

## Assessment of self-medication in patients with rheumatoid arthritis referred to Rafsanjan Rheumatology Clinic during the COVID-19 pandemic

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The COVID-19 disease has affected patients with rheumatoid arthritis (RA). Drug adherence is essential for RA control. This study investigated self-medication among RA patients in the COVID-19 pandemic. This cross-sectional study was performed on 288 patients with RA referred to the Rheumatology Clinic of Rafsanjan in 2021. Data were extracted by a checklist. Patients were examined and the type of used drugs, drug dose, and dose change were recorded. Inclusion criteria were diagnosis of rheumatoid arthritis, care during the last year and being over 16 years of age. Data were analyzed using SPSS/18 software. The mean  $\pm$  SD of patients' age was  $53.3 \pm 12.6$  years and 53.8% of patients were male. The mean  $\pm$  SD duration of the disease was  $7.04 \pm 6.37$  years. Self-medication was observed in all drugs, where Alendronate (100.0%, n = 13), Folic Acid (100.0%, n = 7), Methotrexate (94.1%, n=32), and Prednisolone (89.3%, n = 25) had the highest frequency of changes among other drugs ( $P$  value < 0.001). The mean  $\pm$  SD dose of Hydroxychloroquine increased from  $1358.5 \pm 304.4$  to  $1368.0 \pm 336.2$  mg before and during the COVID-19 pandemic ( $P$  value = 0.319). The odd ratio of self-medication was higher in women (OR = 6.130, 95%CI: 2.915-12.993), RA patients with academic education (OR = 2.727, 95%CI: 1.037- 7.166), and lower in RA patients with a governmental occupation (OR = 0.277, 95%CI: 0.086-0.893). Self-medication of rheumatoid arthritis drugs may occur due to the positive effect of these drugs on COVID-19 disease and further reduced drug accessibility. It is necessary to plan to prevent self-medication in these patients by physicians.

**Keywords:** Rheumatoid Arthritis; Self-Medication; Hydroxychloroquine; Prednisolone; Methotrexate

### Introduction

COVID-19 is a new pandemic spreading worldwide over several months following the first report of atypical cases of pneumonia in Wuhan, Hubei Province, China in December 2019, and has attracted the attention of the international community. The results of epidemiological studies have shown rapid human-to-human transmissibility of this disease [1]. The disease affected about 250 million people and killed about 5 million people in the world by early November 2021, which in turn is a record in infection and death. In Iran, it has caused about 6 million cases of infection and 126 thousand deaths [2]. The very high prevalence of the disease, death in severe cases, and lack of specialized treatment, have turned it into a major threat to the health of people in the community, especially patients with a variety of chronic diseases. The mortality

rate is higher in people with underlying diseases, such as diabetes, heart and lung diseases, as well as patients taking immunosuppressants [3, 4].

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease with a global prevalence of 460 per 100,000 people varying in different geographical areas [5]. It is a chronic systemic disease of unknown etiology which can lead to joint damage, extra-articular manifestation, and physical disability. Inflammation of joints is the most important cause of injury and disability in patients. To prevent the destruction of articular cartilage and bones, it is important to identify and treat it before the destruction begins and in the early stages [6]. It is a multifactorial disorder caused by genetic and non-genetic factors, such as infections, hormones, and the environment [7]. The disease occurs at any age, but

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mainly appears in the fourth and fifth decades of life. Patients with RA are at higher risk of infections, especially pneumonia compared to the general population. This is due to both the physiopathology of the disease and the use of synthetic and biologic drugs controlling the disease [8, 9]. There are also findings on the adverse effects of viral diseases, such as seasonal flu in patients with RA [10, 11].

With the onset of the COVID-19 pandemic as a major health problem, patients with RA have also been affected. Given the patient's condition and deficiency in the immune system and the use of various drugs, such as corticosteroids, the risk of infections and especially the COVID-19 is high in them [8, 12, 13]. Meanwhile, regular treatment and patients' adherence to the treatment regimen is one of the necessities of disease control and reducing the negative side effects as well as severity of the disease; indeed, non-adherence to it is an obstacle to achieving therapeutic goals. Considering the direct and indirect effects of COVID-19 disease and the importance of medication adherence in controlling RA, the present study aims to investigate the frequency of self-medication by RA patients referred to Rafsanjan Rheumatology Clinic during COVID-19 pandemic.

## Materials and Methods

The present cross-sectional study was conducted on patients with RA referred to Rafsanjan Rheumatology Clinic in 2021 during Covid-19 Pandemic. After obtaining informed consent, all patients who regularly referred to the Rheumatology Clinic during the last year (April 2020- March 2021 year), were visited at least once a year, and had complete file and information, were selected. The study population consisted of all patients with RA who met the inclusion and exclusion criteria who were included in the study by census (288 people). The initial information of the patients was extracted from the files available in Rafsanjan Rheumatology Clinic. Then, the patients were examined and questions related to the type of used drug, drug dose, and dose change were determined using the file and by asking the patient. Informed consent was obtained from all patients participating in the study and it was ensured that patients' information would be coded and remain completely confidential. The inclusion criteria consisted of regular referrals during the last year and having at least one visit, diagnosis of RA based on ACR criteria, and age over 16 years. The exclusion criteria included having hematologic malignancies, such as leukemia, lymphoma, and pregnancy. The study variables included age, gender, education, occupation, history of diabetes, hypertension, hyperlipidemia, cardiovascular disease, hypothyroidism, cancer, duration of disease, severity of disease according to DAS28 activity measure, use and dosage of medications including, prednisolone, methotrexate, hydroxychloroquine, folic acid, alendronate, and history of COVID-19 in the individual and family. The severity of RA was determined using the DAS-28 index. The DAS-28 index is used to measure the severity of RA based on clinical information, especially the erythrocyte sedimentation rate (ESR) (mm/hr). The index

is calculated based on the number of swollen joints, the number of joints with local sensitivity, and the ESR number. The acceptable score range of this index is 0-10. DAS-28 index value lower than/equal to 3.2 indicates mild disease activity, 3.2 to 5.2 reveals moderate disease activity, and greater than/equal to 5.2 shows severe disease activity [14]. This study was approved by the Ethics Committee of Rafsanjan University of Medical Sciences under ethics code IR.RUMS.REC.1399.057. The data were analyzed using SPSS 18 software.

The normality of the data was assessed using the Kolmogorov-Smirnov test and graphic evaluation, including drawing of histograms and normal distribution curves, whereby no violation of the test conditions was observed. Paired t-test was used to compare the mean scores of drugs used before and during the COVID-19 pandemic. Finally, the factors affecting the probability of self-medication were investigated using the logistic regression model. In this model, overall percentage correct was 79.1 and the Hosmer & Lemeshow showed that the predicted ranking was consistent with the observations (P value = 0.336). The significance level in the tests was considered 0.05.

## Results

The results revealed that the mean and standard deviation of the patients' age were  $53.3 \pm 12.6$  years with a minimum age of 20 and a maximum age of 84 years. Among the participants, 53.8% (n = 155) of the patients were male, 47.0% (n = 132) had university education, and 70.9% (n = 200) were unemployed. The mean duration of the disease was  $7.04 \pm 6.37$  years and more than half of the patients (55.6%) had moderate disease severity.

Based on the results, a history of diabetes was observed in 0.17% (n = 49), hypertension in 32.6% (n = 94), hyperlipidemia in 32.2% (n = 87), ischemic heart disease in 5.9% (n = 17), and hypothyroidism in 13.5% (n = 39) of the patients. A history of COVID-19 disease was observed in 4.2% (n = 12) of the patients and 20.1% (n = 58) reported a history of COVID-19 in their family.

The results of studying self-medication in patients with RA before and during the COVID-19 pandemic indicated that although the mean dose of hydroxychloroquine increased during the pandemic, it was not statistically significant (P value = 0.319). There was no change either in the mean dose of methotrexate and prednisolone (P value > 0.05).

Figure 1 displays the results of the type of used drug and self-medication during the COVID-19 pandemic. Self-medication can be observed in all drugs; during the COVID-19 pandemic, all patients who were taking alendronate (100.0%, n = 13) and folic acid (100.0%, n = 7) changed their medication. The self-medication in patients who used methotrexate and prednisolone was 94.1% (n = 32) and 89.3% (n = 25), respectively. The lowest frequency of changes was observed in hydroxychloroquine (58.8%, n = 10) and other drugs (39.7%, n = 23) (P value < 0.001).

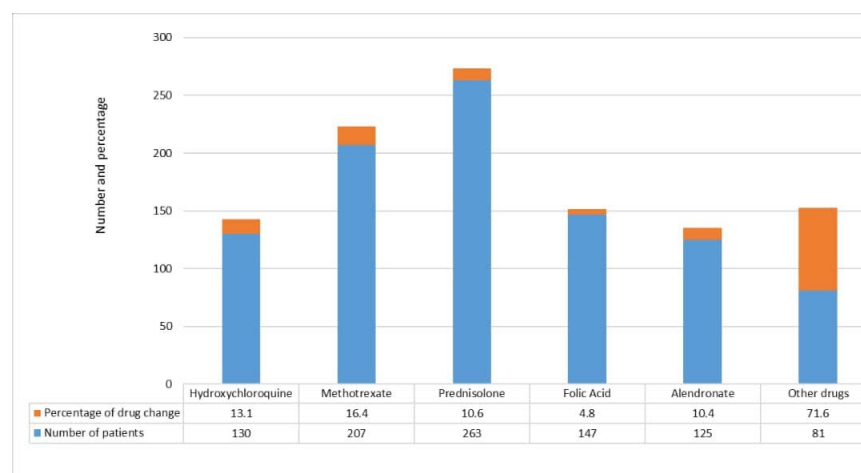
Finally, the results of investigating the factors affecting

**Table 1.** Frequency distribution of demographic and clinical variables of patients with RA referred to Rafsanjan Rheumatology Clinic during the COVID-19 pandemic.

Variables <sup>‡</sup>	Patients with RA
<b>Age (year)</b>	53.3 ± 12.6
<b>Gender</b>	
Male	155(53.8)
Female	133(46.2)
<b>Education</b>	
Illiterate	92(32.7)
Diploma and less	57(20.3)
Academic	132(47.0)
Job Unemployed	200(70.9)
Governmental	40(14.2)
Self-employed	42(14.9)
<b>Disease Duration (year)</b>	7.0 ± 6.4
<b>Disease severity</b>	
Mild	54(19.4)
Moderate	155(55.6)
Severe	70(25.1)
<b>Diabetes</b>	49(17.0)
<b>Hypertension</b>	94(32.6)
<b>Hyperlipidemia</b>	87(30.2)
<b>Ischemic heart disease</b>	17(5.9)
<b>Hypothyroidism</b>	39(13.5)
<b>History of Covid-19 (yes)</b>	12(4.2)
<b>History of Covid-19 in family (yes)</b>	58(20.1)

<sup>‡</sup>: Data are expressed as mean ± standard deviation (SD) and number (%).

RA, rheumatoid arthritis

**Figure 1.** Type of used drug and percentage of arbitrary change of drug in patients with RA referred to Rafsanjan Rheumatology Clinic during the COVID-19 pandemic

<sup>‡</sup>: Chi-square test and significant level *P value* < 0.001.

**Table 2.** Evaluating the dose of drug used for self-medication by patients with RA referred to Rafsanjan Rheumatology Clinic before and during the COVID-19 pandemic.

Used drugs	Before the COVID-19 pandemic	During the COVID-19 pandemic	P value*
<b>HCQ</b>	1358.5 ± 304.4	1368.0 ± 336.2	0.319
<b>Methotrexate</b>	15.8 ± 6.4	15.8 ± 6.4	0.372
<b>Prednisolone</b>	35.6 ± 13.2	35.6 ± 12.8	0.954

\* Paired sample t test and significant level 0.05.

RA, rheumatoid arthritis

HCQ, hydroxychloroquine

**Table 3.** Factor associated with self-medication by patients with RA referred to Rafsanjan Rheumatology Clinic before and during the COVID-19 pandemic

Variables	B	OR	95% CI for EXP(B)		P value <sup>‡</sup>
			Lower	Upper	
<b>Age</b>	.012	1.012	.977	1.049	0.494
<b>Sex</b>					
Men	---	1.000	---	----	----
Women	1.813	6.130	2.915	12.993	<0.001
<b>Education</b>					
Illiterate	---	1.000	---	---	----
Diploma and less	.488	1.629	.560	4.735	.370
Academic	1.003	2.727	1.037	7.166	0.042
<b>Job</b>					
Unemployed	---	1.000	---	----	---
Governmental	-1.285	.277	.086	.893	0.032
Self-employed	.018	1.018	.408	2.538	0.969
<b>Duration of Disease</b>	.008	1.008	.956	1.062	0.772
<b>Severity of Disease</b>					
Mild	---	1.000	---	---	----
Moderate	.207	1.230	.456	3.319	0.682
<b>Severe</b>	-.049	.952	.301	3.015	0.934
<b>Diabetes (%)</b>	-.394	.674	.247	1.842	0.442
<b>Hypertension (%)</b>	.050	1.052	.468	2.362	0.903
<b>Hyperlipidemia (%)</b>	-.307	.735	.327	1.654	0.458
<b>Ischemic heart disease (%)</b>	.971	2.641	.717	9.725	0.144
<b>Hypothyroidism (%)</b>	-.842	.431	.130	1.428	0.169
<b>History of Covid-19 (%)</b>	.219	1.254	.191	8.121	0.819
<b>History of Covid-19 in family (%)</b>	.097	1.102	.449	2.703	0.833

‡: Logistic regression test and significant level 0.05.

the occurrence of self-medication in RA patients using the logistic regression model are reported in Table 3. The results show that the odds of self-medication has been higher in female patients compared to males; this value in females was more than 6 times that of males ( $P$  value  $< 0.001$ ). The odds of self-medication in patients with academic education has also been higher than in illiterate patients ( $P$  value = 0.042). The results also indicated that patients who had a government job had a lower odds ratio for self-medication than those who were unemployed ( $P$  value = 0.032).

## Discussion

The COVID-19 pandemic is one of the major problems in the 21st century for which there is no definitive cure and sufficient scientific information [1]. The effects occurring since the onset of the disease in various aspects of human life are still being identified. Due to the lack of definitive treatment for this viral disease [15], the use of drugs for other diseases, such as antiviral drugs, hydroxy-chloroquine, etc., shown to be effective against the disease and the severity of COVID-19, has increased significantly [16, 17]. Patients with RA need regular use of drugs, such as hydroxychloroquine to control the disease; thus, in such a situation, it is difficult to access the drugs and can have adverse effects on these patients [17]. Based on the results, self-medication was observed in all drugs, including hydroxychloroquine, methotrexate, prednisolone, folic acid, alendronate, and other drugs. Further, methotrexate and hydroxychloroquine had the highest frequency of changes among other drugs. The results also showed an arbitrary increase in the mean dose of hydroxychloroquine during COVID-19, but it was not statistically significant.

In this regard, the results the study by Kim et al. on the effect of increasing hydroxychloroquine consumption in the COVID-19 epidemic indicated a decline in hydroxychloroquine available to rheumatic patients, especially patients with RA and lupus, which can cause dangerous disease recurrence and increase the need for hospitalization [18]. The results of the study by Owens et al. revealed that during the COVID-19 epidemic, due to the therapeutic potential of some drugs, problems have occurred for patients with arthritis and lupus, including patients who regularly use these drugs. Patients have to go to several pharmacies to obtain the medicine they have been prescribed. Some patients have been forced to self-medicate with drugs, such as hydroxychloroquine, which can have unintended consequences [19]. Another study by Niforatos et al. in the United States reported that over-the-counter sales of hydroxychloroquine for the treatment of COVID-19 have led to severe depletion of hydroxychloroquine in pharmacies, adversely affecting the treatment of thousands of rheumatoid patients [20]. The results of

Pushkin's study in North America also showed that after the US President's statement in the public media about the beneficial role of hydroxychloroquine in the treatment of COVID-19, RA patients have become anxious about their treatment status and medications [21]. Mvumbi et al. also stated that uncontrolled use and self-medication with chloroquine and hydroxychloroquine as well as the toxicity caused by excessive use of these drugs may lead to major problems [22]. Gussow et al. reported that after mass media advertising, there is a possibility of hoarding drugs, such as hydroxychloroquine and self-medication. Cases of death and poisoning have also been reported in the United States due to self-medication [23].

The results of the present study also indicated that the odds ratio of self-medication was lower in women with RA, patients with higher academic education, and patients with governmental occupations. Further, although the frequency of women with RA in the study was lower, the number of women visiting for medical care might have decreased, and on the other hand, self-medication and arbitrary use of drugs have increased due to the conditions caused by the COVID-19 pandemic. The WHO introduced COVID-19 as a challenging disease for people with RA regarding self-care management. These patients with immunosuppressive therapy may avoid buying food, walking outdoors, and visiting pharmacies to reduce exposure to the COVID-19 disease [24]. Although self-medication can have negative and positive effects on people's health, it has been clearly observed during the COVID-19 pandemic and has caused a concerning medical challenge [25]. In a study, self-medication was observed in most of the respondents to keep themselves from getting COVID-19 and to reduce respiratory symptoms, mainly due to catching a cold or flu.

The results of multivariate logistic regression revealed the factors associated with self-medication, including age, occupation, and place of residence [26]. Heidarnia et al. reported that the frequency of self-medication was higher in females and people with higher education [27]. Personal assessment of patients during pharmaceutical care is an important strategy to provide guidance on the use of non-prescription medicines and self-medication [28]. On the other hand, the rate of self-medication was higher in people with higher education, probably due to their high self-awareness and sense of insecurity, affected by access to information networks [29].

This finding was also confirmed in patients with RA in the present study. Although self-medication is an important global concern affecting both developed and developing countries [30], it is more common in countries with poor health care systems due to long waiting times in healthcare centers, difficulty in getting a doctor's appointment, inadequate stock of essential drugs, negligence and insufficient beds/space available in medical centers, as well as fewer health care



facilities [31]. Studies have shown that, in general, patients receiving corticosteroids and immunosuppressive drugs are at higher risk for severe COVID-19 [8, 12]. Some studies suggest that selective immunosuppressive drugs, such as tocilizumab may be effective in treating the cytokine storm caused by COVID-19 [32, 33]. Further, hydroxychloroquine and chloroquine, which have an effective role in modulating the immune system, were increasingly used as antiviral therapy in the COVID-19 treatment protocol at the beginning of the disease [34]. These findings, along with media advertisements for consuming some of these drugs, have caused mental conflict in patients with arthritis, and in some cases, patients' access to arthritis drugs has diminished [23]. Thus, patients may change the drug and dose of drug due to subjective perceptions and limited access.

## Conclusion

In the present study, patients with RA reported self-medication and drug dose changes. Given the importance of medication adherence and the fact that some rheumatoid drugs have been identified effective in reducing the severity as well as complications of COVID-19, these patients have faced a new problem of reduced access to drugs. Thus, the necessary measures for drug availability as well as the necessary follow-ups to prevent self-medication in these patients should be considered by physicians and managers.

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## Conflict of interests

Gholamreza Bazmandegan, Zahra Kamiab, Hamid Ostadebrahimi, Bitah Hashemi, Mitra Abbasifard declare that they have no conflict of interest.

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