ORIGINAL ARTICLE
KLİNİK ARAŞTIRMA

Evaluation of Treatment of Patients with SARS-CoV-2 in line with Literature

SARS-CoV-2 Tanısı ile Takip Edilen Olguların Tedavisinin Literatür Eşliğinde Sistematik Olarak Değerlendirilmesi

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SUMMARY

Aims: The present article aimed to evaluate the drug therapy applied to patients who were followed up for SARS-CoV-2, and who were tested positive and negative 2019-nCov.

Material and Methods: A comprehensive and systematic literature search of numerous electronic databases regarding patients SARS-CoV-2 was performed.

Results: Patients with 2019-nCoV can be treated with ceftriaxone, moxifloxacin, oseltamivir, hydroxychloroquine, and patients with poor prognosis can also be given lopinavir/ritonavir.

Conclusions: Not only rRT-qPCR test results and CT findings but also clinical evidence should be considered for the diagnosis of SARS-CoV-2.

Keywords: COVID-19, hydroxychloroquine, Lopinavir/ritonavir, oseltamivir, SARS-CoV-2

ÖZET

Amaç: SARS-CoV-2 tanısı ile takip Edilen, 2019-nCov testi için pozitif ve negatif sonuçlar alınan olgulara uygulanan ilaç tedavisinin literatür eşliğinde değerlendirilmesi amaçlandı.

Materyal ve Metodlar: Elektronik ortamda; 2019-nCoV nedeni ile SARS-CoV-2 tanısı ile takip edilen olgulara ait verilerin, ülke ve dil kısıtlaması olmaksızın literatürde yerini alan araştırma sonuçları ile kıyaslanması gerçekleştirildi.

Bulgular: Seftriakson, moksifloksasin, oseltamivir, hidroksiklorokin ve prognozu kötüye giden olgularda, gerektiğinde lopinavir/ritonavir etken maddeli farmasötikler ile 2019-nCoV'un tedavi edilebileceği gözlemlendi.

Sonuç: SARS-CoV-2 tanısı için sadece rRT-qPCR testi ya da radyolojik olarak CT bulguları ile karar verilmemelidir. Her iki analiz sonuçlarına ek olarak klinik bulgular ile ortak paydada karar verilerek, tanı

Anahtar kelimeler: COVID-19, hidroksiklorokin; lopinavir/ritonavir, oseltamivir, SARS-CoV-2

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INTRODUCTION

As is known, the 2019–20 coronavirus pandemic is an ongoing pandemic of coronavirus disease 2019 (COVID-19) that was first identified in 2019 in Wuhan, Hubei Province, China (1). The first patients infected have suffered from severe pneumonia that has been unresponsive to the treatment or vaccines, and they have been diagnosed with a new CoV, a highly pathogenic CoV type, which is called severe acute respiratory syndrome (ARDS) COV (SARS-CoV-2) (2). Having first been observed in China, the coronavirus cases have widely been reported by various countries in Europe, North America and Asia-Pacific (3). The World Health Organization declared the virus a "pandemic" on March 11, 2020 (4). Europe was reported to be the epicenter of the coronavirus crisis on March 13, 2020 (5), and the virus-related deaths and the number of patients with 2019-nCoV have increased markedly. The incubation period of the virus varies from 2 to 14 days and the mean incubation period is 5 days (6). A variety of reports have suggested that the virus is contagious before the onset of the symptoms (7).

The symptoms include high fever, cough, and shortness of breathing. Some studies have reported that this virus affects not only the respiratory system but also the gastrointestinal tract and causes diarrhoea (8). Additionally, this neurotropic virus has been reported to have a neuro-invasive potential that may affect the central nervous system, and cause symptoms such as headache, nausea, and vomiting (9). Certain reports have suggested that the virus affects directly the respiratory center in the brain stem, thereby, causes sudden ARDS (9). Based on the hypothesis that 2019-nCoV may cause systemic inflammation, penetration into the blood-brain barrier, and olfactory nerve damage, some studies have also reported that it may cause neural damage and anosmia (9).

Special measures that do not require the use of a drug, such as a hand cleaning, use of masks and individual quarantine, training, and interruption of collective activities (10) have been taken to prevent the spread of the virus. However, the virus continues to threaten the world and those who have been infected have presented to hospitals.

The present article aimed to evaluate the drug therapy applied to patients who were followed up for SARS-CoV-2, and who were tested positive and negative 2019-nCov.

MATERIALS AND METHODS

Ethical Consent

The present research was approved by the Local Ethics Committee of Istanbul Medipol University (no. 10840098-604.01.01-E.16450), Faculty of Medicine. The data from both patients and healthy volunteers were obtained from the hospital information management system databases. Approval to use the relevant data was obtained from the hospital administration (13441514-774.99) and Republic of Turkey Ministry of Health (2020-05-12T14_21_29).

A comprehensive and systematic literature search of numerous electronic databases, including Cochrane Collaboration, Cochrane Library, Ovid, Medline, ProQuest, the National Library of Medicine at the National Institutes of Health, PubMed, and Google Search Engine was performed. A combination of keywords was used to retrieve studies broadly associated with the topic of interest, which was performed up to March 31, 2020. The search criteria were as follows: "covid 19 treatment," "covid 19 symptoms," "covid 19 epidemiology," "covid 19 transmissions," "covid 19 mortality," "covid 19 clinical, "and "covid 19 PCR".

Of the studies retrieved, those that met the research criteria were pooled. The following keywords were used to determine a common treatment protocol: "Angiotensin-converting enzyme-2 (Ace2)," "AzithWromycin," "Chloroquine," "Clarithromycin," "Favipiravir," "Hydroxychloroquine," "Lopinavir/ritonavir," "mefloquine," "Naphamostat mesylate," "oseltamivir," and "tocilizumab". Moreover, studies of covid 19 were also screened using the keywords "vaccine" and/or "mesenchymal stem cell application".

The full texts of the appropriate studies were retrieved according to the headings and abstracts, and then the decision of whether to include or exclude these studies was made after a comprehensive review (11). Letters to the editor, bibliographies, reviews, and meta-analyses were excluded from the study. Critical appraisal checklists were used to assess and analyze the quality of the selected studies. Independent assessments of the authors were compared (12). The results were presented in numbers. Three patients with SARS-CoV-2 were randomly chosen. Medical records of these patients were examined, and data extracted were assessed in line with the current literature.

RESULTS

We retrieved 6,166 publications using the keyword "Coronavirus Disease". Of the studies, 40 were clinical trials. 1,795 publications were retrieved using the keyword "covid 19" while 1,471 publications were extracted using the keyword "covid". 1,469 publications were retrieved using the keyword "Coronavirus Disease 2019 (COVID-19)" while the publications extracted increased to 644 using the keyword "2019-nCoV" (**Table 1**).

No studies that investigated patients with 2019-nCoV who had been administered clarithromycin and hydroxychloroquine were found (**Table 2**).

Axial CT without contrast was performed (**Figure1** and **Figure 2**). Samples were taken through the nasopharyngeal swap method for PCR analysis.

The CT images of a 24-year-old male patient with a negative PCR test result revealed parenchymal infiltration in both the right side of the upper lobe of the lungs and in the left side of the lower lobe of lungs in the form of ground glass patterned areas. The patient had a history of hypertension and used an antihypertensive drug with amlodipine active substance at a dose of 10 mg/day. The patient had no other symptoms except acute respiratory failure, high fever, and cough. The patient was referred to the intensive care unit for follow-up and was administered ceftriaxone 2x1 gm/day and moxifloxacin 1x400 mg/day. Besides, oseltamivir 2x75 mg/day and hydroxychloroquine sulphate 2x400 mg/day loading dose followed by 2x200 mg / 4 days maintenance doses were administered orally for a total of five days.

The second patient was a 42-year-old female with a positive PCR test result but negative CT findings. The patient had a history of close contact with a symptomatic case and was admitted to the clinic with complaints of cough and fever. The patient was administered ceftriaxone 2x1 gm/day and moxifloxacin 1x400 mg/day. Besides, oseltamivir 2x75 mg/day and hydroxychloroquine sulphate 2x400 mg/day loading dose followed by 2x200 mg / 4 days maintenance doses were administered orally. At the end of five days of treatment, laboratory findings revealed negative progress, and oseltamivir and hydroxychloroquine sulphate therapy were discontinued. The patient was then administered lopinavir and ritonavir (200/50 mg 2*2 tablets). The total treatment duration was 12 days. The same patient was given ceftriaxone 2x1g / day, moxifloxacin 1x400mg / day IV and lopinavir (200mg) / ritonavir (50mg) oral tablet for seven days.

The third patient was a 60-year-old female with a positive PCR test result and positive CT findings. The patient had both hypertension and diabetes mellitus. The patient was administered ceftriaxone 2x1 gm/day and moxifloxacin 1x400 mg/day. Also, oseltamivir 2x75 mg/day and hydroxychloroquine sulphate 2x400 mg/day loading dose followed by 2x200 mg/day maintenance doses were administered orally. At the end of five days of treatment, laboratory findings revealed negative progress, and the patient was then administered ceftriaxone 2x1 gm/day, moxifloxacin 1x400 mg/day, lopinavir, and ritonavir (200/50 mg 2*2 tablets) for seven days.

Other than hypertension and diabetes mellitus, the patients had no chronic kidney or heart failure. The following laboratory tests and magnetic imaging were performed, and the results were evaluated: complete blood count, C-reactive protein, procalcitonin, kidney and liver parameters, cardiac enzymes, coagulation parameters, arterial blood gas, lactate, and chest X-ray. Cultures were obtained before antibiotic therapy (**Table 3**).

The epicrises of patients revealed that notes that all cases were discharged and were suggested social isolation and medical follow-up at home.

Maltepe Tıp Dergisi Cilt: 12 Sayı: 2/ 2020
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Table 1. Studies associated with Covid.

Keywords	Case report	Clinical Trial	Practice guideline	Review	Systematic review	Meta analysis	Total (Amount)
covid 19 treatment	16	0	1	52	5	0	489
covid 19 symptoms	35	0	1	36	2	0	409
covid 19 epidemiology	6	0	1	32	4	0	385
covid 19 transmission	13	0	1	34	1	0	374
covid 19 mortality	1	0	0	13	0	0	96
covid 19 clinical	20	0	1	56	6	0	560
covid 19 PCR	4	0	0	4	0	0	82

Table 2. Drugs in the Treatment Protocol.

Keywords (Covid 19 +)	Case report	Clinical Trial	Practice guideline	Review	Systematic review	Meta analysis	Total (Amount)
Ace2+covid	0	0	0	14	0	0	70
Chloroquine + covid	0	0	0	9	1	0	52
Hydchloroquine + covid	0	0	0	0	0	3	38
Azithromycin + covid	0	0	0	0	1	0	4
Hydchloroquine + Azithromycin + covid	0	0	0	0	0	0	2
Clarithromycin + covid	0	0	0	0	0	0	0
Oseltamivir+covid	0	0	0	1	0	0	6
Hydchloroquine+ oseltamivir+covid	0	0	0	0	0	0	2
Lopinavir+covid	2	0	0	7	1	0	35
Lopinavir/Ritonavir + covid	2	0	0	6	0	0	33
Hydchloroquine + Lopinavir/Ritonavir + covid	0	0	0	1	0	0	5
Hydchloroquine + oseltamivir + Lopinavir/ritonavir + covid	0	1	0	0	0	0	1
Hydchloroquine +oseltamivir+Lopinavir/ritonavir+Azithromycin + covid	0	0	0	0	0	0	0
Tocilizumab + covid	1	0	0	4	0	0	16
Hydchloroquine + tocilizumab + covid	0	0	0	1	0	0	4
Favipiravir + covid	0	0	0	2	0	0	6
Hydchloroquine + Favipiravir + covid	0	0	0	1	0	0	3
Nafamostat mesylate+covid	0	0	0	0	0	0	0
Mefloquine + covid	0	0	0	0	0	0	1
Vaccine + covid	0	0	0	36	2	0	146
Mesenchymal stem cell + covid	0	0	0	1	0	0	5

Table 3. Laboratory findings of patients.

Age (Years)	**24**	**42**	**60**
Sex	Male	Female	Female
Concomitant disease	Hypertension	None	Hypertension, Diabetes mellitus
Glucose (mg/dL)	77	88	379
Creatinine (mg/dL)	0.75	0,83	0,76
Urea (mg/dL)	38	25	40
Alanine aminotransferase (U/L)	30	11,02	10,99
Aspartate aminotransferase (U/L)	19	12,18	10,03
Lactate dehydrogenase (U/L)	178	150	164
Creatine kinase-myocardial band (U/L)	10	18	14
Troponin I (ng/mL)	<0.010	<0.010	<0.010
White blood cell (0^3/mm3)	6,20	6,57	5,05
Lymphocytes (10^9/L)	1,5	2,52	1,77
Neutrophils (10^9/L)	3,99	3,34	2,74
Platelet (10^9/L)	402	444	145
C-Reactive protein (mg/L)	27	6,85	15
Procalcitonin	0.3	0.4	0.17
D-dimer	177	137	311
PCR test result	Negative	Positive	Positive
CT findings	Positive	None	Positive

Figure 1a; CT of thorax shows that the lung parenchymal aeration and bronchovesicular structures are normal and no pathologies are causing an increase in density of the parenchyma. 1b; Axial CT images of the patient with a negative rRT-qPCR test result. Patch-like ground-glass opacities located in the superior segments of both lung lower lobes and upper lobes, and the subpleural areas.

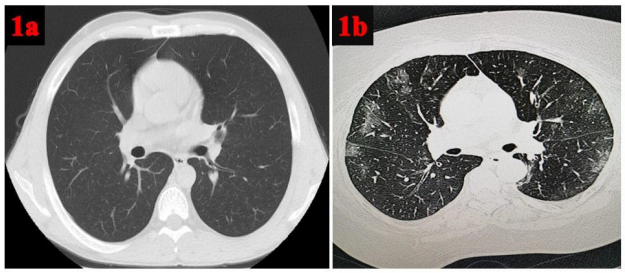
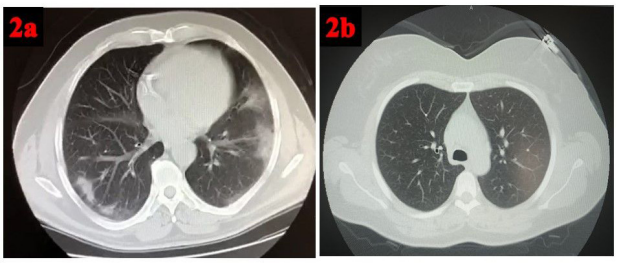


Figure 2a; Axial CT images of a 60-year-old patient with a positive rRT-qPCR test result. Ground-glass opacities located in the lower lobes of both lungs and the left lung lingular segments. 2b; A 42-year-old woman with a positive rRT-qPCR test result but negative CT findings has normal parenchymal images.



Maltepe Tıp Dergisi Cilt: 12 Sayı: 2/ 2020
https:// doi.org/10.35514/mtd.2020.29

DISCUSSION

The most common symptoms include cough, fever, and gastrointestinal failure. Cytokine storm accompanied by ARDS and elevated ferritin and C-Reactive protein can be observed in older patients. The median clinical period ranges from 2 to 7 days and, in some cases, may extend to 14 days. Radiological imaging and real-time reverse transcriptase-polymerase chain reaction (RT-qPCR) are used for diagnosis.

A quantitative (real-time) reverse transcription-polymerase chain reaction (rRT-qPCR) and antibody measurement are considered a gold standard for the detection of this virus. Covid-19 can be detected from respiratory samples by rRT-PCR up to day 28 of the disorder, and the peak point of contamination is reached on day 14. The diagnosis can also be made by detecting IgM and IgG antibodies against the virus. IgM antibodies are detected after 7 to 21 days of the disease whilst IgG antibodies can be detected in the second week.

IgM antibodies reach a peak on day 14 and IgG antibodies reach a peak on day 28. PCR positivity can be detected in the early and window period of the disease, but IgM positivity can solely appear in the window period of the disease. IgG positivity can only be detected in patients who are infected and recovered. Patients with asymptomatic or mild symptoms may have false PCR negativity due to lower viral load. Repetition of the test is recommended within 24 h in the presence of clinical suspicion (13).

Interstitial damage and parenchymal changes are observed during the lung involvement of 2019-nCoV (14). CT plays a marked role in the diagnosis and follow-up of the disease. Chest CT has a high sensitivity but low specificity for the diagnosis of COVID-19 (15). 2019-nCov and other viral pneumonia frequently have similar CT findings. The severity of lung involvement is strictly correlated with the severity of the disease. Thorax CT findings may show different patterns depending on the severity of the disease (16,17). Ground-glass opacities are defined as the partial displacement of the exudate with the air in the airspaces without affecting the vessel and bronchial walls. Ground-glass opacities are also defined as hazy areas with slightly increased density in the lungs due to the filling of air spaces with exudate or interstitial thickening (18). The findings identified in patients with 2019-nCov appear unilaterally or bilaterally in the peripheral and subpleural areas of the lung.

Chung et al. (19) reported that in the first radiological examination of 21 patients, 57% of the findings were detected and some of them were considered the earliest CT finding. These results are compatible with other studies presenting ground glass-opacity (GGO) as the most common imaging finding (up to 98%) (20). Besides, GGO is frequently accompanied by other patterns, including reticular densities, interlobular septal thickening, and consolidation (21). The initial findings of the 2019-nCov cases are mostly bilateral, multilobar GGOs with peripheral or posterior localization in the lower lobes, but GGOs are less common in the right middle lobe (15). Crazy -paving patterns on chest CT can also be observed in the later stages.

Consolidation is defined as an increase in lung parenchymal density due to the replacement of the alveolar air with exudate, in which the walls of the vessels and bronchi become obscure. Multifocal, irregular or segmental consolidation spreading in subpleural areas or along the bronchovesicular bundles can be seen in 2% -64% patients with 2019-nCov (22). The consolidation is also considered an indicator of the progression of the disease. A recent study has reported that the consolidation may occur approximately 2 weeks after the onset of the disease. A consolidation accompanied by GGO is an atypical initial finding in elderly patients. The reticular pattern is seen as countless small linear opacities in CT due to interlobular septal thickening and pulmonary interstitial structures. The formation of this pattern may be associated with interstitial lymphocyte infiltration that causes interlobular septal thickening. Many studies have reported that reticular pattern and interlobular septal thickening in patients with COVID-19 are the most common CT findings after GGO and consolidation (16,23). The crazy-paving pattern (CPP) is defined as the image of GGO with a superimposed thickening of interlobular septal lines.

CPP, widespread GGO, and consolidation may indicate the aggravation of COVID-19 in the progressive stage (17). Vascular dilation, air bubble sign, halo sign, nodules, inverted halo sign/atoll sign, lymphadenopathy, rarely pericardial effusion are also amongst the radiological findings of covid-19. A crucial way to manage a virus outbreak is to postpone and weaken the epidemic peak, in other words, to flatten the epidemic curve. Therefore, excessive patient density can be prevented, and enough time can be saved for the discovery of a vaccine or appropriate treatment (24). Different treatment protocols are used in many countries until both vaccine and virus-specific treatment are found. Pharmacological agents that are used in treatment include chloroquine, hydroxychloroquine, oseltamivir, lopinavir, ritonavir, azithromycin, favipiravir, remdesivir, and tocilizumab.

Chloroquine and hydroxychloroquine are derivatives of 4-aminoquinoline that are commonly used in the treatment of many rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and they also have anti-

malarial effects. Well-tolerated antimalarial drugs can frequently cause side effects such as itching, exacerbation of psoriasis, urticarial, morbilliform or lichenoid drug eruptions, alopecia, allergic contact dermatitis, and rash-likee Steven Johnson syndrome (25,26).

Oseltamivir, a neuraminidase inhibitor and analog of sialic acid, is an antiviral drug used to treat and prevent influenza A and influenza B (27). Lopinavir is an antiretroviral of the protease inhibitor class (28). Lopinavir combined with ritonavir, a protease inhibitor, is used against HIV infections as a fixed-dose (29). Azithromycin, a type of macrolide antibiotic, shows in-vitro activity against Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Mycoplasma pneumoniae (30).

Tocilizumab, also known as atlizumab and marketed under the brand of Actemra®, is an immunosuppressive drug used to treat severe rheumatoid arthritis and systemic juvenile idiopathic arthritis in children. It is a monoclonal antibody against interleukin-6 receptor (34).

Favipiravir was approved for new flu treatment in China on February 15, 2020, but its clinical trials have continued for 2019-nCov treatment (32). Favipiravir is an RNA-dependent RNA polymerase inhibitor. Along with the anti-influenza virus activity, some studies suggest that it can block the replication of flavi-, alpha-, phylo-, bunia-, arena-, noro- and other RNA viruses (33). No significant adverse reaction has been observed in the favipiravir treatment group, and it also has significantly less side effects than the lopinavir + ritonavir group (34,35). Since favipiravir is both metabolized and inhibited by aldehyde oxidase, initial oral loading is required to obtain adequate blood levels. The plasma half-life is approximately 4 h. Persons with liver dysfunction should be monitored for blood concentration and dosage adjustment. Favipiravir or its metabolites have been detected in semen and breast milk. Favipiravir does not pharmacokinetically interact with oseltamivir; however, excessive exposure to acetaminophen has been observed when taken with acetaminophen (36).

When used together with acetaminophen (paracetamol), the dose of acetaminophen should not exceed 3000 mg/day (less in liver failure). When used together with theophylline, the blood concentration of the drug may increase, which causes the development of side effects. Therefore, caution should be exercised when combined use of the relevant drugs. Favipiravir can interact with the following agents: antibiotics such as piperacillin, tazobactam, and pyrazinamide; bronchodilators such as paracetamol, montelukast, and theophylline, which have analgesic and antipyretic effects; anti-hypertensive agents such as pioglitazone, repaglinide, rosiglitazone, moxonidine, and treprostinil (37,38).
The most common side effects of favipiravir are reported as diarrhoea, an elevated serum uric acid level, serum transaminase level, total bilirubin level, and a decreased neutrophil level. Digestive system side effects such as nausea and increased gas and psychiatric symptoms can also be seen. Favipiravir is not recommended during pregnancy due to its teratogenic effects. This pharmacological agent, which is excreted mainly from the kidneys, should be used carefully by nursing mothers since it passes into milk (38).

A treatment protocol has also been created by the Ministry of Health in Turkey (38). The General Directorate of Public Hospitals, Department of Supply Planning, Stock and Logistics Management, Hospital Pharmacy Management Unit published the pharmaceuticals that can be used for SARS-Cov-2 infection on 24.03.2020 (38). Science Committee of the Ministry of Health has prepared a 2019-nCov (SARS-CoV2 Infection) Guideline and indicated the following drugs for the treatment: "Lopinavir 200 mg / Ritonavir 50 mg Film Tablet," "Hydroxychloroquine Sulphate 200 mg Film Tablet," "Oseltamivir 75 mg Hard Capsule," "Azithromycin 500 mg Tablet," "Favipiravir 200 mg Tablet" (38). In accordance with the COVID-19 Adult Patient Management and Treatment Guideline published by the Ministry of Health, regardless of the clinical severity of the disease, the patients with definitive or potential Cov-n19 were given 2x75 mg oseltamivir, 2x200 mg hydroxychloroquine loading dose followed by following 2x400 mg maintenance dose.

In these five days of treatment modality, upon the recommendation of a physician, 500 mg /day azithromycin can be used for the first day, and 250 mg/day azithromycin for the remaining four days. Patients with a severe course that are unresponsive to the first treatment modality can be given favipiravir 2x1600 mg/day loading dose followed by 2x600 mg/day maintenance doses for 5 to 7 days. An alternative to this treatment, patients with a severe course can also be orally given a pharmaceutical preparation containing lopinavir 200 mg/ritonavir 50 mg at a dose of 2x2 for 10 to 14 days (38).

In the relevant guideline, there are also warnings that pharmaceuticals containing both azithromycin and hydroxychloroquine active substances may tend to ventricular tachycardia by prolonging the Q-T interval (38). Therefore, azithromycin should not be used especially in patients with another clinical condition prolonging QT. Patients should be monitored closely by taking daily electrocardiography and when cardiotoxic undesirable effects are observed, firstly, azithromycin should be discontinued and then the dose of hydroxychloroquine should be reduced. Hydroxychloroquine should also be discontinued provided that the cardiological

Maltepe Tıp Dergisi Cilt: 12 Sayı: 2/ 2020
https:// doi.org/10.35514/mtd.2020.29

problems continue (38). No reliable studies have reported that hydroxychloroquine is effective in 2019-nCoV prophylaxis and therefore, the use of hydroxychloroquine in pre-contact prophylaxis is not appropriate and rational (38). Corticosteroid treatment (1-2 mg/kg/day) is recommended in the guideline prepared by the European Society of Intensive Care Medicine- The Surviving Sepsis Campaign, for patients with ARDS who are treated with mechanical ventilation, and methylprednisolone treatment is recommended for 5-7 days. However, it is not recommended in the case of pneumonia without ARDS. The guideline has also reported that the oral bioavailability of favipiravir is > 95% and that there is no significant difference in the administration of favipiravir 30 minutes after a meal or on an empty stomach (38). For patients who cannot be given oral favipiravir for various reasons, the liquid form of the drug is prepared by the hospital pharmacists by using personal protective equipment inappropriate drug preparation areas (38).

Chloroquine and hydroxychloroquine are efficient on SARS-CoV-2 and reported to be efficient in Chinese 2019-nCov patients. In a study, the authors evaluated the role of hydroxychloroquine on respiratory viral loads (39). The analysis of 425 patients, who were diagnosed with definite laboratory tests until January 22, 2019, by researchers in Wuhan, shows that the virus was transmitted from person to person for the first time in mid-December. The first estimates were that the number of patients infected doubled every 7.4 days. The median age of the patients was 59 and the mean incubation period was 5.2 days (39).

French approved 2019-nCov patients were included in a single-arm protocol from early March to March 16 to take 600 mg of hydroxychloroquine per day, and viral loads in nasopharyngeal swabs were tested daily. Depending on their clinical appearance, azithromycin was added to the treatment. Patients who were not treated from another center and those who refused the protocol were included as negative controls. On day 6 after the end, the presence and absence of the virus were considered the endpoint. Azithromycin added to hydroxychloroquine is significantly more effective for virus elimination. Despite the small sample size, our research shows that hydroxychloroquine therapy is significantly associated with viral load reduction/loss in patients with 2019-nCov and its effectiveness is enhanced by azithromycin [39]. In the present study, tablets containing hydroxychloroquine were used in the treatment protocol of patients with negative and / or positive rRT-qPCR test results. Azithromycin was not added to their treatment.

Coronaviruses are neuroinvasive pathogens (9). Given the high similarity between SARS-CoV and SARS-CoV-2, central nervous system involvement may occur in patients with SARS-CoV-2 (9). Symptoms related to central nervous system involvement, such as headache, nausea, and vomiting may occur in patients with 2019-nCov (9).

A study by Li et al. (41) has reported that the 2019-nCov pathogen reaches the central nervous system through the transneuronal and hematogenous route, which causes encephalitis and neuronal damage. The authors have suggested that the mortality and morbidity are higher in patients with CSF positivity and encephalitis and that CSF samples should regularly be taken from patients with higher viral load and severe clinical findings who is followed-up in the intensive care unit, and cranial imaging should also be performed. In that study, no gastrointestinal system symptoms, such as nausea and vomiting, as well as no encephalitis were observed in patients.

The laboratory results for 2019-nCov have revealed that the leukocyte level is generally normal, and 80% of patients experience lymphopenia and mild thrombocytopenia (severe thrombocytopenia is considered a sign of poor prognosis). Procalcitonin level has been normal in many patients; however, alternative diagnoses should be considered in the presence of high procalcitonin levels (41). An elevated CRP level has been reported to be associated with prognosis (42). The increase in troponin I level may be associated with myocarditis in cases with a severe course and approximately 7% of the cases have died due to myocarditis. Some patients have been reported to die due to cardiac arrhythmia, and it has been suggested that troponin I level may be a crucial biomarker in revealing cardiac stress (43).

Three patients that were examined in the present study had a normal WBC level and an elevated CRP level, and these findings were in line with the current literature. The levels of the creatine kinase-myocardial band (<25) and troponin I (<0.010) were also normal. The patients did not experience cardiac complications. According to early reports from China, disseminated intravascular coagulation, prolonged international normalized ratio/prothrombin time, and elevated D-dimers levels were observed in patients with a severe course. However, the patients investigated in the present study had normal D-dimers levels.

Patients with 2019-nCov have been treated with pharmacological agents such as chloroquine, its derivative hydroxychloroquine, oseltamivir, lopinavir, ritonavir, azithromycin, favipiravir, tocilizumab, and stem cell so far. In the present study, the patients were given ceftriaxone 2x1 gm/day and moxifloxacin 1x400 mg/day. Besides, oseltamivir 2x75 mg/day and hydroxychloroquine sulphate 2x400 mg/day loading dose followed by 2x200 mg / 4 days maintenance doses were given orally for a total of five

days. Oseltamivir and hydroxychloroquine sulphate therapy were discontinued for patients with poor prognosis. Then, lopinavir and ritonavir (200/50 mg 2*2) were orally given along with ceftriaxone 2x1 gm/day and moxifloxacin 1x400 mg/day for seven days.

This study has some limitations. That the study had a retrospective design is the first limitation. The second limitation is that the manuscript with a reference-numbered 45 that was cited in the discussion section has been published electronically by the journal without being conducted peer-review process.

CONCLUSION

The literature suggests the use of macrolide antibiotics, favipiravir, an antiviral drug, tocilizumab or mesenchymal stem cell for the treatment of 2019-nCoV.However, the pharmaceuticals containing ceftriaxone, moxifloxacin, oseltamivir, hydroxychloroquine, and lopinavir/ritonavir can be used successfully in the treatment of 2019-nCoV without cytokine storm.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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