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Orijinal Araştırma / Original Article

Comparisons of Treatment Protocols for SARS-CoV-2 in Early Pandemic: Single Center Experience in Turkey

Erken Pandemide SARS-COV-2 Tedavi Protokollerinin Karşılaştırılması: Türkiye'de Tek Merkez Deneyimi

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Abstract

Objective: In this retrospective observational study, we aimed to investigate the COVID-19 treatment protocols applied in our hospital in terms of side effects and 28-day mortality.

Material and Method: All 621 patients diagnosed as COVID-19 and treated with any drugs were included in the study. Inclusion criteria for patients were hospitalization with COVID-19 diagnosis and being over 18 years old. The patients were divided into 4 groups according to the treatments against COVID-19: Group 1 (only favipiravir), Group 2 (hydroxychloroquine (HQ)+ Azithromycin (AZ), Group 3 (only HQ), and Group 4 (HCQ+AZ +antibiotics). The gender, age, medications, underlying comorbidities, possible side effects due to the treatments (cardiotoxicity, hepatotoxicity, nephrotoxicity), and mortality rates were evaluated.

Results: There was no difference in terms of side effects between treatment groups. Mortality rates were lowest in the HQ+AZ group. HCQ+AZ treatment was the most effective treatment protocol.

Conclusion: It can be concluded from the study that the higher mortality rate due to favipiravir may be due to the administration of this drug only to critically ill patients during the initial period of the pandemic. Or the study may lead us to conclude that favipravir not effective in the treatment of COVID-19.

Keywords: COVID-19, favipiravir, hydroxychloroquine, azithromycin, antibiotics

Öz

Amaç: Bu retrospektif gözlemsel çalışmada hastanemizde uygulanan COVID 19 tedavi protokollerini, yan etkileri ve 28 günlük mortaliteyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya COVID-19 tanısı konan ve herhangi bir ilaçla tedavi edilen 621 hastanın tamamı dahil edildi. Hastalar için dahil edilme kriterleri COVID-19 tanısı ile hastaneye yatış ve 18 yaşından büyük olmaktı. Hastalar COVID-19 tedavisine göre 4 gruba ayrıldı: Grup 1 (sadece favipiravir), Grup 2 (hidroksiklorokin (HQ)+ Azitromisin (AZ), Grup 3 (sadece HQ) ve Grup 4 (HCQ+AZ) +antibiyotikler) Cinsiyet, yaş, ilaçlar, altta yatan komorbiditeler, tedavilere bağlı olası yan etkiler (kardiyotoksisite, hepatotoksisite, nefrotoksisite) ve mortalite oranları değerlendirildi.

Bulgular: Tedavi grupları arasında yan etkiler açısından fark yoktu. Mortalite oranları HQ+AZ grubunda en düşüktü. HCQ+AZ tedavisi en etkili tedavi protokolüydü.

Sonuç: Çalışmada, favipiravire bağlı daha yüksek ölüm oranının, pandeminin ilk döneminde bu ilacın sadece kritik hastalara uygulanmasına bağlı olabileceği sonucuna varılabilir. Çalışma, favipravir'in COVID-19 tedavisinde etkisinin olmadığı sonucuna varmamızı sağlayabilir.

Anahtar Kelimeler: COVID-19, favipiravir, hidroksiklorokin, azitromisin, antibiyotikler

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic is still wreaking havoc around the world, and it's become a major cause of death and morbidity. It has caused over 2 million deaths globally since the first case was identified.[1] Patients of advanced age and comorbidities have a higher mortality rate. According to current statistics, global mortality is 6.97 percent, while mortality in our country is 2.71 percent.[2,3] For the proper treatment of the disease, successful and safe therapies with a low side effect profile are still needed. The treatment protocols are based on a small number of randomized clinical trials, experiences from the treatment of past influenza outbreaks and other coronavirus viruses, and expert opinions. Due to the need to formulate a treatment protocol in a hurry since the COVID-19 pandemic is rapidly progressing. Treatment methods are continually changing and becoming more appropriate as new research evidence and global studies become accessible.

Favipiravir and/or hydroxychloroquine (HQ) treatments have been recommended by our country's Ministry of Health since the beginning of the pandemic, according to the COVID-19 Diagnosis and Treatment Guidelines. Also, in the earliest stages of the pandemic, azithromycin (AZ) treatment was also recommended. In addition, various antibiotics were recommended for selected patients.[2] There are several studies examining the side effects of drugs used in the treatment of COVID-19 and their effects on patients' mortality, clinical course, and prognosis.[4-6] However, comparative studies on COVID-19 treatment protocols are limited to the current literature.

In this study, we aimed to retrospectively investigate the COVID-19 treatment protocols applied in our pandemic tertiary care hospital in terms of side effects and 28-day mortality.

MATERIAL AND METHOD

This retrospective, observational study included 621 confirmed COVID-19 patients from a pandemic hospital in our province. Data of the confirmed COVID-19 patients were collected from March 23 to July 1, 2020. Patients diagnosed with COVID-19 according to the World Health Organization (WHO) provisional guideline. A positive result of the SARS-CoV-2 "real-time" reverse transcriptase-polymerase chain reaction (RT-PCR) test in upper respiratory tract specimens of the patients as a definite case, although the SARS-CoV-2 RT-PCR test of the patient was negative, finding an appearance compatible with viral pneumonia in thoracic computed tomography (CT) together with appropriate clinical findings was defined as a possible COVID-19 patient.[2] Exclusion criteria were missing data, age younger than 18 years, patients who were admitted to the intensive care unit (ICU) at the time of admission, and COVID-19 diagnosis was excluded during clinical follow-up, were not included in the study. The patients were divided into 4 groups according to the COVID 19 treatment protocols: Group 1 (only favipiravir), Group 2 (HQ+AZ), Group 3 (only HQ), and Group 4 (HQ+AZ+antibiotics). The gender, age, the medications, underlying comorbidities, possible side effects due to the treatments (cardiotoxicity, hepatotoxicity, nephrotoxicity, elevation of blood uric acid levels), and mortality rates were evaluated. Data were collected from the hospital automation system and transferred to the case forms created by researchers.

Statistical Analysis

The data were analysed with the SPSS Package Program version 22.00 (IBM, Armonk, NY, USA). Number, percentage, mean, median, minimum, maximum and standard deviation were used in the presentation of descriptive data. Chi-Square test was used to compare categorical variables and Kruskal Wallis Analysis was used to compare continuous variables. For statistical significance, $p < 0.05$ was accepted.

Ethical Approval

The study was carried out in accordance with the principles of the 2013 revised Helsinki Declaration. The study was approved by COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Ministry of Health at the date of 04.05.2020 and local ethics committee of our university (dated 03.06.2020, numbered: 2020-08).

RESULTS

A total of 621 patients (256 women and 361 men) diagnosed as COVID-19 (PCR or CT positive) and treated with any drugs were enrolled in the study. The age and gender characteristics of the patients are given in **Table 1**. Most of the patients (n=341, %54,9) were in the HQ +AZ group.

The average age of in group 1 was 66.2±15.7, in group 2 was 56.4±18.8, in group 3 was 49.8±19.5 and in group 4 was 60.7±18.5 years. A statistically significant difference was found between the groups in terms of age (p=0.0001). The median age of group 3 is higher than group 1 and group 4 patients, this difference was statistically significant in the Dunn-Bonferroni corrected paired comparisons (p=0.0001, p=0.001, respectively). The median age of group 2 was lower than group 1, and this difference was statistically significant in the Dunn Bonferroni corrected paired comparisons (p=0.003).

In a comparison of treatment groups with underlying diseases, chronic obstructive pulmonary disease (COPD) and chronic renal failure (CRF) were statistically significantly higher in group 1. There was no significant difference in terms of other diseases and gender (**Table1**).

Levofloxacin (n=55), ceftriaxone (n=46), ceftazidime (n=25), piperacillin-tazobactam (n=17), meropenem (n=16) and imipenem (n=14) were the used antibiotics in group 4.

There was no difference in terms of side effects between the groups according to treatment protocols. In the only favipiravir group, mortality rates were found to be statistically significantly higher. Mortality rates were lowest in the HQ+AZ group (**Table 2**).

Table 1. Summary of demographical characteristics and comorbidities of the patients.

Variables	Total	Favipiravir only (n=49) (Group 1)	HQ+AZ (n=341) (Group 2)	HQ only (n=58) (Group 3)	HQ+AZ + antibiotics (n=173) (Group 4)	P value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Gender						0.687
Female	256 (41.2)	17 (34.7)	146 (42.8)	22 (37.9)	71 (41.0)	
Male	365 (58.8)	32 (65.3)	195 (57.2)	36 (62.1)	102 (59.0)	
COPD						0.026
no	566 (91.1)	41 (83.7)	315 (92.4)	57 (98.3)	153 (88.4)	
yes	55 (8.9)	8 (16.3)	26 (7.6)	1 (1.7)	20 (11.6)	
Diabetes mellitus						0.053
no	526 (84.7)	40 (81.6)	292 (85.6)	55 (94.8)	139 (80.3)	
yes	95 (15.3)	9 (18.4)	49 (14.4)	3 (5.2)	34 (19.7)	
Hypertension						0.053
no	449 (72.3)	30 (61.2)	252 (73.9)	48 (82.8)	119 (68.8)	
yes	172 (27.7)	19 (38.8)	89 (26.1)	10 (17.2)	54 (31.2)	
Cardiac diseases						0.652
no	521 (83.9)	39 (79.6)	291 (85.3)	49 (84.5)	142 (82.1)	
yes	100 (16.1)	10 (20.4)	50 (14.7)	9 (15.5)	31 (17.9)	
Malignancy						0.021
no	593 (95.5)	45 (91.8)	330 (96.8)	58 (100.0)	160 (92.5)	
yes	28 (4.5)	4 (8.2)	11 (3.2)	0 (0.0)	13 (7.5)	
Chronic renal failure						0.029
no	601 (96.8)	45 (91.8)	335 (98.2)	57 (98.3)	164 (94.8)	
yes	20 (3.2)	4 (8.2)	6 (1.8)	1 (1.7)	9 (5.2)	
Organ transplant						1.000
no	619 (99.7)	49 (100.0)	340 (99.7)	58 (100.0)	172 (99.4)	
yes	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.6)	
Immunodeficiency						1.000
no	620 (99.8)	49 (100.0)	340 (99.7)	58 (100.0)	173 (100.0)	
yes	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	
Chronic liver disease						0.595
no	615 (99.0)	48 (98.0)	338 (99.1)	58 (100.0)	171 (98.8)	
yes	6 (1.0)	1 (2.0)	3 (0.9)	0 (0.0)	2 (1.2)	
Rheumatic Disease						0.432
no	615 (99.0)	49 (100.0)	339 (99.4)	57 (98.3)	170 (98.3)	
yes	6 (1.0)	0 (0.0)	2 (0.6)	1 (1.7)	3 (1.7)	

*%: column percentage, p: Chi Square Test, AZ: azithromycin, HCQ: Hydroxychloroquine, COPD: Chronic Obstructive Pulmonary Disease,

Table 2. Summary of side effects and mortality.

Side effects and mortality	Favipiravir only (n=49) (Group 1)	HQ+AZ (n=341) (Group 2)	HQ only (n=58) (Group 3)	HQ+AZ + antibiotics (n=173) (Group 4)	P value
	n (%)	n (%)	n (%)	n (%)	
Cardiotoxicity					0.432
no	49 (100.0)	339 (99,4)	57 (98.3)	170 (98.3)	
yes	0 (0.0)	2 (0,6)	1 (1.7)	3 (1,7)	
Hepatotoxicity					0.358
no	49 (100.0)	328 (96.2)	56 (96.6)	163 (94.2)	
yes	0 (0.0)	13 (3.8)	2 (3.4)	10 (5.8)	
Nephrotoxicity					0.216
no	47 (95.9)	334 (97.9)	58 (100.0)	172 (99.4)	
yes	2 (4.1)	7 (2.1)	0 (0.0)	1 (0.6)	
Exitus					0.0001
no	33 (67.3)	322 (94.4)	54 (93.1)	144 (83.2)	
yes	16 (32.7)	19 (5.6)	4 (6.9)	29 (16.8)	

*%: column percentage, p: Chi-Square Test * HCQ: hydroxychloroquine.

DISCUSSION

COVID-19 is a pandemic that has been causing many deaths globally but there are still not specifically effective antiviral drugs that can currently treat COVID-19. The guidelines prepared according to preliminary results of clinical studies are rapidly changing.[1,2] Due to the variety of drugs used in the treatment of COVID-19, guiding treatment schemes have emerged with the experience in our country and in the world has been released.[7] Only favipiravir, HQ+AZ, only HQ, and HQ+AZ+antibiotics treatment protocols are among the treatment protocols used in our country in early pandemic.

In a retrospective study from Bosnia and Herzegovina; the mortality rate was 5% and the highest mortality rate was in patient over 65 years.[8] The reported COVID-19 related mortality rate was 2.4% in Turkey according to previous study results.[2] We aimed to investigate the optimal treatment by comparing the treatment protocols given, since the continuation of COVID-19 related deaths globally and the fact that the definitive treatment has not yet been found. Additionally, we aimed to compare the side effects and mortality rates of these different treatment protocols.

In our country, the treatment strategy depends on the patient's presence and it should be determined according to the course of the clinical presentation in 48-72 hours of admission. Combination treatments with HQ have a good response to therapy if there is no rapid change in O2 saturation of the patient. Favipiravir was recommended when lung parenchymal infiltration> 50% or in the group with underlying disease or in the group whose saturation is not stable such as intensive care unit patients.[2,7] Favipiravir is an antiviral which is a broad spectrum, that selectively and potently inhibits the Ribonucleic Acid (RNA)-dependent RNA polymerase (RdRp) of RNA viruses, has also been studied in various clinical studies for COVID-19 treatment.[7,9-12] Favipiravir is an intracellular phosphoribosylated precursor to form the active metabolite favipiravir ibofuranosyl-5'-triphosphate (T-705-RTP) was previously used for the treatment of pandemic influenza, has shown potent in vitro activity against SARS COV-2. Overall, favipiravir has shown promising results in clinical studies in multiple countries (such as China, Russia, Japan, the USA, UK, and India). COVID-19 treatment guidelines of many countries have included favipiravir in the treatment protocol.[10] In our country, COVID-19 patients have been treating according to the guidance of the Ministry of Health COVID-19 Guidelines. In early pandemic HQ +AZ, only HQ and HQ +AZ +antibiotics were recommended in non-severe patients' treatments. 5 days of favipiravir treatment was only recommended in severe patients. However, in the subsequent stages of the pandemic, favipiravir started to be used even in the treatment of outpatients.[2] In our study, in which only hospitalized COVID-19 patients were included, increased mortality rates were found in patients who were given only favipiravir treatment compared to the other groups. The reason for this may the treatment recommendations in the early pandemic period when the disease had more unknowns. Or it may be since these patients had already more severe underlying diseases or the clinical presentation of the patients at the time of admission was more severe.

Although there are results supporting the short-term safety of favipiravir,[7,9-15] an early study[13] reported that the most common side effects of favipiravir treatment were mild to moderate diarrhoea, asymptomatic increase in blood uric acid and transaminases, and decreased neutrophil count. In our literature research, we did not find many publications on liver toxicity due to the use of favipiravir treatment. In a controlled study, an increase in liver tests was observed in 2.8% of 35 patients using favipiravir.[13] In a retrospective study from Turkey, it was not reported that liver tests were higher in the hydroxychloroquine group, but significant increases were found in the favipiravir group.[14] We found no hepatotoxicity and cardiotoxicity in the favipiravir group, nephrotoxicity developed in 4.1% of the patients, but there was no statistically significant difference between groups. The reason for the undeveloped toxicity of the drugs may be due to the short-term treatment recommendation.

Hydroxychloroquine is a safer analog of chloroquine and has an antiviral effect against SARS-CoV-2.[7,14,16,17] HQ inhibits SARS-CoV-2's replication in vitro. HQ is a cheap and reliable drug and drug-drug interaction that is low in short-term usage.[17-20] Although it is not known clearly in the treatment of COVID-19, HQ is thought to be a safe drug. In current literature, frequently reported side effects are moderate nausea and diarrhoea, QTc prolongation.[18-21] The usage of HQ in critically ill patients may pose a risk in terms of cardiac toxicities such as ventricular arrhythmias, prolongation of the QT interval, and other cardiac toxicities.[18] In patients with a history of cardiac arrhythmia, daily side effects should be monitored according to the QT distance, and HQ and/or AZ should be discontinued when >300ms.[7]

Seyhan et al.[21] reported that post-treatment QTc measurements of both HQ +AZ group and HQ group were prolonged compared to pre-treatment measurements. In our study, no statistically significant difference was found between the groups in terms of cardiotoxicity. However, we detected cardiotoxicity in 3 patients in the HQ+AZ+antibiotics group, 2 patients in the HQ +AZ group, and in 1 patient in the only HQ group. This can be interpreted as; the possibility of cardiotoxicity increases with the number of growing treatments added to HQ therapy. Ventricular arrhythmia was not detected in our study similarly previous study.[21]

In a study from France, it was reported that HQ therapy was significantly associated with viral load reduction/ loss in COVID-19 patients, and its effect was strengthened with AZ.[2,19,20] In another study from Turkey, AZ was found effective in SARS-CoV-2 RNA-dependent RNA polymerase protein inhibition.[22] A very recently published open-label randomized controlled trial study reported that chloroquine /

HQ treatment added to standard therapy in severe COVID-19 patients caused a significant clinical deterioration, increased risk of renal dysfunction, and increased need for invasive mechanical ventilation.[23] 54.9% of our patients (n=341) were treated with HQ +AZ. With this treatment protocol, cardiotoxicity developed in 2 patients, hepatotoxicity developed in 13 patients, nephrotoxicity developed, and elevation of blood uric acid levels developed in 7 patients, and no statistically significant increase was found in terms of these side effects in comparison with other treatment groups. In addition, mortality occurred in only 5.6% of patients in this group. This rate was the lowest compared to all treatment groups. This may be due to the recommendation of HQ +/- AZ treatment in mild or moderate COVID-19 patients according to the Ministry of Health guidelines.

In addition, other several antiviral medications clinical studies involving oseltamivir, lopinavir, ritonavir, and ganciclovir are used to treat COVID-19, and the treatments recommended in the first months of pandemic in our country were the treatments included in our study. Antibiotic therapy can also be added to treatment for COVID-19 patients, depending on the severity of the concurrent disease. Among the most recommended antibiotics are cephalosporins, quinolones, carbapenems, tigecycline.[24]

In the available literature, no study examining the results of adding different antibiotic treatments to COVID-19 treatment was found. In our study, this group was not examined among themselves. There were 173 patients in this group. The most frequently added antibiotics were levofloxacin (n=55), ceftriaxone (n=46), ceftazidime (n=25). However, data on whether these antibiotics were added empirically or for the treatment of secondary infection could not be reached because the study was retrospective.

In a recent meta-analysis study conducted in 2021,[25] a total of 2702 studies and 12 clinical studies with 1636 patients were analysed. Observational studies have been found to have a moderate risk of bias, and nonrandomized studies have been found to have a significant risk of bias. These meta-analysis data showed that there was no significant difference between favipiravir treatment and standard of care in terms of mortality rate and need for mechanical ventilation in moderate to severe COVID-19 patients. Furthermore, this meta-analysis study revealed no superiority of favipiravir over the standard of care for up to 14 days or other antivirals previously shown to be ineffective for COVID-19, such as hydroxychloroquine, chloroquine, Lopinavir/Ritonavir. It is consistent with the recent meta-analysis findings and may contribute to the literature. The study demonstrated that, the higher mortality rate due to favipiravir was attributed to the administration of this drug to only critically ill patients in the first period of the pandemic. Or the study may lead us to conclude that favipiravir has no effect in the treatment of COVID-19.

CONCLUSION

The study demonstrated that, the higher mortality rate due to favipiravir was attributed to the administration of this drug to only critically ill patients in the first period of the pandemic. Or the study may lead us to conclude that favipiravir has no effect in the treatment of COVID-19. Our study was carried out in our country during the early pandemic period, when treatment protocols were not yet settled and there were many COVID 19 unknowns. Mortality rates were lowest in the HQ+AZ group but this group is not severe COVID 19 patients.

Limitations of the study: The current study has several limitations. It was a single center study and the treatments were given in the first months of pandemic examined.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Ministry of Health at the date of 04.05.2020 and local ethics committee of our university (dated 03.06.2020, numbered: 2020-08).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. https://www.cdc.gov/coronavirus/2019-ncov/index.html [Accessed date:01.March. 2021].
2. Turkish Republic Ministry of Health Covid-19 Guideline (https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf) [Accessed date:01.March. 2021].
3. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/[Accessed date:01.March. 2021].
4. Sun J, Deng X, Chen X, et al. Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System. Clin Pharmacol Ther. 2020;108(4):791-7.
5. Md Insiat Islam Rabby. Current Drugs with Potential for Treatment of Covid-19: A Literature Review. J Pharm Pharm Sci. 2020;23(1):58–64.
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-62.
7. Şener A. COVİD-19 (SARS COV-2) Tedavisi. J Biotechinol & Strategic Health Res. 2020;4:97-104.
8. Arapović J, Skočibušić S. The first two months of the COVID-19 pandemic in Bosnia and Herzegovina: Single-center experience. Bosn J Basic Med Sci. 2020;20(3):396-400.
9. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449-63.

10. Joshi S, Parkar J, Ansari Aet al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021;102:501-8.
11. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: A Simplified Summary. Drug Res (Stuttg). 2021;71(3):166-70.
12. Sreekanth Reddy O, Lai WF. Tackling COVID-19 Using Remdesivir and Favipiravir as Therapeutic Options. Chembiochem. 2021;22(6):939-48.
13. Simonis A, Theobald SJ, Fätkenheuer G et al. A comparative analysis of remdesivir and other repurposed antivirals against SARS-CoV-2. EMBO Mol Med. 2021;13(1):e13105.
14. İzci-Çetinkaya F, Karagöz H, Yıldız O. Comparison of liver safety of favipiravir and hydroxychloroquine in COVID-19 treatment. Klimik Derg 2020;33(3):235-40.
15. Doğan E, Alkan-Çeviker S, Vurucu S, et al.[Investigation of the frequency of adverse effects in patients treated with favipiravir as SARS-CoV-2 treatment]. Klimik Derg. 2021;34(2):95-8.
16. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71.
17. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.
18. Mutlu O, Uygun İ, Erden F. Koronavirüs Hastalığı (COVID-19) Tedavisinde Kullanılan İlaçlar. KOU Sag Bil Derg. 2020;6(3):167-73.
19. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. JAMA Netw Open. 2020;3(4):e208857
20. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949.
21. Seyhan AU, Doganay F, Yilmaz E, et al. Investigation of QT Prolongation with Hydroxychloroquine and Azithromycin for the Treatment of COVID-19. J Coll Physicians Surg Pak. 2020;30(10):153-7.
22. Gedikli MA, Tuzun B, Aktas, A et al. Are clarithromycin, azithromycin and their analogues effective in the treatment of COVID19? Bratisl Lek Listy. 2021;122(2):101-10.
23. Réa-Neto Á, Bernardelli RS, Câmara BMD, et al. An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients. Sci Rep. 2021;11(1):9023.
24. Wang M, Liao Z. SARS-CoV-2 and COVID-19: How much do we know? Acta Virol. 2020;64(3):288-96.
25. Özlüşen B, Kozan S, Akcan RE, et al. Effectiveness of favipiravir in COVID-19:a live systematic review. Eur J Clin Microbiol Infect Dis. 2021;1-9.