The effect of Hydroxychloroquine use due to rheumatic disease on the risk of Covid-19 infection and its course

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June 1, 2021

Abstract

Introduction COVID-19 virus continues to spread and die worldwide. Some studies examining hydroxychloroquine as a prophylactic agent reported that its efficiency and reliability have not been proven so that it must not be used for prophylaxis other than clinical researches. However we think that the results of this study we conducted in a local area will contribute to the literature data. Methods The study was designed as adult patients who were in follow-up taking HC due to their chronic diseases were included. 384 patients who were taking hydroxychloroquine regularly and 299 patients who were not taking hydroxychloroquine were included. The primary outcome of this study is to detect a positive PCR result in patients who received a PCR test and to determine the incidence rate and its course of the disease among those who were taking HC and those who were not taking hydroxychloroquine. Results The majority of the patients (median age: 51.8- range 17-89) were women and housewives. In the patient group using hydroxychloroquine, 22 patients were tested for PCR and only 2 positive patients were found. Covid-19 was detected in 24 (8.02%) of 65 (21.73%) patients who underwent PCR test at Control group (n = 299). PCR positivity was statistically lower in the HK group (n = 2, 0.52%, n = 24, 8.02%, respectively, p = 0.0001). Conclusions Our study supported the fact that there is a lower PCR positivity and symptoms are milder among patients who are using HC regularly, as compared to those who are not using hydroxychloroquine.

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KeyWord: hydroxychloroquine, SARS-CoV-2, Covid-19, prophylaxis, pandemic

İntroduction

According to Chinese authorities, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) (COVİD-19), which is a member of the Coronavirus family, has spread rapidly from China to the rest of the world and stopped the life, leaving its mark on the future after 2020. The covid-19 virus that is extracted from patients with pneumonia at Wuhan is an enveloped single-stranded RNA beta-coronavirus. The genomic sequence of Covid-19 shares 79.5% sequence identity to other coronaviruses that cause Severe Acute Respiratory Syndrome (SARS-CoV). The COVID-19 virus permeates to human alveolar epithelium cells by binding its spike S protein to angiotensin converting enzyme 2 (ACE2) receptor.[1] The number of cases continues to increase since the COVID-19 virus is rapidly transmitted from human to human. The most important property of this virus whose source has not yet clear is the fact that it can rapidly transmit from human to human through droplets and contact. Thus, it has affected large amounts of people in a short time. This was declared by World Health Organization as a pandemic and emergency. Globally, as of 7 January 2021, there have been 85.509.194 confirmed cases of COVID-19, including 1.868.622 deaths, reported to WHO.[2] The infection is still uncontrolled in many countries and continues to show its effect. Its course is not yet sufficiently predicted. To reduce the load of Covid-19, effective vaccines and non-pharmacological intervention strategies such as personal, regional, and global isolation or quarantine and full-scale lockdown are adopted. It has a wide clinical spectrum ranging from asymptomatic patients to those with mild symptoms or those requiring hospitalization and even intensive care unit support and may result in death. The majority of Covid-19 patients who are admitted to the intensive care unit have comorbid diseases so they have more hospitalization complications. Therefore, effective treatment can improve the prognosis.[3] The studies for the treatment of the worldwide spreading Covid-19 virus are in progress. The multi-centered clinical studies in China showed that Chloroquine phosphate, which is a medication primarily used to treat malaria but commonly used for rheumatic diseases, has an apparent efficacy and acceptable reliability for Covid-19-related pneumonia.[4] Chloroquine is used to treat and prevent Malaria, and an anti-inflammatory agent in the treatment of rheumatoid arthritis, lupus erythematosus, and porphyria cutanea tarda. The studies also revealed that it shows a potential wide-spectrum antiviral activity enhancing the endosomal pH needed for virus and cell fusion and intervening with glycosylation of the cellular receptors of SARS-CoV.[5-7] The antiviral and anti-inflammatory activity of hydroxychloroquine (HC) can demonstrate its strong efficiency to treat patients with COVID-19 pneumonia. It was emphasized that there are different opinions about the use of HC among countries, but this should be supported by further studies. Some studies reported that there is no enough information on this subject and recommended the controlled use of HC, while some studies reported that it should be used in the treatment protocols.[4,8] Some studies reported that none of the agents are effective to prevent Covid-19. Some studies examining HC as a prophylactic agent reported that its efficiency and reliability have not been proven so that it must not be used for prophylaxis other than clinical researches. However, the results of ongoing studies on prophylaxis (NCT04308668, NCT04303507, NCT04318015, NCT04318444) will enlighten the discussions on this subject. Our study aims to examine the effects of hydroxychloroquine (HC) on the frequency and course of Covid-19 in patients who were ad-

ministered with HC for their chronic diseases.[9] Considering these findings in the current scientific literature, which were mostly contrary to the potential anti-viral effects of these compounds, we think that the results of this study we conducted in a local area will contribute to the literature data.

Method:

Setting and data source

The study was designed as an observational, retrospective questionnaire study in which adult patients who were in follow-up in the Department of Rheumatology and taking HC due to their chronic diseases were included. All the patients who were in follow-up in the Department of Rheumatology in our hospital between March and April 2020 were scanned via the "hospital digital registration system". Among them, 384 patients who were taking HC regularly were included in the study. 299 patients who were not taking HC were included in the control group. The study protocol was reviewed and approved by Izmir Bakircay University Ethics Board. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Written informed consent was not necessary because no patient data has been included in the manuscript. And the patients are phoned and their verbal consents were obtained.

Study population

We used the data of patients who were in follow-up in the Department of Rheumatology. The patients who were continuing to take HC in this period were assigned as the experimental group, while those who were not taking HC were assigned as the control group. The patients who applied to the Rheumatology Department but were not diagnosed with rheumatic disease were excluded. The patients are phoned and their verbal consents were obtained. The consents were obtained verbally since it was not appropriate for the patients to come to the hospital in terms of contamination risk in the Covid-19 pandemic process. It was emphasized that their data will not be shared in any way. The information on their demographical characteristics (age, gender, occupation), primary diseases, other medications than HC they used, the dose of HC they received, whether they had Covid-19, whether they were administered with PCR test as a potential case, if so the results of the test (From the individual's self-declaration or central result system referred to as "PHMS" Public Health Management System), whether people who they were living together or those with whom they had close contact were diagnosed with Covid-19 and received Covid-19 treatment, were recorded. Information on the course of disease (follow-up at home, hospitalization, intensive care unit, exitus) was collected from the hospital registration system or the patients themselves.

Main outcomes and measures

The primary outcome is to detect a positive PCR result in patients who received a PCR test and to determine the incidence rate of the disease among those who were taking HC and those who were not taking HC.

Statistical analysis

The statistical analysis was performed using SPSS 22 (SPSS Inc., Chicago, IL) software program. The demographic data were analyzed based on the means and standard deviation and the Chi-square test was used for group comparisons. Continuous data were expressed as mean $\pm$ standard deviation and categorical parameters were computed as percentages, where appropriate. If $p<0.05$, then the result was considered statistically significant.

Results

The patients who were taking HC agents due to rheumatic disease and those in the control group were examined (Figure 1). It was seen that the majority of patients were female and housewives (Figure 2, Table 1). The median age was 51.8 years (from 17 to 89) and the majority of them were in the 50-60 age band (Figure 3). It was found that 56 (14.6%) patients had comorbidity (14.6%), while 34 (8.9%) had diabetes and 9 (2.3%) had hypertension (2.3%). All the patients were taking HC 1x1/day or 2x1/day. Thirty-two (8.33%) patients who were included in the study could not be reached by phone. Based on the phone calls,

the number of patients who were in close contact with Covid-19 patients was 15 (3.9%). The number of the patients who underwent Covid-19 examination for any reason was found to be 5.72%(22/384). Only 2 (0.52%) patients under our observation were diagnosed with Covid-19. Both of them were mild cases and without hospitalization. When we examined 299 patients who were under follow-up because of their rheumatic diseases but were not taking HC, PCR positivity was detected in 24 (8.02%) of 65 (21.73%) patients who received a PCR test. It was also found that two patients who were not using HC died due to Covid-19. When we compared the PCR positivity rate between the patients who were taking HC (n=2) and those who were not using HC (n=24), we found that the PCR positivity was statistically lower in the HC group (Respectively n=2 0.52%, n=24 8.02%, p=0.0001).

One of the Covid-19 patients was a 42-year-old teacher and the other was a 48-year-old housewife. Both of them had connective tissue disease. The phone calls with the patients revealed that the teacher patient has not worked during the pandemic period but her husband contacted other patients (for about 1 hour) when their daughter got sick. Then first her husband and then she was diagnosed with Covid-19 (PCR and thorax CT positive). She healed at home with mild myalgia and fever which lasted for few days. The other patient who was a housewife had no contact with a confirmed Covid-19 patient. But her husband was a plumber and had a plumbery. She had an irritable cough and her thorax CT was compatible with viral pneumonia but healed at home without any complication.

Discussion

Severe acute respiratory syndrome (SARS) is caused by a newly discovered coronavirus (Covid-19). No effective prophylactic or post-exposure therapy is currently available.[10] Some disease-modifying agents commonly used to treat patients with rheumatic diseases/autoimmune disorders, such as HC and colchicine, are explored as potential treatments for COVID-19. However, their prophylactic roles are still not certain.[11] Hydroxychloroquine was first approved for medical use in the USA in 1955.[1] The studies showed that these molecules inhibit viral DNA and RNA polymerase enzymes and also inhibit viral protein glycosylation and viral proliferation. The virus binds to target cells by angiotensin-converting enzyme 2 (ACE2). HC was preferred in SARS treatment because it can inhibit the terminal glycosylation of ACE2 and modify cytokine release. It was thought that it can be used in Covid-19 treatment.[6] It was observed that in clinical use, HC prevented the progress of virus-related pneumonia. In March 2020 hydroxychloroquine (HC) was reported to have a positive effect in a Covid-19 treatment open-label non-randomized clinical trial. In this study, hydroxychloroquine and azithromycin were used to prevent bacterial infection, and no treatment was applied to the negative control group. 20 of 36 patients were administered with azithromycin and 600 mg/day HC. A significant decrease in viral load was found on day 6, as compared with the control group.[12] However, Rosendaal reported that there were great methodological deficits in this study and the results did not support the results on the efficiency of hydroxychloroquine in Covid-19.[13] Similarly, Goldman et al. stated in their comment that randomized controlled studies are needed for the data to be significant.[14] The difference of our study from the study by Gautret et all. is that our study was not an intervention and treatment study and it was only an observational study for patients with HC use history. Currently, there is still no suggestion to use antiviral agents as prophylaxis for Covid-19 but many studies are in progress to evaluate the effects of treatment as well as prophylaxis.[9] We hope that the results of the ongoing studies will give us more insight into prophylaxis and help with prophylaxis agents, which will reduce the rapid spread of the disease. Another study reviewed all available resources to overview the potential role of HC in preventing the spread of COVID-19 and to determine a reasonable schedule for its use as prophylaxis. It was stated that there were very limited clinical data on the prophylactic role of HC. It was reported that HC is used for prophylaxis because it showed reductions of exacerbation of pneumonia, duration of symptoms, and delay of viral clearance, all in the absence of severe side effects. As a result, they said that further information can be obtained only by wide prospective randomized studies.[15] We hope that our data and a meta-analysis of the results of similar observational studies and ongoing randomized studies serve to justify the large-scale use of prophylactic HC. Although research on the use of HC in the control of COVID-19 is still preliminary, the potential use of these drugs is supported by factors such as their usability in the treatment of rheumatic and infectious diseases such as malaria, low cost and history of use. Furthermore, HC is increasingly pre-

ferred because it is a less toxic derivative of CQ and showed better results in inhibiting the proliferation of SARS-CoV-2.[16] The review study by Preira reported that a meta-analysis was conducted to investigate the effects of using CQ and HC in 16,679 patients with rheumatic disease, but their effects on cardiomyopathy and neuropathy were not confirmed. In the systematic literature review, he examined cardiac complications associated with CQ and HC and noted that cardiac disorders related to CQ or HC were rare, but a prolonged administration resulted in serious adverse effects. He emphasized that there is no evidence on the preventive effect of HC on Covid-19 and suggested that sharing HC use information will lead to healthier results.[16] Our main purpose was to determine whether HC can be used or not, instead of reaching a conclusion. We aim to share our data that will likely to contribute studies with larger participation.

In a data analysis conducted in Israel, all COVID-19 cases were screened and it was found that 36 patients were using HC regularly and only three (0.23%) patients were COVID-19 positive.[11] In our study, 384 patients who were using HC were screened and it was found that 2 (0.52%) of 22 patients who were examined were Covid-19 positive, and 24 (8.02%) of 65 patients who were not using HC and examined were Covid-19 positive. In the study by Boulware et al., randomly selected 821 asymptomatic Covid-19 patients were administered with placebo and HC after the exposure. They reported that there was no difference between the two groups and no serious adverse effect was seen.[17] Rajasingham et al. did not find a significant decrease in the incidence of Covid-19 based on the prophylaxis results of 1483 health professionals before the HC exposure (400 mg HC twice a week and 400 mg HC and placebo twice a week).[18] Abella et al. conducted a randomized, double-blind, placebo-controlled study on a population of health professionals but early stopped the study since they predicted that there would be no significant difference. However, they did not report any serious side effects.[19] Although there are no many studies suggesting the use of HC for prophylaxis, more reliable data will be obtained if all researchers shared their data and the results of randomized controlled studies are provided. It seems that; Covid-19 will continue to be a threat to the world.

Conclusion

Our study supported the fact that there is a lower PCR positivity and symptoms are milder among patients who are using HC regularly, as compared to those who are not using HC. Whether prior exposure prophylaxis is effective in populations at high risk is a separate question and studies are continuing and will continue. If our results are reproduced in other ongoing studies, our results will be verified.

Limitations

We do not know the rate of patients who are using HC regularly among all suspected Covid-19 cases. We examined only the HC patients in an isolated area. The lack of precisely recorded comorbidities in our all data directed us to only the patients who were registered and using HC regularly. Another limitation was the lack of data of patients who could not be reached by phone and of those in the control group. Another limitation was the fact that the contact histories of patients were evaluated only based on the self-declaration. It is difficult to determine who contacted Covid-19 patients, which doesn't make much sense today.

Author contributions: All the authors contributed intellectually and directly to the preparation of this article, and read and approved the current version of the article for publication.

Conflicting interests: The Author(s) declare(s) that there is no conflict of interest.

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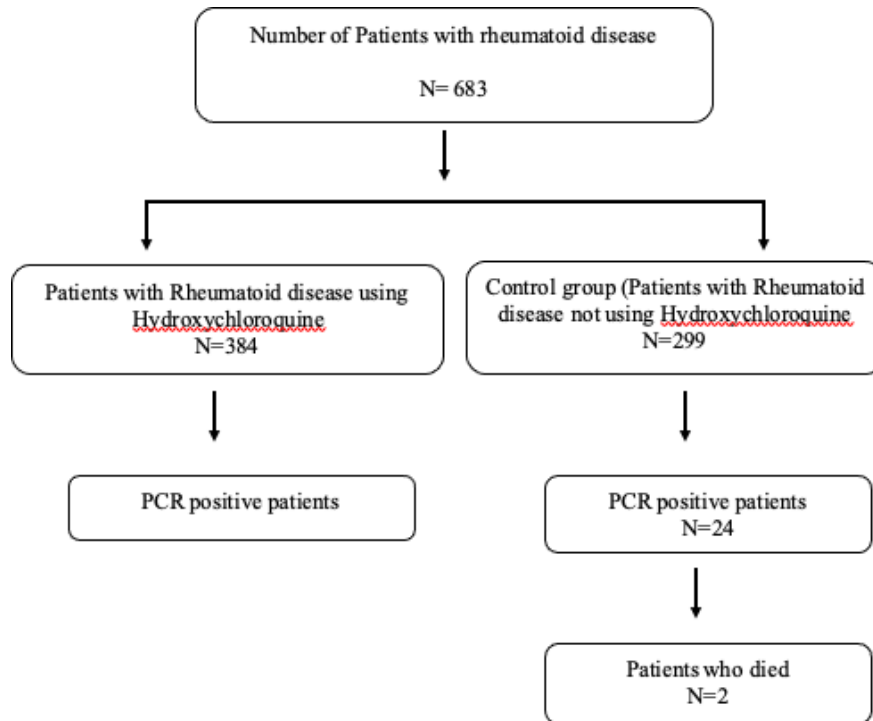
Figure 1. Working flow chart

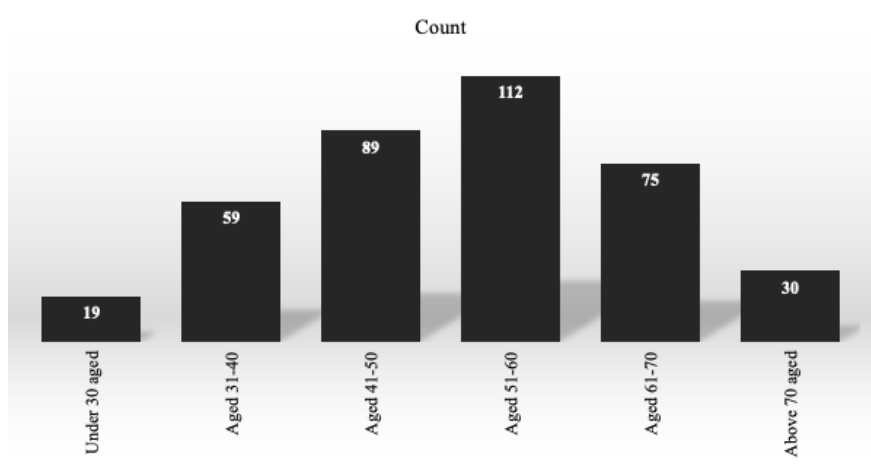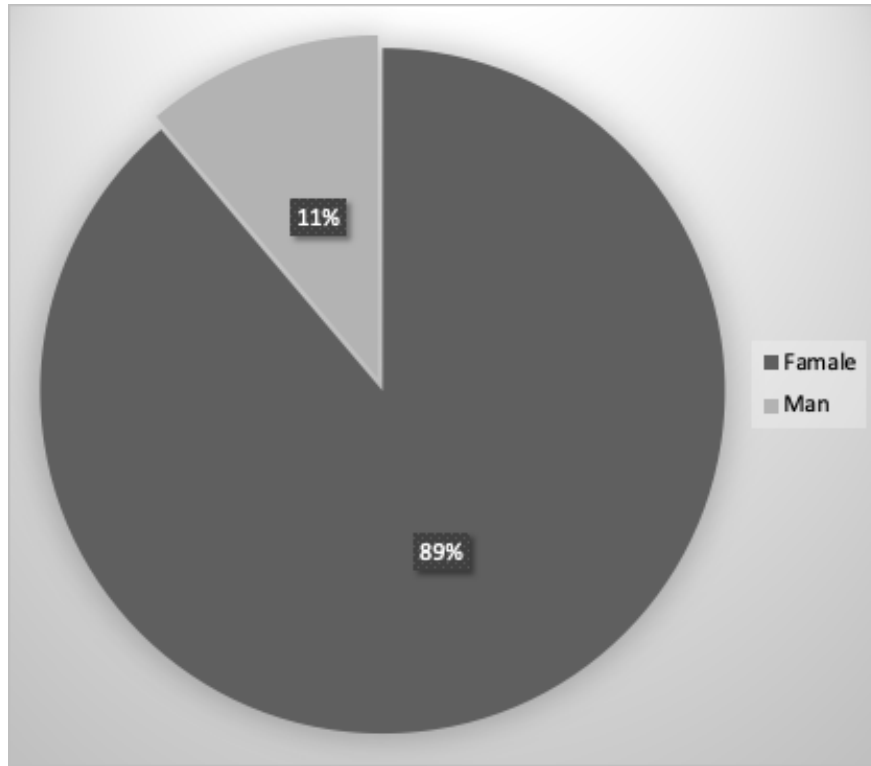Figure 2. Gender distribution of patients using hydroxychloroquine

Figure 3. Distribution of patients using hydroxychloroquine by age groups

Table1. Occupational distribution of patients

Occupation	n	%
Housewife	233	60.7
Retired	47	12.2
Officer*	24	6.3
Self-employment	34	8.9
Student	3	0.8
Worker	30	7.8
Missing	13	3.4
Total	384	100.0

* Civil servants include 9 healthcare workers (4 nurses, one doctor, 4 others) and 5 teachers)

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Table1.docx available at https://authorea.com/users/417382/articles/524514-the-effect-of-hydroxychloroquine-use-due-to-rheumatic-disease-on-the-risk-of-covid-19-infection-and-its-course

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