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Coronavirus Pandemic

Comparing the clinical outcomes of Remdesivir and Interferon beta-1a in hospitalized COVID-19 patients: A cross-sectional retrospective single-center study

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Abstract

Introduction: The effectiveness of remdesivir (RDV) and interferon beta-1a (IFNβ-1a) was assessed and compared in patients hospitalized with *coronavirus disease of 2019 (*COVID-19).

Methodology: A total of 162 hospitalized COVID-19 patients were divided into two groups: the RDV group and the IFNβ-1a group. Through laboratory tests and a physical examination, the patient's clinical condition was evaluated.

Results: RDV and IFNβ-1a treatments significantly decreased fever, cough, shortness of breath, and weakness in COVID-19 patients (All $p < 0.001$). RDV treatment significantly decreased shortness of breath, erythrocyte sedimentation rate (ESR), and creatinine, relative to IFNβ-1a treatment ($p < 0.03$, $p = 0.001$, and $p < 0.004$, respectively). RDV treatment significantly decreased Lactate Dehydrogenase (LDH) in COVID-19 patients ($p = 0.006$). The mean time of hospitalization was 8.9 days in the RDV group and 8.2 days in the IFNβ-1a group. There was no statistical difference between the two groups. The IFNβ-1a group had a considerably lower rate of intensive care unit (ICU) admission than the RDV group ($p = 0.006$).

Conclusions: No difference in clinical outcomes was found between RDV and IFNβ-1a treatments. RDV was more effective than IFNβ-1a in moderating the inflammatory response in COVID-19 patients by reducing LDH and ESR. The IFNβ-1a group had a considerably lower rate of ICU admission than the RDV group.

Key words: Remdesivir; interferon beta-1a; hospitalized patients; COVID-19.

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Introduction

On March 11, 2020, the World Health Organization (WHO) announced that the coronavirus disease of 2019 (COVID-19) is a pandemic, driven by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which posed a serious threat to global health and placed substantial strain on healthcare systems around the world [1]. More than 641 million infections were reported, with over 6.8 million people dying as a result. Every day, around 270,000 cases of infection are recorded [2]. Even though widespread use of COVID-19 vaccinations has considerably lowered hospitalization and death rates, administration of medications is still required for the care of hospitalized patients. Many clinical guidelines from the WHO, the Infectious Diseases Society of America, and the National Institutes of Health (NIH) have suggested the administration of various medications, such as glucocorticoids, antiviral agents, anticoagulants, etc. [3].

Remdesivir (RDV) was the first antiviral to be granted emergency approval by the European Medicines Agency, with a specific use to treat cases of COVID-19 illness with pneumonia, needing supplementary oxygen [4]. RDV is a nucleotide analog prodrug that suppresses RNA polymerase activity in some pathogenic coronaviruses by intracellularly metabolizing into an analog of ATP. RDV has been

evaluated in COVID-19 because preclinical models of SARS-CoV-2 have demonstrated antiviral efficacy both *in vitro* and *in vivo* [5,6]. In the majority of published trials, RDV often demonstrated a shorter recovery time without affecting important endpoints like death or the requirement for endotracheal intubation in patients hospitalized with moderate-to-severe COVID-19 [7-9]. Therefore, ongoing clinical trials are being conducted to determine the RDV efficiency in the different subgroups of patients [10].

Interferons (IFNs) are naturally created by virus-infected cells to warn other cells about a threat and to induce an antiviral state in uninfected cells. IFNs also stimulate immune cells to fight off a viral infection. In addition, patients with a severe coronavirus infection frequently exhibit inadequate or late IFN production [11]. Interferon-1a (IFN-1a) stood out as a promising treatment for COVID-19 for several reasons. First, IFNβ-1a exhibits antiviral effects against SARS-CoV-2 *in vitro*. Secondly, SARS-CoV-2 infection has been linked to inadequate or irregular type I IFN responses. Additionally, observation and functional investigations have revealed that a greater probability of severe COVID-19 is connected with a lack of type I IFN responses, either by neutralizing autoantibodies against type of IFNs or hereditary gene mutations [12].

These preclinical and clinical findings support the notion that treatment with RDV and IFNβ-1a could improve outcomes in COVID-19 patients. In this report, our purpose was to assess and compare the therapeutic effectiveness of RDV alone and IFNβ-1a alone in hospitalized COVID-19 patients.

Methodology

Study design and setting

The present research involved a group of COVID-19 patients treated with RDV and IFNβ-1a, who were hospitalized at Razi Hospital of Guilan University of Medical Sciences from September 2020 to March 2021. This investigation adheres to the Helsinki Declaration. The Ethics Committee of Guilan University of Medical Sciences accepted the study (IR.GUMS.REC.1400.353). Informed consent to use the de-identified data was given to each patient.

Study inclusion criteria

(1) Age ≥ 18 years, with pneumonia necessitating additional oxygen therapy; (2) diagnosed pneumonia by CT (computed tomography) scan; (3) tachypnea (breathing > 30 per minute); (4) hypoxia (oxygen saturation < 94% on room air or PaO_2/FiO_2 (partial pressure of oxygen in the arterial blood to fractional inspired oxygen) < 300 mmHg); or (5) imaging showing lung involvement > 50%.

The exclusion criteria

(1) Pregnancy or breastfeeding; (2) aspartate transaminase (AST) or alanine transaminase (ALT) levels larger than 5 times the upper limit of normal; (3) moderately or severely immunocompromised patients; (4) getting additional antiviral medications, like tocilizumab; and (5) patients not getting corticosteroids (due to probable effect of corticosteroids on disease course, all included patients had received corticosteroids) [13].

The necessary data were taken from the hospital's electronic medical records. These data comprised patients' age, COVID-19 symptoms, clinical parameters, pre-existing diseases, the severity of COVID-19, ventilator support, lung CT scan abnormalities, and lab results (Table 1). The patients were divided into two groups: RDV and IFNβ-1a treatment.

The COVID-19 severity was classified as moderate when lower respiratory tract disease was detected during clinical evaluation or imaging, and the person's oxygen saturation (SpO_2) was less than 94% on room air at sea level. It was classified as severe in individuals who have SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%. For those with respiratory failure, septic shock, and/or multiple organ dysfunction, it was rated as critical [14].

Procedures

For the RDV group, intravenous RDV was given in a single dose of 200 mg on day 1, and then 100 mg once a day for 5 days, within 48 hours of admission. For the IFNβ-1a group, subcutaneous injection of IFNβ-1a at a dose of 250 μg began on the first day of hospitalization and continued every other day until the fifth day. Also, patients of both groups received 6 mg/day of intravenous dexamethasone for 10 days or until discharged. Patients with acute respiratory distress syndrome needing ICU (intensive care unit) hospitalization were given dexamethasone 20 mg once a day for 5 days, then 10 mg once daily for 5 days.

Statistical analysis

Quantitative data were described using the mean and standard deviation (SD), whereas qualitative data were described using frequency and percentage.

Levene's test and the Kolmogorov-Smirnov test were employed to check the homogeneity of variances and the normality assumption, respectively. Independent t-tests, paired t-tests, McNemar's test, Pearson's chi-square test, and Fisher's exact test were used to analyze the data. Also, in cases where there was a significant difference before the intervention, quadratic nonparametric ANCOVA was employed to compare the intervention's needs. SPSS software version 28 was used for the data analysis. All tests had a significance threshold of 0.05.

Results

This cross-sectional, retrospective, single-center study included 302 people who were admitted with a COVID-19 diagnosis. Out of the 200 enrolled patients, 81 were assigned to each research group by the inclusion criteria. The mean age in the RDV and IFNβ-1a groups was 59.06 and 55.59 years, respectively. As is shown in Table 1, the clinical state of the patients at study admission was similar in both treatment groups. The most frequent symptoms in all groups were shortness of breath, coughing, weakness, and fever or chills. There were no considerable differences in common comorbidities between the groups. Arterial hypertension and diabetes were the most relevant pre-conditional diseases. The prevalence for the most common comorbidities was hypertension (25.9% in the RDV group and 28.4% in the IFNβ-1a group), diabetes (21% in the RDV group and 20.3% in the IFNβ-1a group), ischemic heart disease (13.6% in the RDV group and 14.8% in the IFNβ-1a group), hyperlipidemia (12.3% in the RDV group and 13.6 % in the IFNβ-1a group), lung disease (7.4% in the both group),

Table 1. Patients' clinical status on admission day.

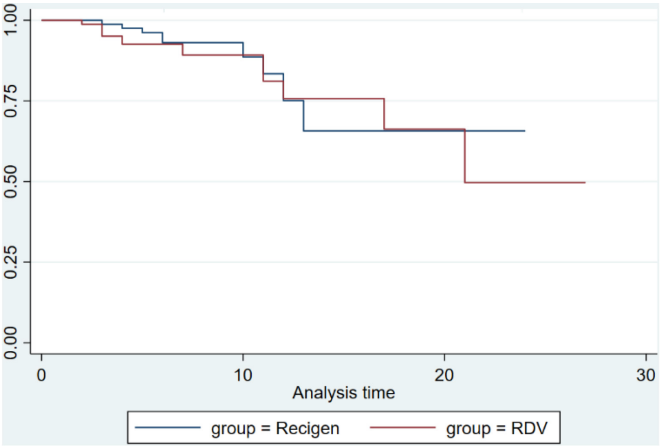
	RDV group (n = 81)	IFNβ-1a group (n = 81)	*p*
Age (years), mean (SD)	59.06 (15.71)	55.59 (15.69)	0.162
Symptoms			
Fever/chills, n (%)	44 (54.3%)	48 (59.3%)	0.632
Cough, n (%)	51 (63%)	58 (71.6%)	0.236
Shortness of breath, n (%)	60 (74.1%)	58 (71.6%)	0.581
Weakness, n (%)	50 (61.7%)	44 (54.3%)	0.339
Sore throat, n (%)	2 (2.5%)	2 (2.5%)	1.000
Headache, n (%)	2 (2.5%)	9 (11.1%)	0.105
Nausea/vomiting, n (%)	12 (14.8%)	20 (24.7%)	0.167
Diarrhea, n (%)	6 (7.4%)	8 (9.9%)	0.579
Clinical parameters			
SBP (mmHg), mean (SD)	116.73 (16.01)	121.02 (20.87)	0.143
DBP (mmHg), mean (SD)	72.37 (10.65)	74.80 (11.68)	0.161
Respiratory rate (acts/min), mean (SD)	20.55 (7.79)	19.36 (2.72)	0.201
Pulse rate (per minute), mean (SD)	87.14 (14.03)	89.96 (13.83)	0.262
Oxygen saturation, mean (SD)	91.84 (5.16)	92.24 (4.90)	0.791
Pre-conditionally diseases			
Hypertension	21 (25.9%)	23 (28.4)	0.725
Diabetes	17 (21.0%)	16 (20.3%)	0.909
Lung disease	6 (7.4%)	6 (7.4%)	1
Renal disease	3 (3.8%)	4 (4.9%)	0.712
Ischemic heart disease	11 (13.6%)	12 (14.8%)	0.822
Hyperlipidemia	10 (12.3%)	11 (13.6%)	0.816
Hypothyroidism	4 (4.9%)	5 (6.2)	0.732
Others	9 (11.1%)	4 (4.9%)	0.149
Severity of COVID-19			**0.268**
Moderate	38 (46.9%)	36 (44.4%)	0.75
Severe	34 (42.0%)	41 (50.6%)	0.27
Critical	9 (11.1%)	4 (4.9%)	0.14
Ventilator support			
Not requiring supplemental oxygen	21 (25.9%)	24 (29.6%)	0.89
Oxygen support with nasal	40 (49.4%)	35 (43.2%)	0.43
Oxygen support with face mask	20 (24.7%)	22 (27.2%)	0.72
Lung CT abnormalities, n (%)			
Mild	6 (12.2%)	8 (19.5%)	0.602
Moderate	14 (28.6%)	12 (29.3%)	0.602
Severe	29 (52.9%)	21 (51.2%)	0.602
Laboratory findings			
WBC (10^9/L), mean (SD)	8.56 (7.48)	8.39 (4.35)	0.939
ESR (mm/hr), mean (SD)	60.69 (24.66)	58.83 (28.28)	0.658
CRP (mg/L), mean (SD)	1.90 (0.83)	2.03 (0.78)	0.628
BUN (mg/d), mean (SD)	24.77 (22.84)	23.62 (20.51)	0.736
LDH (U/L), mean (SD)	1061.35 (1005.08)	848.46 (353.11)	0.075
Creatinine (mg/dL), mean (SD)	1.31 (0.97)	1.52 (1.99)	0.399

hypothyroidism (4.9% in the RDV group and 6.2% in the IFNβ-1a group), and renal disease (3.8% in the RDV group and 4.9% in the IFNβ-1a group). It should be mentioned that the baseline COVID-19 severity was the same. Among all patients, 75 (46.29%) had severe COVID-19 (34 in the RDV group and 41 in the IFNβ-1a group), whereas 13 (8.02%) had critical COVID-19 (9 in the RDV group and 4 in the IFNβ-1a group).

Likewise, there were no considerable differences in ventilator support between the groups. The overall percentage of patients in the RDV group and the IFNβ-1a group that needed nasal oxygen support was 49.4% and 43.2%, respectively. Additionally, 24.7% of patients in the RDV group and 27.2% in the IFNβ-1a group needed face mask oxygen support. During the entire treatment period, 25.9% of patients in the RDV group and 29.6% of patients in the IFNβ-1a group did not require any oxygen support. On the day of admission, chest X-ray and lung CT were done. Of the patients, 55.5% (90 of 162 individuals, 49 in the RDV group and 41 in the IFNβ-1a group) had positive chest abnormalities. Patients with severe pneumonia in the IFNβ-1a group were 51.2% and in the RDV group were 52.9%. No considerable differences existed across the groups.

As shown in Table 2, neither the clinical parameters nor the symptoms varied significantly between the groups. A comparison of the secondary outcomes between the two research groups revealed no differences, except for ICU admission. The mean time of hospitalization in the RDV group was 8.91 ± 4.9 days, and in the IFNβ-1a group was 8.2 ± 4.2 days.

Figure 1. The Kaplan-Meier plot shows the survival of people under each treatment over time.



There was no statistically significant difference between the two groups. Mortality was seen in 22 patients, with 13 patients in the RDV group (16%) and 9 patients in the IFNβ-1a group (11.1%), but there was no noticeable difference between the two groups (Kaplan-Meier plot and log-rank test, $p = 0.587$, Figure 1). The rate of ICU admission varied significantly between the groups. Seven patients were admitted to the ICU in the IFNβ-1a group and twenty in the RDV group; this difference was statistically significant (Chi-Square test, $p = 0.006$). Nine out of twenty patients admitted to the ICU in the RDV group passed away. There was no significant difference in the laboratory parameters between the groups, except for the Erythrocyte Sedimentation Rate (ESR) and creatinine

Table 2. Patients' clinical status during the treatments.

	RDV group (n = 81)	IFNβ-1a group (n = 81)	*p*
Symptoms			
Fever/chills, n (%)	1 (1.2%)	1 (1.2%)	1
Cough, n (%)	3 (3.7%)	2 (2.5%)	1
Shortness of breath, n (%)	1 (1.2%)	3 (3.7%)	0.620
Weakness, n (%)	5 (6.2%)	2 (2.5%)	0.443
Clinical parameters			
SBP (mmHg), mean (SD)	111.12 (12.62)	112.24 (14.91)	0.615
DBP (mmHg), mean (SD)	69.29 (9.59)	70.64 (9.44)	0.379
Respiratory rate (acts/min), mean (SD)	19.93 (2.38)	19.83 (1.90)	0.763
Pulse rate (per minute), mean (SD)	82.01 (12.49)	82.11 (10.63)	0.956
Oxygen saturation, mean (SD)	94.54 (5.12)	95.27 (4.29)	0.359
Outcomes			
Hospital stay (days), mean (SD)	8.91 (4.90)	8.20 (4.20)	0.329
ICU admission, n (%)	20 (24.7%)	7 (8.6%)	0.006
ICU death, n (%)	9 (11.1%)	7 (8.6%)	0.599
Death in the hospital, n (%)	4 (4.9%)	2 (2.5%)	0.681
Death, n (%)	13 (16.0%)	9 (11.1%)	0.360
Laboratory findings			
WBC (10^9/L), mean (SD)	11.43 (3.77)	8.49 (3.67)	0.863
ESR (mm/hr), mean (SD)	47.58 (18.02)	62.14 (13.85)	0.001
CRP (mg/L), mean (SD)	2.09 (0.49)	2.06 (0.55)	0.653
BUN (mg/d), mean (SD)	34.37 (20.44)	31.39 (19.51)	0.345
LDH (U/L), mean (SD)	767.02 (288.42)	835.75 (410.43)	0.220
Creatinine (mg/dL), mean (SD)	1.30 (0.72)	1.85 (1.53)	0.004

level. The mean of the ESR and creatinine in the RDV group was considerably less than that of the IFNβ-1a group (Chi-Square test, $p = 0.001$, and $p = 0.004$, respectively).

As shown in Tables 2 and 3, the two study groups were comparable in all clinical characteristics and laboratory measures. The RDV and IFNβ-1a treatments significantly decreased fever, cough, shortness of breath, and weakness in COVID-19 patients (Chi-Square test, all $p < 0.001$). The RDV treatment considerably reduced the shortness of breath in comparison to the IFNβ-1a treatment (Chi-Square test, $p = 0.03$). In COVID-19 patients, the IFNβ-1a treatment considerably raised oxygen saturation and significantly lowered systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) (Paired t-test, $p < 0.001$, $p = 0.003$, $p = 0.02$, and $p < 0.001$, respectively). Similar results were also observed in RDV treatment. The RDV treatment considerably raised oxygen saturation and significantly decreased SBP and PR in the COVID-19 patients (Paired t-test, $p < 0.001$, $p = 0.10$, and $p = 0.012$, respectively).

On the admission day and the day before discharge/death, laboratory parameters were collected. In COVID-19 patients, the IFNβ-1a treatment significantly increased creatinine levels relative to the RDV treatment (Paired t-test, $p < 0.02$). The RDV treatment significantly increased the white blood count (WBC) relative to the IFNβ-1a treatment (Paired t-test, $p < 0.001$). The RDV treatment significantly decreased the ESR relative to the IFNβ-1a treatment (Paired t-test, $p < 0.001$). Moreover, the RDV treatment significantly decreased Lactate Dehydrogenase (LDH) in COVID-19 patients (Paired t-test, $p = 0.006$). The RDV and IFNβ-1a treatments significantly increased the blood urea nitrogen (BUN) in COVID-19 patients (Paired t-test, all $p < 0.001$), but there were no considerable differences between the treatments.

Discussion

The current investigation was a cross-sectional, retrospective, single-center study that assessed and compared the efficacy of treatment with RDV and IFNβ-1a in COVID-19 patients. In the current study, the RDV and IFNβ-1a treatments showed substantial improvements in fever, cough, shortness of breath, weakness, and oxygen saturation in the COVID-19 patients. The RDV treatment significantly decreased shortness of breath, ESR, and creatinine, relative to IFNβ-1a treatment. Moreover, the RDV treatment significantly reduced LDH in COVID-19 patients. However, RDV treatment significantly increased WBC in the COVID-19 patients, relative to the IFNβ-1a. The RDV and IFNβ-1a treatments significantly increased the BUN in the COVID-19 patients. The IFNβ-1a group has a considerably lower rate of ICU admission than the RDV group.

The wild-type, alpha, and delta strains of SARS-CoV-2 predominated and corresponded with the second and third waves of the pandemic. Vaccines were originally being produced during this time, and subsequently began to be used more and more frequently. In the 2nd and 3rd waves of the pandemic, shortness of breath, cough, weakness, and fever/chills were the most frequent symptoms [15]. According to the present data, 54.31% of the patients had severe and critical COVID-19, and 55.5% of the patients had positive chest abnormalities. In the current study, RDV and IFNβ-1a improved clinical outcomes in COVID-19 patients. As the primary outcome, the clinical

Table 3. Patients' clinical response comparison.

	Within group difference		Between group difference
	RDV group (n = 81)	IFNβ-1a group (n = 81)	
	p	*p*	*p*
Symptoms			
Fever/chills	< 0.001	< 0.001	0.999
Cough	< 0.001	< 0.001	0.999
Shortness of breath	< 0.001	< 0.001	0.035
Weakness	< 0.001	< 0.001	0.443
Physiological parameters			
SBP	0.010	0.003	0.615
DBP	0.064	0.021	0.379
Respiratory rate	0.517	0.101	0.763
Pulse rate	0.012	< 0.001	0.956
Oxygen saturation	< 0.001	< 0.001	0.359
Laboratory findings			
WBC	< 0.001	0.939	< 0.001
ESR	< 0.001	0.230	< 0.001
CRP	0.254	0.818	0.653
BUN	< 0.001	< 0.001	0.345
LDH	0.006	0.798	0.220
Creatinine	0.890	0.026	0.004

implications did not differ between the IFNβ-1a and the RDV groups, with some exceptions. The RDV treatment significantly decreased shortness of breath, ESR, and creatinine, relative to IFNβ-1a treatment.

The RDV is an FDA-approved therapy in hospitalized COVID-19 patients 12 years of age and older, weighing at least 40 kg. Only healthcare facilities equipped to deliver acute care with inpatient hospital care should be used to administer that [16]. On the application of RDV in COVID-19, several randomized trials have been performed [7]. According to Spinner *et al*., five days of RDV treatment increased the likelihood of clinical improvement [9]. Discrepantly, Mahajan *et al*. reported that a five-day treatment with RDV did not improve clinical outcomes in patients suffering from moderate to severe COVID-19 [16]. According to research by Ader *et al*., the application of RDV during the care of hospitalized COVID-19 patients neither results in clinical improvements on days 15 or 29 nor decreased mortality or SARS-CoV-2 RNA copy number [17]. The data of the present study showed that RDV improved clinical outcomes in COVID-19 patients. Modeling studies of SARS-CoV-2 infection have shown that early administration of antivirals, before reaching the peak viral load, is important for antiviral effectiveness. This might explain the inconsistency in the outcome of different studies [18].

In patients with COVID-19 pneumonia, the laboratory results highlighted that LDH is secreted during tissue destruction and participates in a variety of pathophysiological processes. Multiple investigations have found that LDH can predict poor results and a bad prognosis in cancer patients [19-21]. Aggarwal *et al.* evaluated laboratory outcomes and clinical aspects of COVID-19 hospitalized patients and found an increased level of LDH in 80% of them. LDH appears to be a useful biomarker to follow patients with severe COVID-19 [21]. Since LDH is found in the lung tissues, patients with severe COVID-19 infection discharge more LDH into the bloodstream, demonstrating a severe form of interstitial pneumonia. As a result, it appears that the LDH level anticipates COVID-19 severity and death in patients with viral infections and is connected to a worse prognosis [22].

ESR is a typical hematological test that identifies and tracks the rise in inflammatory activity produced by one or more diseases, such as infections in the body [23]. Some investigations have suggested that ESR functions as an inflammatory biomarker in the emergence of severe COVID-19 [24]. According to Go *et al.*, elevated ESR rates have been linked to respiratory failure, and their measurement can be utilized to forecast interstitial lung disease and mortality in dermatomyositis [24]. The results of our study showed that treatment with RDV reduced LDH in COVID-19 patients. The RDV also significantly reduced ESR compared to IFNβ-1a, indicating that RDV is more effective in mitigating the inflammatory response in COVID-19 patients than IFNβ-1a. Also, our study showed that RDV significantly increased WBC in COVID-19 patients. A previous study by Sedighi *et al.* found that RDV therapy dramatically lowered ESR and significantly increased WBC in COVID-19 patients, which is in line with our findings [25].

RDV had no positive impact on the length of hospitalization, ICU admission, and mortality in COVID-19 patients, compared to the IFNβ-1a group. According to Psicoya *et al.*, RDV did not substantially reduce the mortality rate [16]. Another comprehensive study conducted by Rochwerg *et al.* found that while RDV may lower mortality, it has no significant effect on the length of hospitalization [26]. Regarding the length of hospitalization, it is noteworthy that RDV has a 5-day therapy duration that prohibits the discharge of patients less than 5 days. This implies that even if the clinical symptoms have resolved, patients must remain in the hospital to complete the course of medication [27]. In this study, the average length of hospitalization for the RDV group was 8.9 days. Hadadi *et al.* reported that RDV therapy failed to enhance 9-month survival in COVID-19 patients or patients with severe illness. They showed that RDV therapy could improve in-hospital survival in patients who had severe COVID-19 [27]. The timing of RDV administration may play a crucial role in terms of effectiveness in reducing mortality. Early RDV therapy may improve clinical results and lower mortality rates [28]. As a result, to optimize the potential advantages of RDV, future studies should investigate the best time to take RDV based on the severity of the disease.

Our findings revealed that treating COVID-19 patients with IFNβ-1a improved clinical outcomes in COVID-19 patients. The results supported Monk *et al*.'s findings that COVID-19 hospitalized patients tolerated IFNβ-1a fairly well, with a range of clinical results indicating an improvement in the health of COVID-19 patients [29]. The effectiveness of IFNs against the coronavirus family was initially observed in SARS-CoV-2. After the SARS pandemic subsided, IFN was once again suggested as a cure for another coronavirus, namely Middle East Respiratory Syndrome (MERS). IFNs, particularly type I, are thus still intriguing alternatives for current epidemics [30]. IFNβ-1a may be a useful treatment for SARS-CoV-2

infections, according to Hensley *et al.* Accordingly, IFN-1a showed strong antiviral properties and an acceptable safety profile, indicating its effectiveness in treating coronavirus [31]. In reaction to viral infections, the body naturally produces IFNs. These can activate interferon-stimulated genes (ISGs) and raise angiotensin-converting enzyme inhibitor 2 (ACE2). Although overexpression of ACE2 may increase the risk of SARS-CoV-2 infection, it may protect the lung cells from extra damage by inactivating angiotensin [30].

As a discrepancy, Sosa *et al.* found that patients with confirmed SARS-CoV-2 infection who received early IFNβ-1a had a substantially decreased duration of hospitalization, death, ICU admission, and intubation rate [31]. The current study found that while IFNβ-1a therapy reduced ICU admissions for COVID-19 patients compared to RDV therapy, there were no substantial differences in hospitalization length or mortality rates between the two groups. IFNβ-1a recipient patients with moderate/critical COVID-19 experienced fewer ICU admissions than RDV. It is of note that all ICU-admitted patients in the IFNβ-1a group passed away. There are several reasons why IFNβ-1a might not enhance ICU survival rates; in comparison to IFNβ-1a therapy, RDV treatment significantly lowered ESR. Additionally, RDV significantly decreased LDH in COVID-19 patients. A recent pooled analysis of 9 studies revealed an association between elevated LDH levels and disease severity and mortality [22]. Elevated ESR readings have been related to respiratory failure, and their measurement can predict mortality in dermatomyositis and interstitial lung disease [24]. Early IFNβ-1a therapy may significantly decrease mortality rates. If administered too late, its potential benefits may be diminished [32]. Patients hospitalized in the ICU frequently have several comorbidities and differing responses to treatment. IFNβ-1a may not be effective for many patients, particularly those with severe pre-existing conditions [33]. In this study, arterial hypertension and diabetes were the most relevant pre-existing diseases. The combination of diabetes and hypertension significantly increases the risk of severe COVID-19 outcomes, including hospitalization, ICU admission, and mortality [34].

Rahmani *et al*. conducted another randomized clinical trial, in which the IFNβ-1b treatment showed notable clinical improvement, with a noteworthy decrease in mechanical ventilation and ICU admission [35]. A systematic review and meta-analysis of randomized controlled trials (RCTs) by Chen *et al.* was dedicated to investigating the efficacy of IFN-β-containing regimens in patients with COVID-19. A non-significant difference was noted in the 28-day mortality rate for any cause between the study and control groups. The study group was admitted to a lower-rate ICU than the control group. Subsequently, IFN-β was not connected with an increased risk of any adverse or serious adverse events when compared with the control group. Although IFN-β does not contribute to increasing the survival of hospitalized patients with COVID-19, it may assist in reducing the risk of ICU admission [36]. In contrast to the findings of the current study, Davoudi-Monfared *et al.* reported a randomized clinical trial of IFNβ-1a effectiveness and safety in COVID-19 patients. It proved that combining IFNβ-1a with the national protocol drugs not only considerably raised the discharge rate on day 14 but also diminished 28-day mortality. Patients' survival rates improved dramatically after receiving IFN-1a in the early stages of the disease [37]. Inadequate laboratory data limited our capacity to assess the clinical effectiveness of IFNβ-1a and RDV in critically ill COVID-19 patients in the ICU. Considerably, randomized clinical trials with a large sample size are needed to assess IFN-β's benefit precisely.

There were some limitations to the present study. First, this study was carried out at a single center on the Iranian population; future multicenter randomized clinical trials in various demographics are necessary. Secondly, we conducted a short-term follow-up examination. Thirdly, the absence of COVID-19 control patients was still another drawback. This is so because we had a staffing shortfall during COVID when the study was done. Fourthly, we did not have enough information about Laboratory findings of COVID-19 patients, such as C-Reactive Protein (CRP). Yet, a lack of CT scan after the end of treatment is another problem.

Conclusions

According to the study findings, RDV alone and IFNβ-1a alone are effective in improving the clinical results of patients with COVID-19, in a real-world setting in Iran. The clinical outcome was not statistically different between the IFNβ-1a and the RDV groups, with some exceptions. The RDV treatment significantly decreased shortness of breath, ESR, and creatinine relative to IFNβ-1a treatment. Moreover, RDV significantly reduced LDH in COVID-19 patients. Also, the IFNβ-1a group had a considerably lower rate of ICU admission than the RDV group. We hope that this study will help clarify the IFNβ-1a and

the RDV role in COVID-19 treatment.

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Conflict of interest

No conflict of interest is declared.

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