TREATMENT ADHERENCE OF COVID-19 PATIENTS
GETTING MEDICATION AT HOME

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Abstract: Introduction: Turkey has adopted outpatient treatment of COVID-19 since the beginning of the pandemic. In the outpatient treatment of COVID-19 in Turkey, only hydroxychloroquine was initially used, favipiravir was added to the treatment, and finally, hydroxychloroquine was removed from the treatment and only favipiravir was used. Our study aims to examine the adherence to the recommended treatment of people diagnosed with COVID-19 who have received outpatient treatment without hospitalization and their attitudes and declared behaviors towards using the medications they were given free of charge.

Methods: This follow-up study was conducted between February 15, 2021, and May 15, 2021, by telephone survey method in the Lüleburgaz District of Kirklareli City. The study participants were 4368 people who were diagnosed with COVID-19 with a positive PCR test in Lüleburgaz District between February 15 and May 15, 2021, and were given hydroxychloroquine and/or favipiravir drugs for home use after being deemed suitable for outpatient treatment according to the guidelines of the Republic of Turkey Ministry of Health.

Results: 88.1% (n = 3849) of the survey respondents reported using the given medications regularly, while 11.9% (n = 519) did not use them regularly. The most important socio demographic factor affecting the regular use was age, and the patient-centered factor was the sense of trust. Conclusion: In the fight against COVID-19, measures to increase the sense of trust of patients who are expected to adhere to the treatments should be considered a priority.

Keywords: COVID-19, Favipiravir, Hydroxychloroquine, Medication Adherence, Outpatient Therapy.

INTRODUCTION

Since the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020, the disease has remained on the world’s number one health agenda. On the same day as the WHO pandemic declaration, the first case of COVID-19 in Turkey was officially announced (1). The first case initiated discussions about the treatment of people diagnosed with COVID-19 because, as of the date of the first case in Turkey, there is no proven and approved treatment agent for the treatment of Covid-19 (2). Since then, COVID-19 treatment recommendations have been published by the Republic of Turkey Ministry of Health. These recommendations can be examined in two groups of hospitalized patients and for follow-up at home (outpatient treatment) (3). In the first published guidelines for outpatient treatment, only hydroxychloroquine was recommended, favipiravir was added to the treatment with the phrase “and/or”, and finally hydroxychloroquine was removed from the treatment guidelines and only favipiravir was recommended for outpatient treatments (4). This study aims to examine the adherence to the recommended treatment of people diagnosed with COVID-19 who have received outpatient treatment without hospitalization and their attitudes and declared behaviors towards using the given medications free of charge.

The Republic of Turkey Ministry of Health Treatment Recommendations for Outpatient COVID-19 Patients

In the first guidance published by the Republic of Turkey Ministry of Health on March 23, 2020, it was recommended that patients with the following characteristics be hospitalized and monitored for possible severe disease and complications (3):

- Those over 50 years old
- Those with underlying diseases (cardiovascular diseases, immunosuppressive conditions, especially DM, HT, cancer, chronic lung diseases),
in the guideline published on July 71x59 for free (7). drugs have been delivered to the patients’ residences context, free hydroxychloroquine and/or favipiravir a presidential decree issued on April 14, 2020. In this scope of COVID-19 in Turkey are ruled to be free by mentioned earlier (4). recommended the use of favipiravir only with the dose table pneumonia treated on an outpatient basis but recom with asymptomatic, uncomplicated, or mild-moderate recommendation of hydroxychloroquine for patients updated on May 7, 2021, the Ministry removed the in the “COVID-19 Adult Patient Treatment” guideline some time as hydroxychloroquine and/or favipiravir. The treatment guidelines published by the Republic of Turkey Ministry of Health have changed dynamically during the pandemic and were changed frequently according to the recommendations of the science council established by the ministry (5). For the use of hydroxychloroquine in the guide published on April 12, 2020, it is mentioned: “The available scientific data are asymptomatic and do not strongly support the start of hydroxychloroquine for individuals who have tested positive for COVID-19 PCR. However, based on general information that early start of medications is more effective, hydroxychloroquine can be started if the physician evaluating the patient approves and on the condition of being careful about side effects” (4). In the guideline published on July 31, 2020, favipiravir was added to the treatment of outpatient patients with the phrase “and/or”, to load 2 x 1600 mg (8 tablets of 200 mg) on the first day and then 2 x 600 mg (3 tablets of 200 mg) for the four following days (4, 5, 6).

The Republic of Turkey Ministry of Health’s recommendation for outpatient treatment continued for some time as hydroxychloroquine and/or favipiravir. In the “COVID-19 Adult Patient Treatment” guideline updated on May 7, 2021, the Ministry removed the recommendation of hydroxychloroquine for patients with asymptomatic, uncomplicated, or mild-moderate pneumonia treated on an outpatient basis but recommended the use of favipiravir only with the dose table mentioned earlier (4).

All inpatient and outpatient treatments within the scope of COVID-19 in Turkey are ruled to be free by a presidential decree issued on April 14, 2020. In this context, free hydroxychloroquine and/or favipiravir drugs have been delivered to the patients’ residences for free (7).

Treatment Adherence

The adherence of patients to regulated treatments has been discussed for many years. At a meeting of the World Health Organization in 2001, the concept of treatment adherence was defined as “the extent to which the patient follows the medical instructions” (8). According to this definition, patients are perceived as people who are instructed by health care providers and who must follow these instructions. However, in the modern treatment approach, it is envisaged that health care providers will inform the patients, offer alternative methods of treatment and leave the choice to the patient. In other words, there should be cooperation between the service providers and the service receivers regarding the nature of the health service to be provided (9). In this context, the concept of treatment adherence has been redefined, and the definition of “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” has been adopted (10). Patients’ adherence to regulated treatment is one of the most crucial factors affecting treatment success. Low treatment adherence increases morbidity and mortality rates and therefore creates a great additional cost for health systems. Numerous studies prove the negative consequences of low treatment adherence for chronic diseases such as asthma, diabetes, and cardiovascular disorders, as well as infectious diseases such as HIV and tuberculosis (11).

MATERIAL AND METHODS

Study Design

This follow-up study was conducted between February 15, 2021, and May 15, 2021, by telephone survey method in the Lüleburgaz District of Kırklareli City. Kırklareli is a city of approximately 360,000 residents in northwest Turkey. Approximately 42% of the total population of Kırklareli lives in Lüleburgaz, the largest district of the city. There are a total of five hospitals in Lüleburgaz, one public and four private. Primary health services are provided by 48 family physicians working in 16 family health centers, in addition to a healthy life center affiliated with the District Health Directorate. There are also private physician and dentist offices, as well as medical centers in the district. In addition, five ambulance stations for emergency medical services are available.

Target Population and Sampling

The target population of the study consists of 5322 people who were diagnosed with COVID-19
by testing positive for PCR in Lüleburgaz District between February 15 and May 15, 2021, and who were given hydroxychloroquine and/or favipiravir drugs for use at home, deemed suitable for outpatient treatment according to the guidelines of the Republic of Turkey Ministry of Health. In our study, there was no sampling, and the aim was to reach all patients who started outpatient medication. People who were called twice on two different days after their drug use ended but could not be contacted by phone or who refused to participate in the study were excluded from the scope of the study. 4368 people who could be reached by phone agreed to participate in the study (N = 4368). The participation rate of the study is 82.1%.

Data Collection
The telephone survey method was applied in the collection of data. A two-stage questionnaire developed by researchers consisting of questions about demographic information and disease processes was applied to the people who agreed to participate in the study. In the demographics section, age, gender, marital status, number of children, education status, occupation, health insurance, and economic status are included. We asked participants about the drugs given to use in relation to disease processes, whether they used the given drugs regularly, the factors affecting their regular use of their medications, whether the drugs had side effects, and the factors that affected their decisions if they did not use their medications regularly, and their recent status.

Ethical Consideration
For the study, permissions were obtained from the Ethics Committee of The Institute of Health Sciences of Kırklareli University dated 15. 02. 2021 and numbered 2021/9 and from the Research Applications Review and Evaluation Commission of the Kırklareli Provincial Health Directorate dated 05. 04. 2021 and numbered 2021/6.

Table 1. Distribution of the medications given to the respondents for use and their status of use

| Status of use                        | Recommended Medications               |
|--------------------------------------|---------------------------------------|
|                                      | Hydroxychloroquine (Only) n (%)       |
|                                      | Favipiravir (Only) n (%)               |
|                                      | Hydroxychloroquine + Favipiravir n (%)|
|                                      | Total n (%)                            |
| Used all the medications as recommended | 33 (0.8)                              |
|                                       | 2354 (53.9)                           |
|                                       | 1461 (33.5)                           |
|                                       | 3848 (88.1)                           |
| Didn’t use the Hydroxychloroquine     | 17 (0.4)                              |
|                                       | 0 (0.0)                               |
|                                       | 113 (2.6)                             |
|                                       | 130 (3.0)                             |
| Didn’t use the Favipiravir            | 0 (0.0)                               |
|                                       | 242 (5.5)                             |
|                                       | 9 (0.2)                               |
|                                       | 251 (5.7)                             |
| Didn’t use both Hydroxychloroquine and Favipiravir | 0 (0.0) |
|                                       | 0 (0.0)                               |
|                                       | 138 (3.2)                             |
|                                       | 138 (3.2)                             |
| Total                                | 50 (1.1)                              |
|                                       | 2596 (59.4)                           |
|                                       | 1722 (39.4)                           |
|                                       | 4368 (100.0)                          |

Statistical Analysis
SPSS 22 (Statistical Program for Social Sciences) software was used in the analysis of the data. Descriptive statistics are presented as numbers, percentages, standard deviations, and averages. The distribution of data was verified by Kolmogorov Smirnov and Shapiro Wilk Tests. Chi-square and binary logistic regression modeling were used in the analysis of the data that were not normally distributed. The suitability and efficiency of the model were evaluated by the Hosmer and Lemeshow test.

RESULTS
The average age of the respondents was 42.7 ± 14.9 (min 18, max 102), with an average age of 43.2 ± 15.3 (min 18, max 102) for women and 42.2 ± 14.4 (min 18, max 92) for men. It is seen that 1.1% (n = 50) of the respondents were treated only with hydroxychloroquine, 59.4% (n = 2596) only with favipiravir, and 39.4% with a combination of hydroxychloroquine and favipiravir. 88.1% (n = 3849) of the respondents reported that they used the given medications regularly, while 11.9% (n = 519) reported not using them regularly. The distribution of the medications given to the respondents for use and their status of use is seen in Table 1.

The three most common responses of the respondents who reported regular use of the medications when asked about the factors affecting their regular use were detected as “because I trusted the medical team that came home” with 49.7% (n=2170), “because the Ministry of Health recommends so” with 19.8% (n=865) and “because of having symptoms of the disease” with 10.3% (n = 449). When respondents who reported not regularly taking the medications they were given (n = 519) “what they meant by not taking them regularly”, the three most common responses were “given one drug, I never used it” with 37.2% (n = 193), “I was given two drugs, I never used both” with 16.0% (n = 83) and “given one drug, I started using it,
### Table 2. Comparison of some sociodemographic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19

| Sociodemographic characteristics | Were the medications used regularly? |   |   |   |
|----------------------------------|--------------------------------------|---|---|---|
|                                  | Yes n (%)                             | No n (%) | Total n (%) |
| **Gender**                       |                                       |           |             |
| Female                           | 1902 (43.5)                           | 277 (6.3) | 2179 (49.9) |
| Male                             | 1947 (44.6)                           | 242 (5.5) | 2189 (50.1) |
| **Age by group average (Average age of the group = 42.7)** | | | |
| Younger                          | 1881 (43.1)                           | 341 (7.8) | 2222 (50.9) |
| Older                            | 1968 (45.1)                           | 178 (4.1) | 2146 (49.1) |
| **Marital status**               |                                       |           |             |
| Single                           | 745 (17.1)                            | 154 (3.5) | 899 (20.6)  |
| Married                          | 2898 (66.3)                           | 336 (7.7) | 3234 (74.0) |
| Widow / Divorced                 | 206 (4.7)                             | 29 (0.7)  | 235 (5.4)   |
| **Children**                     |                                       |           |             |
| None                             | 944 (21.6)                            | 181 (4.1) | 1125 (25.8) |
| 1 child                          | 815 (18.7)                            | 118 (2.7) | 933 (21.4)  |
| 2 children                       | 1525 (34.9)                           | 151 (3.5) | 1676 (38.4) |
| 3 or more                        | 565 (12.9)                            | 69 (1.6)  | 634 (14.5)  |
| **Education**                    |                                       |           |             |
| Below high school degree         | 1794 (41.1)                           | 172 (3.9) | 1966 (45.0) |
| High school degree               | 1142 (26.1)                           | 180 (4.1) | 1322 (30.3) |
| Above high school degree         | 913 (20.9)                            | 167 (3.8) | 1080 (24.7) |
| **Total**                        | 3849 (88.1)                           | 519 (11.9)| 4368 (100.0)|

### Table 3. Comparison of some socioeconomic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19

| Socioeconomic characteristics | Were the medications used regularly? |   |   |   |
|-------------------------------|--------------------------------------|---|---|---|
|                               | Yes n (%)                            | No n (%) | Total n (%) |
| **Income generating job**     |                                       |           |             |
| Yes                            | 2249 (51.5)                          | 339 (7.8) | 2588 (59.2) |
| No                             | 1600 (36.6)                          | 180 (4.1) | 1780 (40.8) |
| **Health insurance**           |                                       |           |             |
| No                             | 483 (11.1)                           | 55 (1.3)  | 538 (12.3)  |
| General health insurance (for unemployed citizens without social security) | 446 (10.2) | 62 (1.4) | 508 (11.6)  |
| Other*                         | 2920 (66.8)                          | 402 (9.2) | 3322 (76.1) |
| **Monthly income**             |                                       |           |             |
| None                           | 606 (13.9)                           | 109 (2.5) | 715 (16.4)  |
| Below the national min. wage   | 256 (5.9)                            | 22 (0.5)  | 278 (6.4)   |
| National min. wage             | 917 (21.0)                           | 119 (2.7) | 1036 (23.7) |
| Above the national min. wage    | 2070 (47.4)                          | 269 (6.2) | 2339 (53.5) |
| **Perceived economic status**  |                                       |           |             |
| Very bad / bad                 | 458 (10.5)                           | 67 (1.5)  | 525 (12.0)  |
| Middle                         | 2872 (65.8)                          | 376 (8.6) | 3248 (74.4) |
| Good / very good               | 519 (11.9)                           | 76 (1.7)  | 595 (13.6)  |
| **Total**                      | 3849 (88.1)                          | 519 (11.9)| 4368 (100.0)|

* Social security, private health insurance, etc.
but I quit” with 14.5% (n = 75). When respondents who reported not taking the medications regularly were asked about the factors that affected their lack of regular use of their medications, the three most common responses were mild symptoms with 50.9% (n = 264), distrust of medications with 17.5% (n = 91) and side effects of medications with 16.4% (n = 85). The three most common side effects reported by those who reported quitting the medications due to side effects were nausea and vomiting 34.1% (n = 29), palpitations with 17.6% (n = 15), and abdominal pain 16.5% (n = 14).

A comparison of some sociodemographic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19 is seen in Table 2.

A comparison of some socioeconomic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19 is seen in Table 3.
Some sociodemographic and socioeconomic factors that are thought to affect the regular use of the given medications by the respondents were analyzed by the binary logistic regression method. The results of the binary logistic regression analysis are shown in Table 4.

When respondents were asked about their current health status as of the moment the survey was conducted, 86.7% (n = 3786) reported that they had fully recovered, while 13.3% (n = 582) still had some complaints. The usual complaints reported to be ongoing, weakness and loss of appetite with 5.2% (n = 228), cough with 2.5% (n = 111), general muscle and joint pain with 2.2% (n = 96), shortness of breath with 1.6% (n = 72) and loss of smell and taste with 1.2% (n = 53) were detected. The comparison of the respondents’ regular use of the given medications with the ending of their complaints due to COVID-19 is seen in Table 5.

### DISCUSSION

Discussions are still ongoing about the outpatient treatment of the COVID-19 pandemic that has affected the world. Various medications have been tried alone or in combinations in different countries, and numerous publications have been issued (12, 13). Several medications have even been tried to be used for pre-exposure prophylaxis against COVID-19 (14). Although Turkey has not supported the use of medications for pre-exposure prophylaxis since the beginning of the pandemic, it is a country that has adopted the outpatient treatment of COVID-19. In the outpatient treatment of COVID-19 in Turkey, only hydroxychloroquine was initially used, favipiravir was added to the treatment and finally, hydroxychloroquine was removed from the treatment and only favipiravir was used in the outpatient treatment (4). Naturally, the first question that comes to mind here is to what extent the patients who are prescribed outpatient treatment adhere to the treatments arranged for them. Many studies have been conducted to examine the factors affecting patients’ adherence to treatments related to various diseases. In a systematic review examining these studies, factors affecting treatment compliance are categorized as “patient-centered factors”, “therapy-related factors”, “social and economic factors”, “healthcare system factors”, and “disease factors” (15). Our study observed that among the patient-centered factors such as demographic, psychosocial, and economic characteristics, age is the most affecting factor for the treatment adherence, and the treatment adherence increases as the age of the patients increases. Again, the fact that the patient is educated at least at the high school level increases the treatment adherence compared to being less educated.

One of the crucial discussions in the outpatient treatment of COVID-19 is how to decide which patient will take outpatient treatment and which patient will be hospitalized. Some studies envisage supporting the decision to be made in this regard with laboratory examinations (16). However, no laboratory examination was suggested in the guidelines of the Republic of Turkey Ministry of Health to make this decision, and the decision-making was left to the initiative of the physicians working in the field, provided that they complied with the algorithms in the guidelines (4). Some studies report that it is important for the patient to have confidence in the physician and accept and adhere to the treatment (17). When respondents of our study survey were asked about the factors affecting their regular use of their medications, the most common response was “because I trust the medical team that comes home”. Of course, it is not enough that patients have confidence only in the physician, but also that they have confidence in the recommended treatment methods and medications. As in many countries of the world, research on the effectiveness and reliability of medications was carried out also in Turkey (18, 19, 20). The results have been discussed not only within the academic community but by the whole society, especially through social media platforms (21). The wariness of medications was the second most common cause of the respondents reporting that they did not use the medications regularly, while two of the most important reasons for regular use of the medications reported by respondents was their trust in the medical team that comes home.
in the healthcare team visiting them at home and the recommendation of the Ministry of Health. In light of these findings, it has been confirmed once again that psychosocial factors, one of the patient-centered factors are effective in the regular use or non-use of the medications, and that the sense of trust in the society is one of the most important factors affecting adherence to the treatment given.

The third most common reason of the respondents who reported that they did not regularly use the medications was the “side effects of the medications”, one of the treatment-related factors included taste, method of application, duration, and complexity of the treatment and side effects. Studies have been carried out in the past years to examine factors affecting compliance with medications used for various diseases, and the results are that side effects are one of the most negatively affecting causes of therapy compliance (22, 23). Therefore, when setting strategies in cases that require widespread medication use such as outpatient treatment of COVID-19, it is once again understood that the side effects of medications should be taken into account.

In our study, the effect of the social and economic factors such as patient income and cost of the medication on the treatment adherence has not been observed, and such an effect was not expected anyway. Because, as previously emphasized, all outpatient medications are provided free of charge by the healthcare system and delivered to the residences of patients by medical teams. Similarly, since all patients diagnosed with COVID-19 who decided to take an outpatient treatment at their residences are served where they are without long waiting periods, as expected, no negative feedback was received on the healthcare system-related factors.

Disease-related factors such as disease symptoms and the severity of the disease were found to affect the regular use or non-use of the medications. Respondents who reported using the medications regularly indicated that there were signs of the disease in the third place as the reason for their regular use, whereas the participants who reported that they did not use the medications regularly indicated that the symptoms of the disease were mild, causing their behavior most often. A Danish study reported that physicians had a significant impact on patient adherence (24). Therefore, it is thought that by extending the time that physicians can allocate to patients as much as possible and taking measures to increase patient-physician communication, patients can be made more conscious about using medications according to recommendations, not symptoms, and thus the treatment adherence can be increased.

Many studies examining the efficiency of hydroxychloroquine and/or favipiravir treatment have been conducted and it has been reported that these medications can be used effectively in the treatment of COVID-19 (25, 26, 27). In our study, no statistically significant difference between the regular use of the given medications by the respondents and the ending of their complaints due to COVID-19 was detected. Since our study is based on the statements of the respondents, in other words, since the current conditions of the respondents were not determined by medical consultations and examinations, it is thought that this finding cannot be used to interpret the effectiveness of the medications.

Our study was carried out based on the statements of people who have been diagnosed with COVID-19 and who have been called by phone. It is not known whether those who refused to participate in the study used the medications given to them or not or how their final health conditions are. This is the crucial limitation of our research.

CONCLUSION

In our study, we determined that age is the most critical sociodemographic factor affecting the use of free medications by patients taking outpatient treatment after receiving a COVID-19 diagnosis and psychosocial factors are the most important determinants that positively or negatively affect the treatment adherence. It has been concluded that these factors should be taken into account in the planning for future measures against the disease. Measures to increase patients’ trust expected to adhere to the treatments should be a priority.

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Author Contributions

Idea/Concept: AÖP + ÇÇ / Design: AÖP + ÇÇ / Supervision/Counseling: AÖP + ÇÇ / Data Collection and/or Processing: AÖP + ÇÇ / Analysis and/or Interpretation: AÖP / Literature Review: AÖP + ÇÇ / Writing the Article: AÖP + ÇÇ / Critical Review: AÖP + ÇÇ
Sažetak

**PRIDRŽAVANJE PREPORUČENOG TRETMANA KOD KUĆNOG LEĆENJA COVID-19 PACIJENATA**

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**Uvod:** Turska je usvojila ambulantno lečenje Kovid-19 od početka pandemije. U ambulantnom lečenju Kovid-19 u Turskoj, prvobitno je korišćen samo hidroksihlorokin, tretmanu je onda dodat favipiravir, a na kraju, hidroksihlorokin je uklonjen iz lećenja i korišćen je samo favipiravir. Naša studija ima za cilj da ispitati koliko su se osobe sa dijagnozom Kovid-19 koji su bili na ambulantnom lećenju bez hospitalizacije pridržavali preporučenog tretmana i njihove stave ve i ponašanje prema korišćenju lekova koje su dobili besplatno.

**Metode:** Ova studija praćenja sprovedena je između 15. 2. 2021. i 15. 5. 2021. metodom telefonskog istraživanja u okrugu Lüleburgaz, grada Kırklareli.

Učesnici studije su 4368 pacijenta kojima je dijagnostikovan Kovid-19 pozitivnim PCR testom u okrugu Lüleburgaz između 15. februara i 15. maja 2021. godine, komija su izdati lekovi hidroksihlorokin i/ili favipiravir za kućnu upotrebu nakon što su smatra ni pogodnim za ambulantno lećenje prema smernica ma Ministarstva zdravlja Republike Turske.

**Rezultati:** 88,1% (n = 3849) ispitanika navodi da redovno koristi date lekove, dok ih 11,9% (n = 519) ne koristi redovno. Najvažniji socio-demografski faktor koji je uticao na redovnu upotrebu bila je starost, a faktor usredsređen na pacijenta bio je osećaj poverenja.

**Zaključak:** U bori protiv Kovid-19, mere za povećanje osećaja poverenja pacijenata od kojih se očekuje da se pridržavaju lećenja treba da budu prioritet.

**Ključne reči:** Kovid-19, Favipiravir, hidroksihlorokin, pridržavanje lekova, ambulantna terapija.

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