Treatment Experience in Patients with COVID-19: Preliminary Results from Kocaeli Turkey

COVID-19 Hastalarında Tedavi Deneyimi: Kocaeli,Türkiye'den İlk Sonuçlar

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Abstract

INTRODUCTION: The first case of pandemic was reported on March 11th of 2020 in Turkey.
METHODS: We attempted a retrospective analysis of COVID-19 patients who were admitted at first month of pandemic in Kocaeli University Hospital. Cases were defined as COVID-19 by clinical, laboratory (RT-PCR) and imaging (CT) criteria. From March 15th to April 20th, 80 cases were hospitalized. Hydroxychloroquine (HCQ), azithromycin (AZM) and oseltamivir (OSM) are recommended for treatment. We aim to share the results of this early treatment strategy.
RESULTS: Among the 80 patients; 14 (17.5%) received HCQ alone, 25 (31.2%) received HCQ and AZM, and 41 (51.2%) received HCQ, AZM and OSM. In the group receiving HCQ treatment, 3.7% were hospitalized for less than 5 days and 13.8% for 5 days and longer; In the group receiving HCQ and AZM treatment, 20% were hospitalized for less than 5 days and 11.3% for 5 days and longer. In the group treated with HCQ, AZM and OSM, 42.5% were hospitalized for less than 5 days and 8.8% for 5 days and longer. (p= 0.0001). The co-administration of the three drugs may be synergistic. When used in combination with AZM and OSM in the early period, it shortened the duration of hospitalization. Since there is not much data about it in the literature yet, we wanted to share our positive experience.
DISCUSSION AND CONCLUSION: Early treatment resulted in early recovery, decreased requirement for intubation, and a very low mortality rate. In this cohort, early diagnosis and treatment with COVID-19 appear to be associated with good outcome.

Keywords: SARS-CoV-2, COVID-19, hydroxychloroquine, early treatment.

Öz

GİRİŞ ve AMAÇ: Türkiye'de ilk pandemi vakası 11 Mart 2020'de bildirildi. Bu zamana kadar tüm ülkeler kendi teşhis ve tedavi protokollerini belirledi.
YÖNTEM ve GEREÇLER: Kocaeli Üniversitesi Hastanesine pandemin in ilk kayın dayatan COVID-19 hastalarının retrospektif analizi yapıldı. Vakalar klinik, laboratuvar (RT-PCR) ve görüntüleme (CT) kriterlerine göre COVID-19 olarak tanımlandı. Türkiye Tıbbi Pandemi Konseyi, Türkiye'de COVID-19'un erken tedavisi için hidroksiklorokin (HCQ), azitromisin (AZM) ve oseltamivir (OSM) kullanımını önermiştir. Bu raporda, bu erken tedavi stratejisinin sonuçlarını paylaşmayı hedefliyoruz.
BULGULAR: Pozitif RT-PCR testi veya tipik BT bulguları ile teşhis edilen 80 hasta arasında; 14'ü (% 17.5) yalnızca HCQ aldı, 25'i (% 31.2) HCQ ve AZM aldı ve 41'i (% 51.2) HCQ, AZM ve OSM aldı. HCQ tedavisi alan grupta,% 3,7'si 5 günden az ve% 13,8'i 5 gün ve daha uzun süre hastanede kalmıştır; HCQ ve AZM tedavisi alan grupta,% 20'si 5 günden az ve% 11,3'ü 5 gün ve daha uzun süre hastanede kalmıştır. HCQ, AZM ve OSM ile tedavi edilen grupta,% 42,5'i 5 günden az ve% 8,8'i 5 gün ve daha uzun süre hastanede kalmıştır. Fark istatistiksel olarak anlamlıydı (p = 0.0001). Üç ilacın birlikte uygulanması, COVID-19 hastalığına karşı sinerjik bir etkiye sahip olabilir. İlk aydaki verilerle elde ettiğimiz sonuçlar, erken dönemde AZM ve OSM ile birlikte kullanıldığında bozulmayı önlediği ve hastanede kalış süresini kısalttığı oldu. Henüz literatürde çok fazla veri olmadığı için olumlu deneyimlerimizi paylaşmak istedik.
TARTIŞMA ve SONUÇ: Deneyimlerimize dayanarak, erken tedavinin erken iyileşme, entübasyon gereksiniminin azalması ve çok düşük ölüm oranıyla sonuçlandığını makul buluyoruz. Bu ilk kohortta, COVID-19 ile erken teşhis ve tedavi, iyi sonuçla ilişkili görünmektedir.

Anahtar Kelimeler: SARS-CoV-2, COVID-19, hidroksiklorokin, erken tedavi

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INTRODUCTION

COVID-19 disease is caused by SARS-CoV-2, a virus belonging to the Coronavirus family. SARS-CoV-2 has caused a global pandemic since December 2019. The first case of the pandemic in Turkey was reported on March 11th of 2020. The symptoms range from a mild cough to severe respiratory distress, usually accompanied by fever and myalgia, and can lead to 2-4% mortality when multiple organ failure develops. Nearly 20% of COVID-19 patients present with severe coagulation abnormalities, which may result in sudden deaths (1-4).

Countries throughout the world make efforts to reduce the incidence, morbidity, and mortality of COVID-19 by breaking the chain of human-human transmission through imposed social distancing and quarantine. In this process, there are differences in strategy for the diagnosis and treatment between countries.

Turkish Medical Pandemic Council initially recommended the use of hydroxychloroquine (HCQ), azithromycin (AZM) and, oseltamivir (OSM) upon the diagnosis of COVID-19 disease. Throughout the pandemic, the treatment protocols changed, due to the lack of a single effective regimen. While OSM was initially given alongside HCQ and AZM, it was later removed from the protocol by the end of the first month.

In this report, we aim to share the results of this early treatment strategy.

MATERIALS AND METHODS

We evaluated a retrospective single-center analysis of COVID-19 patients who were admitted at the first month of the pandemic period in Kocaeli University Medical Faculty Hospital. From March 15th to April 20th, 80 cases were hospitalized. Cases were defined as COVID-19 (+) by clinical, laboratory (Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)) and imaging (chest computer tomography (CT)) criteria.

Oro-nasopharyngeal swabs for PCR tests were taken from each patient with fever, dry cough, other respiratory problems, muscle pain, weakness, and/or underlying disease with symptoms suggestive of each SARS-CoV-2 infection. Also, all patients underwent a CT scan. The CT findings were reported in 4 categories. 1: normal findings; 2: typical COVID-19 findings; 3: atypical for COVID-19, but COVID-19 cannot be excluded, 4: pathological findings other than COVID-19. CT findings.

RT-PCR

Oro-nasopharyngeal swab samples were used for COVID-19 diagnosis using RT-PCR. COVID-19 RT-qPCR Kit includes one-step reverse transcription (RT) and real-time PCR (qPCR) (RT-qPCR) targeting SARS-CoV-2 (2019-nCoV)-specific RdRp (RNA-dependent RNA polymerase) gene fragment. RT PCR test was performed in the Medical Microbiology Laboratory of Kocaeli University Hospital using Roche LightCycler 480 II. Analytical and clinical performances of the kit (COVID-19 RT-

qPCR Tespit Kiti, Bioeksen, İstanbul, TURKEY) was evaluated by the "Turkish Ministry of Health, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products (HSGM)". The Reverse transcription step was 45°C for 15 min, RT PCR conditions were as follows: One cycle of 94°C for 13 min and amplification and detection was 45 cycles of 95°C for 5 sec and 55°C for 35 sec. Amplification curves obtained in the FAM/HEX channels and non-sigmoidal curves were accepted as negative. The oligonucleotide set targeting the human RNase P gene functions as a control of the sampling, nucleic acid extraction, and inhibition.

Treatment protocol

Turkish Medical Pandemic Council's initial treatment recommendations for early treatment of hospitalized patients included HCQ, AZM, and OSM for 5 days, diagnosed either PCR positivity or CT findings with clinical symptoms. HCQ (first day 2x400mg p.o.; 200 mg twice daily) plus AZM (500 mg once daily), plus OSM (75mg twice daily) for 5 days.

During this period we began the treatment with HCQ, AZM, and OSM, simultaneously. AZM was excluded in cases with QT prolongation on ECG (14/80;17.5%). Adults >18 years were included. Pregnant women or patients with G6PD deficiency (based on the patient's declaration only) were not included. Later, in compliance with the recommendations of the Turkish Medical Pandemic Council, we excluded oseltamivir. Our patients without response to the early treatment regimen received favipiravir after this treatment. We gave a 5-day treatment with favipiravir 2x1600mg p.o. for initial loading and then 2x600mg for maintenance. When this regimen did not result in adequate improvement we applied tocilizumab 400mg s.c. on the first day, 200mg on the second, and 200mg on the 3rd day, 800mg in total.

RT-PCR of oro-nasopharyngeal swabs and chest CT were performed in all cases. We evaluated in this study the early treatment regimens in 3 groups.

Group I: HCQ
Group II: HCQ + AZM
Group III: HCQ + AZM + OSM

We also added prophylactic or therapeutic doses of anticoagulants in the regimens of our hospitalized patients with risk factors. The treatment was continuously adjusted using the follow-up laboratory results.

Statistical analysis

MedCalc Statistical Software version 19.2.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) used for statistical analysis. The sociodemographic, clinical, laboratory variables were evaluated using the Chi-squared and Annova test to compare the difference between patients. We evaluated the length of hospital stay with Kaplan-Meier statistical analysis.

The statistical significance was set as p < 0.05.

Ethics statement

Data presented herein were collected retrospectively from routine care using the electronic health recording system of the hospital with the permission rules of the Health Minister evaluated (2020-05-13T161042) for the processing of personal data. After that permission, this non-interventional retrospective-single center study has been approved by our institutional ethics board committee (Kocaeli University N°: 2020–05-21).

RESULTS

Of the 80 patients who received treatment in our hospital between March 15th-April 20th, 39 (48.7%) were males and 41 (51.2%) were females. There was no difference between the 3 groups in terms of age, gender, co-morbidities, and positive RT-PCR results. PCR was positive in 64% of the patients hospitalized. The demographic features are shown in Table 1. Approximately half of the patients (49%) had co-morbid diseases such as diabetes mellitus, chronic lung, cardiac, kidney or liver diseases.

Among the 80 hospitalized patients, diagnosed with a positive RT-PCR test, or typical CT findings; 14 (17.5%) received HCQ, 25 (31.2%) received HCQ and AZM, and 41 (51.2%) received HCQ, AZM, and OSM. Our 3 patients without response to the early treatment regimen received favipiravir after this treatment. From the three patients, one patient who developed cytokine storm under favipiravir treatment required tocilizumab. Hence, our treatment calendar consisted of three stages. The patients who did not respond to the early stage of treatment received favipiravir. We managed the timing of all these medications by closely monitoring the clinical findings (O2 saturation, fever, worsening in symptoms) and biochemical parameters (increase in ferritin, CRP, LDH, AST, D-dimer, troponin, or decrease in fibrinogen and worsening lymphopenia). When biochemical parameters were evaluated at the hospital admission, there was no statistically significant difference in ALT, AST, CPK, CRP, D-dimer, LDH values, but there was a significant difference in lymphocyte counts. (Table 2). IL-6 blockade with tocilizumab also gave good results for the treatment of cytokine release syndrome in COVID-19.

According to PCR results (n = 80), 65% of the patients were with 5 days or shorter hospital stay and 35% with longer than 5 days hospital stay. Within the group with a hospital stay of longer than 5 days, 21% were RT-PCR negative and 78% were RT-PCR positive. The difference was not statistically significant but by a little difference (p = 0.0513).

Table 1. Demographic features according to the treatment groups

Treatment groups	HCQ (14)	HCQ + AZM (25)	HCQ + AZM + OSM (41)	Total	P value
Gender (M/F)	6/8 (7.5/10)	11/14 (13.8/%17.5)	22/19 (27.5/23.7)	39/41 (48.7/51.2)	0.665
Age	40.8 ±15,05	44±18,4	48,3±16,4		0.334
65 years > or <	12/2 (15/2.5)	20/5 (25/6.2)	31/10 (38.7/12.5)	63/17 (78.7/21.3)	0.715
Co-morbidities (-/+)	9/5 (11.3/6.2)	15/10 (18.8/12.5)	18/23 (22.5/28.7)	42/38 (52.5/47.5)	0.278
RT-PCR (- /+)	2/12 (2.5/15)	6/19 (7.5/23.7)	21/20 (26.2/25)	29/51 (36.2/63.8)	0.327**
CT (N./C./At.C.)*	7/2/3 (9.2/2.6/3.9)	9/13/2 (11.8/17.1/2.6)	7/25/8 (9.2/32.9/10.5)	23/40/13 (30.3/52.6/17.1)	0.025
5 days > or < Hospitalization	3/11 (3.7/13.8)	16/9 (20/11.3)	34/7 (42.5/8.8)	53/27 (66.2/33.8)	0.0001

Abbreviations: M: male, F: female, HCQ: hydroxychloroquine, AZM: azithromycin, OSM: oseltamivir, RT-PCR: *reverse transcription polymerase chain reaction* , Ct: cycle of thresold
*CT: chest computer tomography: N normal; C: typic COVID-19; at.C: atypic COVID-19 findings
**Between positive RT-PCR results

Table 2. Biochemical markers according to the treatment groups

Biochemical markers	HCQ	HCQ + AZM	HCQ + AZM + OSM	P value
ALT	35.6±28.9	23.5±13.7	34.5± 26.7	0.16
AST	46.7±53.9	25.6±9.7	37.7±30	0.12
CPK	87.7±49.8	104.8±70.9	144.9±126.5	0.25
CRP	28.3±45.3	24.4±54	61.3±75.7	0.06
D-dimer	0.95±1	0.54±0.56	1.09±1.5	0.23
LDH	280±166.9	227.7±92.2	319.9±259.3	0.25
Lymphocytes	1869.2±1126.4	1761.8±755.1	1155.1±481.4	0.001

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, CPK: creatinine phosphokinase, CRP: C- reactive protein, LDH: lactate dehydrogenase, HCQ: hydroxychloroquine, AZM: azithromycin, OSM: oseltamivir

In the group receiving HCQ treatment, 3.7% were hospitalized for less than 5 days and 13.8% for 5 days and longer; In the group receiving HCQ and AZM treatment, 20% were hospitalized for less than 5 days and 11.3% for 5 days and longer. In the group treated with HCQ, AZM and OSM, 42.5% were hospitalized for less than 5 days and 8.8% for 5 days and longer. The difference was statistically significant (p= 0.0001) (Figure 1).
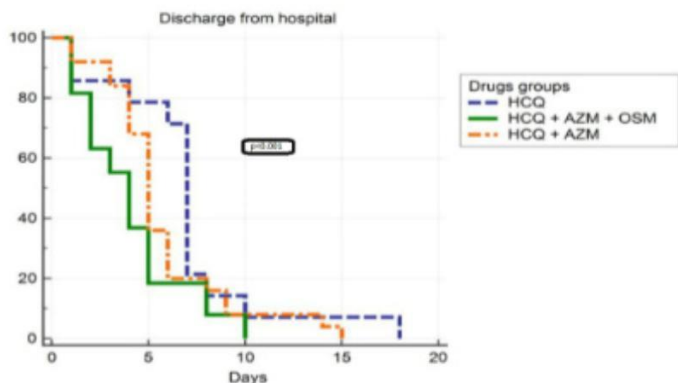

Figure 1: Hospital stay of three treatment group

The majority 95% of patients responded to these treatment regimens. Three patients with progressive respiratory problems, recurrent fever, increased ferritin levels or CRP, or progressive lymphopenia received favipiravir near the end of the 5-day treatment. Two patients responded very well to favipiravir. The third patient without response to favipiravir received tocilizumab after favipiravir. All three recovered and were discharged in good health. One patient, with malignancy who had received chemotherapy a week ago, required intubation in the intensive care unit (ICU) but was lost despite all efforts

DISCUSSION

Previously, Herpes (eg Epstein-Barr virus) or Influenza viruses have been shown to provoke a cytokine storm in patients without underlying immunological disease (5). A severe cytokine storm caused by a viral factor is a new finding. The need for the development of effective therapeutics to prevent the cellular entry and replication of Coronavirus resulted in repurposing potential antivirals (lopinavir, remdesivir, OSM, AZM, ribavirin, and HCQ towards V-ATPase, protein kinase A, SARS-CoV spike glycoprotein/ACE-2 complex and viral proteases) for the treatment of SARS-CoV-2 infection (6). In Turkey, three protocols emerged with the following aims: one treatment protocol using HCQ, AZM and OSM aimed at preventing the initial attachment of the virus, another protocol using antiviral drugs such as favipiravir, lopinavir when the initial regimen failed, and the following protocol using tocilizumab IL-6 blockers when cytokine storm began develop. The use of these protocols were recommended by the Turkish Medical Pandemic Council and was adopted in our institution.

We used both RT-PCR and CT in our hospital for the diagnosis of COVID-19. Either RT-PCR or CT positive and the patient has symptoms or having underlying diseases (chronic lung, cardiac, kidney, liver diseases, diabetes mellitus etc.), have been treated by hospitalization.

Zareifopoulos N et.al. (7) mentions a point of controversy in their study on the management of mild cases of confirmed infection. The repurposing of antivirals with potentially severe side effects may result in greater damage in cases of mild disease which may be self-limiting. However, in our experience, close clinical follow-up helps solve newly arising problems using simple measures. This is why we believe early hospitalization and close observation help detect the early signs of significant complications (such as a cytokine storm) and intervene in a timely manner. We had limited ICU patient experience. We believe this was caused by our policy of early hospitalization / treatment and control of the underlying diseases as well as COVID-19.

Our experience in the treatment increased over time which enabled us to limit the number of patients requiring ICU care. Although advanced age and underlying disease are known to be associated with an unfavorable outcome, we have also observed young patients who followed a severe course of the disease, hence the difficulty of predicting the outcome. In our patients, the underlying disease was not associated with an increased risk of worse clinic outcomes, although this may change over time with an increasing number of patients. The death of one patient in our study group was associated with underlying malignancy. With the increased use of chest CT scans during the pandemic, two additional patients were newly diagnosed with lung cancer. Anticoagulant therapy has also gained importance in preventing complications as our understanding of their mechanism increases.

WHO includes HCQ in its list of essential medicines because of proven in vitro activity against SARS-CoV-2, by increasing endosomal pH required for virus-cell fusion. HCQ also has immunomodulatory activity and enhances the activity of regulatory T cells (8-10). The study by Andreania J et. al. (11) has shown that HCQ and AZM have a synergistic effect in vitro on SARS-CoV-2 at concentrations compatible with those accumulated in human lungs. Several recoveries have been reported using lopinavir/ritonavir in combination with the anti-flu drug OSM. Remdesivir (which has been previously administered in cases of Ebola), HCQ, favipiravir and co-administered darunavir and umifenovir have also recently been reported as having anti-SARS-CoV-2 effects (12-16). Although there was not a very balanced distribution in the distribution of our CT findings, the typical COVID-19 findings of the group receiving triple therapy were as high as 33% in CT, and interestingly, this group left the hospital with triple therapy in a shorter time.

The role of HCQ in the treatment of COVID-19 is not fully known at the beginning of pandemic. First of all Chen et al. from China share their results with 62 patients that they found HCQ improved the clinical recovery and pneumonia assessed by chest

CT scan. Singh et.al. conducted in their meta-analysis of three studies on HCQ and concluded no benefit on viral clearance and increase in mortality (17). The results we obtained with the data in the first month were that when used in combination with AZM and OSM in the early period, it prevented deterioration and shortened the duration of hospitalization. Since there is not much data about it in the literature yet, we wanted to share our positive experience. Although the treatments were completely determined according to the suitability of the patient, the biochemical parameters of the group receiving triple treatment were more disrupted, but those who received this treatment also improved more quickly.

As Million M et.al.(18) mentioned in their study from France in the context of a pandemic with a lethal respiratory virus, we believe that early detection of positive cases and carefully controlled treatment together with HCQ+AZM+OSM (especially in Influenza season) should be used in individuals with mild symptoms before signs of severity appear. Treatment strategies in the world have also differed a lot. The use of HCQ has been at the forefront of the three countries (China, France and Turkey) in the systematic early treatment protocol. Although there are studies about HCQ increasing mortality or excessive side effects, we did not find any of them when used at the right time and with proper follow-up (19, 20). Our experience with the early treatment protocol (dual or triple combination) was positive about the effect on not progressing to severe clinical course. Clearer results will be achieved as treatment experiences are shared from all countries.

CONCLUSION

For diseases caused by viral agents, there are generally no effective antiviral drugs. However, with symptomatic treatment, we do generally help the body save time to beat the factor. Although no specific drug currently exists against COVID-19, the repurposing of drugs we used has been effective in helping patients heal without the need for treatment in ICU. We also believe that early treatment is one of the mainstays of achieving early recovery and a low mortality rate. In this initial cohort, early diagnosis and treatment of COVID-19 appear to be associated with good outcome.

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