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Original article

How different is the status of depression and anxiety in patients with rheumatoid arthritis receiving methotrexate with sulfasalazine or hydroxychloroquine?

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Abstract: *Background* — Depression and anxiety are among the most common clinical manifestations in patients with rheumatoid arthritis (RA). Sulfasalazine and hydroxychloroquine are important medications used to treat these patients.
Objective — The goal of this study was to compare the occurrence of depression and anxiety in RA patients taking sulfasalazine or hydroxychloroquine for at least six months.
Methods — This study included 300 patients with RA referred to inpatient or outpatient departments of a public hospital in northern Iran who were treated with two combination regimens of methotrexate and sulfasalazine or methotrexate and hydroxychloroquine. Participants were assessed on the standard Hospital Anxiety and Depression Scale (HADS) for symptoms of depression and anxiety.
Results — The mean HADS depression subscale score was 6.77±3.98 in the hydroxychloroquine group and 3.50±3.53 in the sulfasalazine group ($p<0.001$). The mean HADS anxiety subscale score was 7.66±4.43 in the hydroxychloroquine group and 5.34±4.35 in the sulfasalazine group ($p<0.001$). Multiple linear regression analysis revealed a significant difference in the incidence of depression and anxiety between the two treatment groups.
Conclusion — A higher prevalence of depression and anxiety was observed in RA patients treated with methotrexate and hydroxychloroquine versus those treated with methotrexate with sulfasalazine.

Keywords: hydroxychloroquine, sulfasalazine, depression, anxiety, rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is characterized as a chronic disease with systemic inflammation, which is also associated with a number of associated complications and subsequent disability [1]. The global prevalence of RA is reported at the level of 460 cases per 100,000 population, which varies in different regions depending on the definition of the disease, geographic characteristics, and study design [2]. Several studies have reported an increase in the incidence and/or prevalence of RA in some countries in recent years [3-5].

Psychiatric comorbidities such as depression and anxiety predominate in patients with RA, which can be explained by the onset of RA per se or by other concomitant factors, such as disease activity, response to treatment, and outcome [6-8]. The presence of comorbid psychiatric disorders in patients with newly diagnosed RA may exacerbate clinical symptoms, such as fatigue, stress, and sleep disorders, and may also affect health-promoting lifestyles including dietary habits, physical activity, adherence to treatment, and therefore, daily physical activity [9, 10]. These psychiatric disorders may affect the patient's perception and reporting of pain and other symptoms, and may also impair the patient's sense of recovery. Moreover, given the similarity of some clinical features of depression and anxiety disorders with those of RA, these mental disorders can be ignored and not diagnosed and treated in a timely manner [9]. A review of the literature showed that chronic inflammation can impair physiological responses to stress, such as effective coping behavior, which can lead to depression and its worse impact on outcome. In patients with RA, the severity of pain is not always associated with the activity of the immunological disease and the inflammatory process; it was shown that noninflammatory pain secondary to depression, anxiety, sleep disorder and other psychiatric consequences should be considered in these patients [6].

Methotrexate, hydroxychloroquine (HCQ), and sulfasalazine (SSZ) are among the most important disease-modifying antirheumatic drugs (DMARDs) in patients with RA [11]. Patients with RA and comorbid depression or anxiety are expected to have earlier discontinuation of treatment protocols and poor resistance to methotrexate and other antirheumatic therapies. Several studies have evaluated these psychiatric disorders in RA patients treated with various antirheumatic medications [12].

According to a review of the literature, HCQ treatment has been associated with many neuropsychiatric side effects, including increased speech ability/excessive talkativeness, increased psychomotor activity, irritable mood, auditory hallucinations, grandiose delusions, and suicide attempts. Although the exact

mechanisms of psychiatric side effects in HCQ users are not clear, the dopaminergic or anticholinergic effects of chloroquine or HCQ, as well as lysosomal dysfunction due to accumulation of HCQ in cell lysosomes, may contribute to manifestations of such side effects [13]. Similarly, SSZ can influence cell activity by altering folate metabolism and lead to the development of neuropsychiatric symptoms. However, data in this context are sparse, and there is no consensus in the literature regarding HCQ/SSZ therapy and the risk of psychiatric side effects. This issue can be explained by the low prevalence of neuropsychiatric side effects of SSZ and HCQ, as well as the short duration of treatment in previous studies. Nonetheless, in patients receiving SSZ/HCQ over a long period of time, it is possible to identify neuropsychiatric side effects [14].

For these reasons, we conducted the present study to investigate the risk of depression and anxiety in patients with RA receiving long-term treatment with SSZ or HCQ. The secondary objective was to compare the severity of depression/anxiety between the two groups.

Material and Methods

Study design

This observational research was conducted as part of a case-control study that included patients with RA who were admitted for follow-up examinations at a public referral hospital in Babol, northern Iran, during 2021-2022.

Study participants

All participants received standard treatment, including low-dose methotrexate, low-dose prednisolone, SSZ, HCQ, or biologics as needed to achieve remission. Doses of the medication were adjusted during the follow-up examination taking into account the response to treatment by calculating DAS-28 and clinical examination. The participants were divided into two groups depending on the medications they were receiving: Group 1 (methotrexate and SSZ) and Group 2 (methotrexate and HCQ).

The inclusion criteria were as follows: patients with a confirmed diagnosis of rheumatoid arthritis, approved by a rheumatologist; outpatients; 18 years of age and older; signed informed consent to participate in the study.

The exclusion criteria were as follows: inability to answer the study questions; comorbidity of advanced diseases, such as heart failure, chronic kidney disease, etc.; dementia or mental retardation; taking other antirheumatic drugs during the course of the study.

Participants took standard doses of prescribed drugs (methotrexate: 7.5 mg weekly; SSZ: 1 g daily; HCQ: 400 mg daily) for at least six months. The diagnosis of RA was confirmed by the criteria of American College of Rheumatology (ACR) / European Alliance of Associations for Rheumatology (EULAR) [15].

Study variables and measurement procedure

Baseline characteristics, including age, gender, education level, and duration of RA, were collected through direct patient interviews.

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) at least 6 months after starting antirheumatic treatment. This scale includes seven depression questions and seven anxiety questions and is considered a powerful tool for assessing anxiety and depression in outpatients, as well as for assessing the severity of emotional disorders. Each part of the HADS questionnaire is scored from zero to three. Anxiety or depression symptoms ranging from 0 to 7 points are considered normal, 8 to 10 points suggest mild grade, 11 to 14 points are indicative of a moderate severity, and 15 to 21 points confirm severe anxiety or depression symptoms. The validity and reliability of the Persian translation of the HADS questionnaire was established in a previous study [16].

Two trained medical interns conducted the questionnaires for our study.

Participants were assessed six months after the onset of prescribed treatment protocols, and the status of symptoms of depression and anxiety was evaluated.

Sample size

Given a confidence factor of 0.95 and a power of 0.80, the sample size was calculated as 150 for each group, with a total of 300 patients examined.

Statistical data processing

The data were statistically analyzed using the SPSS-18 software package. Qualitative variables were expressed as percentages and compared using a chi-squared test. Quantitative variables were compared using the t-test. Multiple logistic regression analysis with odds ratio (OR) calculations was employed to determine an independent relationship between depression/anxiety and SSZ/HCQ. A p-value ≤ 0.05 was considered statistically significant.

Table 1. Baseline characteristics of two study groups

Characteristics		*Patients with rheumatoid arthritis receiving*		*P-value (Chi-squared test)*
		methotrexate and sulfasalazine n=150 N (%)	methotrexate and hydroxychloroquine n=150 N (%)	
Gender	Male	23 (15.3)	25 (16.7)	0.075
	Female	127 (84.7)	125 (83.3)	
Education level	Illiterate	37 (24.7)	20 (13.3)	0.025
	Primary education	59 (39.3)	55 (36.7)	
	Secondary education	37 (24.7)	46 (30.7)	
	Higher education	17 (11.3)	29 (19.3)	
Duration of rheumatoid arthritis (years)	<5	90 (60.0)	76 (50.7)	0.036
	5-10	26 (17.3)	45 (30.0)	
	>10	34 (22.7)	29 (19.3)	

Table 2. Severity of depression and anxiety in two study groups based on HADS scores

Characteristics		*Patients with rheumatoid arthritis receiving* methotrexate and sulfasalazine n=150 N (%)	*Patients with rheumatoid arthritis receiving* methotrexate and hydroxychloroquine n=150 N (%)	*P-value*
Severity of depression symptoms based on HADS score	Normal status (HADS≤7)	128 (85.3)	86 (57.3)	<0.001
	Mild depression (HADS:8-10)	16 (10.7)	45 (30.0)	
	Moderate depression (HADS:11-14)	4 (2.7)	16 (10.7)	
	Severe depression (HADS:15-21)	2 (1.3)	3 (2.0)	
Mean score of HADS depression subscale		3.50±3.53	6.77±3.98	<0.001
Severity of anxiety symptoms based on HADS score	Normal status (HADS≤7)	114 (76.0)	72 (48.0)	<0.001
	Mild anxiety (HADS:8-10)	18 (12.0)	41 (27.3)	
	Moderate anxiety (HADS:11-14)	12 (8.0)	29 (19.3)	
	Severe anxiety (HADS:15-21)	6 (4.0)	8 (5.3)	
Mean score of HADS anxiety subscale		5.34±4.35	7.66±4.43	<0.001
Mean score of HADS		8.86±7.18	14.36±7.83	<0.001

Table 3. Multiple linear regression model for predicting depression and anxiety in patients with rheumatoid arthritis receiving methotrexate and hydroxychloroquine, compared with patients taking methotrexate and sulfasalazine

Characteristics	*Unstandardized regression coefficient*	*Standard error*	*95% CI*	*P-value*
Predictive model for depression				
Receiving hydroxychloroquine	3.39	0.44	2.52-4.26	<0.001
Gender (female to male ratio)	0.53	0.60	-0.65-1.71	0.378
Age	0.002	0.02	-0.04-0.05	0.941
Duration of RA	0.04	0.04	-0.03-0.12	0.267
Level of education	-0.92	0.59	-2.09-0.25	0.123
Predictive model for anxiety				
Receiving hydroxychloroquine	2.48	0.27	1.58-9.14	0.006
Gender (female to male ratio)	0.67	0.05	-0.65-1.71	0.378
Age	0.004	0.01	-0.05-0.06	0.883
Duration of RA	0.01	0.02	-0.07-0.10	0.741
Education level	-1.23	-0.10	-2.60-0.14	0.078

Results

A total of 300 patients with RA were examined in two study groups. The mean age was 52.58±9.67 years in the group receiving methotrexate and SSZ, and 50.14±10.50 years in the second group receiving methotrexate and HCQ (p=0.038). The average duration of RA in Group 1 and Group 2 was 6.77±7.05 years and 6.66±5.36 years, respectively (p=0.036).

The baseline characteristics of these groups are presented in *Table 1*. The two groups had significant differences in educational attainment (p=0.025).

The severity of symptoms of depression and anxiety, along with mean HADS scores in the groups, are presented in *Table 2*. There was the significant difference between the two groups in terms of the severity of depression and anxiety, as well as the mean HADS score (p<0.05). The mean HADS depression scores in patients treated with SSZ and HCQ were 3.50±3.53 and 6.77±3.98, respectively. The mean HADS anxiety scores were 5.34±4.35 in Group 1 vs. 7.66±4.43 in Group 2 (p<0.001).

Using a multiple linear regression model for predicting symptoms of depression, we demonstrated that patients treated with HCQ were significantly more likely to be depressed than those treated with SSZ (B=3.39; p<0.001); but other variables, including gender, age, duration of RA, and level of education, did not differ significantly. An anxiety prediction regression model also showed that anxiety was significantly higher in patients treated with HCQ than in patients treated with SSZ (B=2.48; p=0.006). No significant effect was observed for other variables, including gender, age, disease duration, and education level (*Table 3*).

Discussion

Our study showed a significant prevalence of depression and anxiety in RA patients taking HCQ, compared with those receiving SSZ. We found a limited number of published studies to compare our findings with them.

A systematic review and meta-analysis showed that the prevalence of suicidal thoughts and suicide attempts in patients with rheumatic diseases was 26% and 12%, respectively [17]. Another systematic review and meta-analysis found a 47% greater risk of developing depression in RA patients vs. the controls; however, the effect of different treatments on depression or anxiety in these patients was not quantified and reported [18]. Similar to our findings, a study by Ribeiro et al. showed that patients treated with methotrexate and leflunomide experienced less suicidal ideation than those treated with HCQ or biological agents [19]. In addition, a study by Mascolo et al. on the development of adverse neuropsychiatric events after treatment with HCQ in elderly people diagnosed with rheumatic diseases proposed suicidal ideation as one of the severe manifestations that should be considered in such patients [20].

Contrary to our findings, a multinational network cohort study examining the risk of depression, suicide, and psychosis in RA patients treated with HCQ revealed no increased risk of depression, suicidal ideation, or psychosis in individuals receiving this drug compared with those receiving SSZ [21]. Risk factors that predispose RA patients taking HCQ to depression and other neuropsychiatric manifestations include female gender, family history of psychiatric disorders, exposure to other interacting drugs the person is taking, alcohol use, and concomitant use of

glucocorticoids [20]. Several mechanisms of action were listed for HCQ. An important action that may contribute to its neuropsychiatric adverse reactions is the disruption of the functioning of lysosomes and autophagy. These effects may mimic lysosomal storage disorders and are also associated with neuropsychiatric manifestations in patients taking this medicine [21]. Differences in the study population and the type of scales used to examine psychiatric disorders in RA patients may influence the results and explain differences shown by various studies.

The outbreak of COVID-19 and the consideration of HCQ as a proposed prophylactic or therapeutic agent during the first waves of pandemics prompted several studies to investigate the effect of this drug on the anxiety in patients receiving it [22, 23]. Different results were reported regarding this issue. A 2020 study by Jindal et al. established that COVID-19 patients who were prescribed HCQ experienced the same frequency of anxiety, compared with the control group. This result is inconsistent with our findings [23]. An experimental study evaluating neuropsychiatric behavior and expression of related molecules in the brain at different times after HCQ intake concluded that the drug increased anxiety behavior both 24 hours and 10 days after ingestion. Furthermore, this drug reduced the mRNA expression of some interleukins, corticotropin-releasing hormone, and the serotonin transporter in the brain, some of these effects being dose-dependent [22]. The short duration of HCQ use in individuals diagnosed with COVID-19 vs. patients with rheumatic disease may explain the difference in results between different studies.

In the current study, we did not conduct a structured clinical interview with participants, nor did we take into account confounding factors, such as use of medications that could play a role in causing symptoms of depression and anxiety (e.g., patients taking corticosteroids). Besides, we did not screen patients for symptoms of depression and anxiety before initiating antirheumatic drug treatment. These points constitute the limitations of our study.

Conclusion

Depression and anxiety are more common in patients with rheumatoid arthritis receiving methotrexate and hydroxychloroquine, compared with those taking methotrexate and sulfasalazine.

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Ethical approval

The research protocol has been approved by the Ethics Committee of Babol University of Medical Sciences, Iran, with the registration code MUBABOL.HRI.REC.1396.174.

Conflict of interest

Authors declare no conflicts of interest.

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