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Remdesivir experience in patients diagnosed with COVID-19 in a tertiary hospital

Üçüncü basamak bir hastanede COVID-19 tanılı hastalarda remdesivir deneyimi

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Abstract

Purpose: Remdesivir is an adenosine nucleotide analog antiviral drug recommended in these treatment combinations. While vaccine and drug studies are underway in the treatment of COVID-19, remdesivir is also being studied in terms of efficacy, safety, and potential side effects. Therefore, we aimed to share our experiences of patients who were diagnosed with COVID-19 and treated with remdesivir in our hospital.

Material and method: Patients over 18 years of age, who were diagnosed with COVID-19 in our hospital between March 15 and March 30, 2020, based on positive RT-PCR and/or thoracic computed tomography (CT) results studied from nasopharyngeal samples, were screened retrospectively. Those who had received Remdesivir treatment were included in our study.

Results: 23 patients were included in our study. Eighteen (79.2%) of the patients were male and 5 (20.8%) were female. Remdesivir initiation time was 8.4±2.6 days from the onset of symptoms and 6±2.6 days from the time of diagnosis. In the follow-up period, we had to hospitalize 18 patients (78.2%) in the intensive care unit (ICU). 14 (60.8%) needed a mechanical ventilator. Post-treatment follow-up showed that 15 (65.2%) recovered, and 8 (34.8%) resulted in mortality.

Conclusion: Since inflammation is as critical as the replication of the virus in the pathogenesis of COVID-19 disease, the use of remdesivir in combination with other antiviral and anti-cytokine therapies may increase the effectiveness. We believe that we need new studies in this regard.

Key words: COVID-19, remdesivir, treatment.

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Öz

Amaç: Remdesivir, COVID-19 tedavi kombinasyonlarında önerilen bir adenozin nükleotid analogu antiviral bir ilaçtır. COVID-19 tedavisinde aşı ve ilaç çalışmaları devam ederken, remdesivir de etkinlik, güvenlik ve olası yan etkiler açısından incelenmektedir. Bu nedenle hastanemizde COVID-19 tanısı alan ve remdesivir ile tedavi edilen hastalarımızın deneyimlerimizi paylaşmayı amaçladık.

Gereç ve yöntem: 15 Mart-30 Mart 2020 tarihleri arasında, hastanemize başvuran ve nazofarengeal örneklerden çalışılan RT-PCR testi pozitif olan ve/veya toraks bilgisayarlı tomografi (BT) sonuçlarına göre COVID-19 tanısı alan 18 yaş üstü hastalar retrospektif olarak tarandı. Remdesivir tedavisi alanlar çalışmamıza dahil edildi.

Bulgular: Çalışmamıza 23 hasta dahil edildi. Hastaların 18'i (%79,2) erkek, 5'i (%20,8) kadındı. Remdesivir başlama süresi semptomların başlangıcından itibaren 8,4±2,6 gün ve tanı anından itibaren 6±2,6 gündü. Takip döneminde 18 hastayı (%78,2) yoğun bakım ünitesine (YBÜ) yatırmak zorunda kaldık. 14'ünde (%60,8) mekanik ventilatöre ihtiyaç duydu. Tedavi sonrası takiplerinde ise 15 hastanın (%65,2) taburcu edildiği ve 8 hastanın (%34,8) ölümle sonuçlandığını gösterildi.

Sonuç: COVID-19 hastalığının patogenezinde virüsün replikasyonu kadar inflamasyon da önemli olduğundan remdesivirin diğer antiviral, antisitokin tedaviler ile kombine şekilde kullanımı ile etkinliğinde artış olabileceği ve bu konuda da yapılacak yeni çalışmalara ihtiyaç olduğu düşünülmüştür.

Anahtar kelimeler: COVID-19, remdesivir, tedavi.

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Introduction

On December 31, 2019, the World Health Organization (WHO) reported pneumonia cases of unknown etiology in Wuhan, China's Hubei province. On January 7, 2020, the disease was reported to be caused by a new coronavirus (2019-nCoV) which was not previously detected in humans, and this new disease was named COVID-19. In March, the WHO recognized the current situation as a pandemic due to the spread of the virus in many countries. The first case in our country was announced on March 11, 2020, and the pandemic continues at full speed in Turkey and the rest of the world [1].

Many protocols have been developed to treat COVID-19 since the first day it emerged, and many clinical studies on these treatment methods have been initiated and are ongoing. However, no effective treatment has been found yet in this regard. Antimalarial drugs such as chloroquine (CQ) and hydroxychloroquine (HCQ); antiviral drugs such as favipiravir (FAV), lopinavir/ritonavir, and remdesivir; interleukin antagonists such as tocilizumab and anakinra; recombinant human monoclonal antibodies; steroid therapies; immunoglobulin therapies; anticoagulant therapies and convalescent plasma are used in treating the disease and preventing its complications [2].

Remdesivir is an adenosine nucleotide analog antiviral drug recommended in these treatment combinations. It was originally developed to treat Ebola disease and has been effective in vitro for all coronaviruses, including 2019-nCoV [3]. It has also been used in the treatment of COVID-19 disease in Turkey and all over the world. While vaccine and drug studies are underway in the treatment of COVID-19, remdesivir is also being studied in terms of efficacy, safety, and potential side effects. Therefore, we aimed to share our experiences of patients who were diagnosed with COVID-19 and treated with remdesivir in our hospital.

Materials and methods

Patients over 18 years of age, who were diagnosed with COVID-19 in our hospital between March 15 and March 30, 2020, based on positive RT-PCR and/or thoracic computed tomography (CT) results studied from nasopharyngeal samples, were screened retrospectively. Those who had received Remdesivir treatment were included in our study. All of the patients receiving Remdesivir received the drug intravenously for 5 days in a loading dose of 1x200 mg/day and a maintenance dose of 1x100 mg/day, following the standard procedure. Supportive treatments, except for antiviral therapy, such as low molecular weight heparin, vitamin C, and steroid were applied to all patients in the same way in patients with severe pneumonia.

COVID-19 pneumonia severity

Mild to moderate pneumonia; Patients with symptoms such as fever, muscle/joint pain, cough, and sore throat who had a respiratory rate of <30/min, SpO2 level >90% in room air, and signs of mild to moderate pneumonia on chest X-ray or tomography;

Severe pneumonia; Patients with symptoms such as fever, muscle/joint pain, cough, and sore throat who had a tachypnea (≥30/min), SPO_2 level ≤90% in room air, and signs of bilateral diffuse pneumonia on chest X-ray or tomography [1]. Data about the patients were generated in the SPPS 20.0 program and statistical analysis was performed. $P<0.05$ was considered statistically significant. This study was approved by Ethics Committee of University of Health Sciences Antalya Trainning ang Research Hospital with the date 26.11.2020 and the number 18/8. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Our study included twenty-three patients admitted in our hospital after being diagnosed with COVID-19 and treated with remdesivir. All patients were diagnosed based on the (+) result in RT-PCR and the presence of COVID-19 pneumonia signs in CT. 22 patients included in the study had RT-PCR positivity and pneumonia findings on CT. One patient was diagnosed only with pneumonia findings on CT. SPO_2 level of the patients was ≤94 when remdesivir treatment was initiated. Eighteen (79.2%) of the patients were male and 5 (20.8%) were female. The

mean age of the patients included in the study was 53.3±11.6. We reviewed their underlying diseases 34.8% of the patients had diabetes mellitus (DM), 26.1% had hypertension (HT), 21.7% had obesity, 8.7% had the chronic obstructive pulmonary disease (COPD), and 13% had asthma. 60.9% of them were smokers.

Before the remdesivir treatment, 20 patients (87%) used favipiravir (FAV), 1 (4.3%) used hydroxychloroquine (HCQ), and 2 (8.7%) used both drugs. The patients had received other treatments for an average of 5.6±2.01 days before remdesivir. Remdesivir initiation time was 8.4±2.6 days from the onset of symptoms and 6±2.6 days from the time of diagnosis.

In the follow-up period, we had to hospitalize 18 patients (78.2%) in the intensive care unit (ICU). 14 (60.8%) needed a mechanical ventilator. Post-treatment follow-up showed that 15 (65.2%) recovered, and 8 (34.8%) resulted in mortality. Table 1 shows the general characteristics of the patients. Patients were divided into two groups by days from the onset of symptoms to the initiation of remdesivir, as less than 10 days and more than 10 days. The regression analysis performed on these groups showed no significant differences in terms of mortality.

We evaluated the laboratory parameters of the patients before and at the end of the remdesivir treatment. We found that their C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and fibrinogen levels were significantly lower (*p*-value was 0.001, 0.005, 0.000, and 0.001, respectively). On the other hand, their Alanine aminotransferase (ALT) and blood urea nitrogen (BUN) values were higher than the pretreatment state (*p*-value was 0.004, and 0.003, respectively). Table 2 shows the other laboratory parameters.

We divided the patients included in the study into two groups as recovered and deceased and checked whether there was a difference between the two groups in the parameters followed. However, we observed no difference between the groups in the parameters checked. The characteristics of the patients by the groups are shown in Table 3.

Discussion

Since the first appearance of the disease in the Wuhan province of China in 2019 and its spread in our country in March 2019, our experience with its diagnosis and treatment has improved. However, there are still no clear treatment protocols. Many countries have different protocols for effective drugs and treatment methods. Chloroquine, HCQ, FAV, lopinavir/ritonavir, umifenovir, galidesivir, and remdesivir are thought to be effective in this respect [4].

In addition to these drugs, other treatments are also available to suppress the cytokine storm and prevent disease complications. The need to find safe, effective and rapid treatment methods for the treatment of the disease continues.

Remdesivir is an antiviral agent that inhibits RNA-dependent RNA polymerase (RdRp) that is effective in the early phase of the disease. It is known that early termination of RNA transcription decreases viral replication, reducing viral load in the lungs, ultimately improving pulmonary function [5]. It has been used in treating the Ebola, SARS-CoV, and MERS-CoV viruses. Since it has a long half-life, it offers the advantage of using a single dose per day, and the recommended dose for COVID-19 is 1x200 mg, continuing with a maintenance treatment of 1x100 mg after loading. The treatment should be completed in 5 days. In late May, it became the first drug to be licensed by the FDA for use in COVID-19 disease [6]. Although it has been the first licensed drug, its effects on the prognosis and mortality of the disease and its side effects are not fully known, and as far as we know, there are no studies published on this subject in our country.

All patients included in the study had received an average of 5.6±2.01 days of HCQ, FAV, or HCQ+FAV pre- or post-hospitalization until remdesivir was provided. The time from the onset of symptoms to the use of remdesivir was 8.4±2.6 days. In a study involving 1062 participants, the average time from the onset of symptoms to the use of remdesivir was 9 (6-12) days. Better treatment response was received when remdesivir treatment started within the first 10 days after symptom onset [7]. In another study conducted in China, remdesivir was used within an average of 9 days from the onset of

Table 1. General characteristics of the patients

	Number (n)	Percentage (%)
Gender Female	5	21.7
Male	18	78.3
Age (years)		
Underlying disease		
DM	8	34.8
HT	6	26.1
CAD	1	4.3
Asthma	3	13.0
COPD	2	8.7
Obesity	5	21.7
Malignancy	1	4.3
Smoking	14	60.9
Other antiviral treatments received before remdesivir		
Hydroxychloroquine (HCQ)	1	4.3
Favipiravir (FAV)	20	87.0
HCQ+FAV	2	8.7
Days from the onset of symptoms until the initiation of remdesivir	Avg 8.4±2.6	
Duration of other treatments received before remdesivir (days)	Avg 5.6±2.01	
Duration of hospitalization (days)	Avg 22.2±11.08	
Duration of intense care (n:18)	Avg 16.9±7.93	
Duration of using a mechanical ventilator (days) (n:14)	Avg 11.9±7.34	
Presence of ARDS at the initiation of treatment		
Yes	12	52.2
No	11	47.8
Pneumonia severity at the initiation of treatment		
Mild to moderate	2	8.7
Severe	21	91.3
Presence of ARDS at the initiation of treatment 1 patient missing		
Yes	12	8.7
No	11	91.3
Convalescent plasma treatment		
Yes	20	87.0
No	3	13.0
Cytokine apheresis application		
Yes	5	21.7
No	18	78.3
Result		
Recovery	15	65.2
Death	8	34.8
Mortality <7 days	1	4.3
Mortality 7-14 days	1	4.3
Mortality 14-28 days	3	13.0
Mortality over 28 days	3	13.0

Table 2. Laboratory values

	Initiation of remdesivir treatment (x±SD)	End of remdesivir treatment (x±SD)	*p*
Leukocyte (WBC)/mm^3	11173.9±4591.02	12739.1±4845.49	0.212
Lymphocyte	713.0±341.52	801.1±378.12	0.144
Neutrophile/Lymphocyte ratio	15.8±9.37	17.5±14.3	0.784
C-reactive protein	140.6±81.75	62.7±50.95	0.001*
Procalcitonin	0.4±0.24	0.4±0.34	0.993
Blood urea nitrogen (BUN)	19.3±7.71	25.2±11.5	0.003**
Creatinine	1.5±3.39	0.7±0.42	0.323
AST	47.5±29.1	52.4±34.4	0.223
ALT	35.8±20.87	66.6±88.99	0.004**
LDH	560.1±223.99	380.6±163.5	0.000**
D-Dimer	2040.0±241.95	813.5±842.47	0.002**
Ferritin	749.9±611.87	480.1±333.92	0.005**
Fibrinogen	548.4±241.45	372.9±133.20	0.001**
Interleukin-6	77.8±95.89	×	

*p<0.05, paired-t-test
** p<0.05, Wilcoxon test
× IL-6 values of patients were not analyzed at the end of the treatment

Table 3. Characteristics of the patients by groups

	Recovered (n:15/%)	Deceased (n:8/%)	*p*
DM	5 (33.3)	3 (37.5)	0.596
HT	3 (20)	3 (37.5)	0.334
Asthma	2 (13.3)	1 (12.5)	0.731
COPD	2 (13.3)	0	0.415
Obesity	2 (13.3)	3 (37.5)	0.208
Smokers	10 (66.7)	4 (50)	0.337
Other antiviral treatments received before remdesivir Hydroxychloroquine (HCQ) Favipiravir (FAV) HCQ+FAV	 0 14 (93) 1 (6.7)	 1 (12.5) 6 (75.0) 1 (12.5)	 0.320
Duration of other treatments received before remdesivir (days)	5.9±1.64	5.2±2.65	0.494
Days from the onset of symptoms until the initiation of remdesivir	8.2±1.65	8.7±3.95	0.720
Hospitalization in the intensive care unit	10 (66.7)	7 (87.5)	0.288
Intensive care stay	16.4±6.58	17.5±9.81	0.780
The need for a mechanical ventilator	6 (40)	8 (100)	**0.006**
Duration of using a mechanical ventilator	9.7±4.13	13.5±8.99	0.354
Pneumonia severity at the initiation of treatment Mild to moderate Severe	 2 (13.3) 13 (86.7)	 0 8 (100)	 0.415
The total duration of hospitalization	22.5±10.25	21.5±13.21	0.780

symptoms, and better clinical improvement was observed in the group who started the treatment early [8]. In another study conducted by Grein et al. [9] including 61 patients, the time to begin the treatment after the onset of symptoms was 12 days on average. Compared to the others, in our study, remdesivir treatment started in the earliest period after the onset of symptoms. We found no difference in mortality when we divided the patients into two groups by days from the onset of symptoms to the initiation of remdesivir, as less than 10 days and more than 10 days.

Although the patients who received treatment had severe pneumonia, 65.2% (15) of them recovered. In another study, 84% of the patients treated with remdesivir recovered in the 28-day follow-up [9]. Mortality rates in the placebo group and the remdesivir group were compared in the study involving 1062 patients. Although there was a lower mortality rate in the remdesivir group, it was not statistically significant [7]. Remdesivir was compared to HCQ, lopinavir, and interferon in a study conducted by the World Health Organization (WHO) including 405 hospitals and 11330 patients in 30 countries. No significant difference was found between the groups in terms of hospital stay and mortality [10]. The clinical recovery rate after treatment with favipiravir in patients with severe pneumonia was 71% in 7 days [11]. In the study conducted with lopinavir/ritonavir, no significant difference was found between its effect on clinical recovery and recovery time in the group receiving lopinavir-ritonavir and the group receiving standard care. The 28-day mortality rate was 19.2% [12].

The most important contribution of laboratory parameters in COVID-19 disease is that they guide us in identifying prognosis. Parameters such as C-Reactive protein, IL-6, ferritin, D-Dimer, fibrinogen, absolute lymphocyte count, and neutrophil-lymphocyte rate are also critical in defining the prognosis of COVID-19 disease, in addition to the factors such as the underlying disease, severity of pneumonia, and the presence of ARDS [1]. In our study, we evaluated laboratory parameters at the beginning and end of remdesivir treatment and detected a significant decrease in CRP, ferritin, LDH, and fibrinogen levels.

In the light of the data obtained from several studies, it is known that remdesivir may have some side effects such as hypotension, arrhythmia, dyspnea, pneumothorax, anemia, lymphopenia, hyperglycemia, septic shock, nausea, vomiting, diarrhea, constipation, acute renal failure, headache, rash, delirium, ALT, high levels of AST, hypernatremia and hypokalemia [7, 8, 13, 14]. In our study, we observed no side effects that would require drug discontinuation. ALT and BUN values increased at the end of the treatment. Similar to this result in our study, another study reported that 32 of 53 patients developed side effects such as an increase in liver enzymes, acute renal failure, diarrhea, and hypotension [9]. In another study, 10% of patients developed nausea, 6% hypokalemia, and 5% headache [15].

In conclusion, conducted with a small group of 23 patients followed up with severe pneumonia, our study is an observation report on remdesivir treatment. It is the first study in our country on remdesivir treatment and its results. Broader, randomized, placebo-controlled studies can provide more reliable results. Since inflammation is as critical as the replication of the virus in the pathogenesis of COVID-19 disease, the use of remdesivir in combination with other antiviral and anti-cytokine therapies may increase the effectiveness. We believe that we need new studies in this regard.

Limitations of the study

1- Absence of a control group

2- The effect of redeliver on viral load remains unanalyzed

3- A small group of patients

Conflict of interest: No conflict of interest was declared by the authors.

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Contributions of the authors to the article

A.S.K. conceived the idea. A.S.K. collected the data. F.K. performed the calculations, data analysis and created figures. A.S.K., K.D.O. and F.K. interpreted and discussed the results. K.D.O. and F.K. provided critical feedback. A.S.K. wrote the manuscript with input from all authors. All authors discussed the results, reviewed and commented on the manuscript.