delayed initiation of treatment. In our study, patients may have experienced significant disease progression prior to receiving antiviral therapy, which could diminish the efficacy of these treatments.

However, this effect was seen specifically in patients who were already on anti-CD20 agents. Our findings suggest that the efficacy of RDV in shortening the hospitalization length may be influenced by the presence of anti-CD20 agents, while the use of IFNβ in combination with anti-CD20 agents may lead to longer hospital stays. The immune response in MS patients, particularly those on anti-CD20 therapies, may differ significantly from that of other populations.

Rituximab and ocrelizumab are monoclonal antibodies that specifically target the surface molecule CD20 (Cragg et al., 2005) and are widely used to treat autoimmune diseases such as MS (Hawker et al., 2009). In our study, approximately half of MS patients admitted with COVID-19 had received 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) (Chisari et al., 2022).

Rituximab specifically binds to CD20-positive B-lymphocytes, triggers cell-mediated apoptosis, and selectively depletes CD20+ B-cell activation (Chisari et al., 2022; Hartinger et al., 2022). B cells serve various roles, such as differentiating into plasma cells to produce antibodies and facilitating the activation of T cells through antigen presentation (Lisak et al., 2012),production of soluble neurotoxic factors (Lassmann 2018), and the switch to memory cells (Jelcic et al., 2018). 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 cessation (McLaughlin et al., 1998; van der Kolk et al., 2002).

Our results suggest that the presence of anti-CD20 agents significantly affects the efficacy of RDV. Specifically, we observed that patients treated with rituximab had longer hospital stays when receiving IFNβ concurrently. This aligns with literature indicating that B-cell depletion can hinder the adaptive immune response, leading to worse outcomes in COVID-19 patients and a prolonged duration of COVID-19 infection (Chisari et al., 2022; Hueso et al., 2020; Mehta et al., 2020). In addition, the decreased immunoglobulin G levels in MS patients due to B-cell depletion (Kado et al., 2016) 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 (Furlan et al., 2021). 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. Despite the growing body of literature on antiviral therapies for COVID-19, there remains a significant gap in evidence specifically examining the efficacy of RDV in multiple sclerosis patients, highlighting the need for further research to understand its potential benefits and safety in this vulnerable population.

In trials conducted on the general population of COVID-19 patients, there is a lack of consensus on the clinical effectiveness of RDV (Okoli et al., 2024). At present, the guidelines for the use of RDV against

COVID-19 vary, leading to inconsistent recommendations, and the World Health Organization (WHO) acknowledges the uncertainty surrounding its optimal role (Chisari et al., 2022). In a clinical trial conducted by Spinner et al. (Spinner et al., 2020), 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, 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 IFNβ 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 mortality rate, hospitalization length, and 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.

According to observations in the course of virus infections such as SARS and MERS (De Wit et al., 2016), early administration of IFN-β , before starting a cytokine storm, appears to be safe and effective in treating OVID-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 IFN-β1a in treating severe COVID-19 (Hashemi-Meshkini et al., 2022; Kalil et al., 2021; Mary et al., 2020). A randomized controlled trial evaluating the efficacy of IFN-β1a in patients with severe COVID-19 showed a significantly lower 28-day mortality rate (Davoudi-Monfared et al., 2020; Jakimovski et al., 2018). Another study revealed that the combination of IFN-β1a with RDV did not show superiority over using RDV alone in hospitalized patients with COVID-19 pneumonia (Kalil et al., 2021). The WHO Solidarity Trial did not show any additional advantages of using interferons in conjunction with supportive care (Hueso et al., 2020). A more recent study also did not find any additional advantages of using IFN-β1a in combination with RDV (Hueso et al., 2020). 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 IFN-β has shown promise in treating COVID-19, its effectiveness in treating other diseases, such as MS, may differ. A literature review on interferon β in MS found that it has wide immunomodulatory effects, resulting in its efficacy in treating MS (Bellucci et al., 2023; Jakimovski et al., 2018). However, it is unclear whether IFN-β alone or in combination with other drugs is effective in treating MS patients with COVID-19.

Based on our findings, RDV and/or IFN therapy was administered more frequently in patients with affected lung(s) or in patients with O_2 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.

Some limitations in our study are worth noting. Firstly, it is important to note that the efficacy of antiviral therapy may be associated with the number of days after symptom onset; however, we did not have access to this data. The variability in the time interval between symptom onset and treatment initiation—a crucial factor for evaluating antiviral drugs—remains a limitation of our study. Secondly, we lacked information on the initiation date of oxygen supplementation or invasive oxygen therapy, which could further influence patient outcomes. Thirdly, recent studies have shown an increased incidence of severe COVID-19 among patients treated with anti-CD20 therapies such as rituximab or ocrelizumab (Januel et al., 2023). While our analysis accounted for anti-CD20 therapies as a confounding factor to clarify the impact of antiviral therapy on COVID-19 severity, this focus may limit the generalizability of our findings to patients receiving other DMTs. Future studies should consider including a broader range of DMTs to provide a more comprehensive understanding of how various treatments interact with antiviral therapy and influence severity in hospitalized MS patients with COVID-19. Finally, another critical limitation is the absence of detailed data on vaccination status among participants. During the data collection period from March 2019 to

August 2021, only 2.9% (29 patients) of our study received at least one dose of a COVID-19 vaccine before hospitalization. Due to this low vaccination rate, vaccination status was not included in the analyses to control for potential bias.

Conclusion

There is insufficient evidence to guide clinical recommendations on using antiviral agents in MS patients for COVID-19 treatment. 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. Patients who are not on anti-CD20 therapies may respond differently to antiviral treatments, and recognizing these differences is crucial for clinical practice. In the case of RDV, administering 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 MS 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 disease-modifying therapies 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 using antiviral agents in MS patients with COVID-19.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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