

Self-reported symptoms in a cohort of rheumatoid arthritis and lupus erythematosus during the COVID-19 quarantine period

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Abstract

Background. During the first three months of the COVID-19 pandemic in the Philippines, there was a supply shortage of hydroxychloroquine and methotrexate. This problem with medication access and the life changes resulting from the COVID-19 pandemic may predispose patients with rheumatoid arthritis (RA) or lupus erythematosus (LE) to disease flares.

Objective. This study aims to investigate self-reported symptoms of disease flares among patients with rheumatoid arthritis or lupus erythematosus during the COVID-19 pandemic.

Methods. A total of 512 completed online surveys from patients with LE or RA were collected. The gathered data included sociodemographic characteristics, self-reported physical symptoms, health service utilization, and availability of hydroxychloroquine and methotrexate.

Results. Seventy-nine percent of respondents had lupus, while 21% had RA. One-third of the cohort had contact with their attending physician during the two-month quarantine period prior to the survey. Eighty-two percent were on hydroxychloroquine and 23.4% were on methotrexate; but 68.6% and 65%, respectively, of those prescribed had irregular intake of these medicines due to unavailability. The current health status was reported as good by 66.2%; 24% had no symptoms during the two-week period prior to the survey. The most common symptoms experienced were joint pain (67.4%), muscle pain (46.3%), headache (35.4%), and skin rash (25.4%). Five percent had a combination of these four most common symptoms. There was a higher proportion of patients with irregular supply of hydroxychloroquine with joint pains (54.9% versus 41.7%, $p=0.012$) and rash (24.7% versus 9.8%, $p<0.001$, Table 3).

Conclusion. In our cohort of RA or LE, the majority reported at least one symptom that may indicate disease flare. There were more patients with joint pains or rash among those with irregular supply of hydroxychloroquine.

Introduction

The 2019 coronavirus disease (COVID-19) pandemic has significantly affected the world six months ago and will continue to do so until an effective treatment or a vaccine is discovered. The infection has affected millions and caused the death of almost half a million individuals globally [1]. Containment measures that have been in place since the middle of March 2020, including community quarantine and physical distancing, have slowed down the spread of the infection. However, this has significantly limited the access of patients with chronic diseases to medical care. The supply of medicines, including hydroxychloroquine and methotrexate, is severely limited [2]. The off-label use of hydroxychloroquine for treatment and self-medication for prophylaxis for COVID-19, and the halt of importation of medicines from India have adversely affected the availability of these drugs. Several medical organizations, including the Philippine Rheumatology Association, have issued statements against irrational use of hydroxychloroquine [3]. As a result, many patients in the Philippines with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), among other rheumatologic diseases, remained unable to maintain their supply of medications, especially during the two-month period from March 16 to May 31, 2020, when the enhanced community quarantine was in place.

Hydroxychloroquine, an anchor medication for SLE, has been a focus of much attention due to its purported benefits in the care of COVID-19 patients. Several randomized clinical trials were underway to determine its

efficacy and safety in treatment or post-exposure prophylaxis for COVID-19. As of this writing, the National Institutes of Health and World Health Organization halted the use of this anti-malarial drug for showing no benefit in treating patients with COVID-19 and in preventing the development of symptoms among exposed individuals [4,5].

Hydroxychloroquine is recommended for all patients with lupus, at a dose not exceeding 5 mg/kg real body weight. It is effective in controlling lupus rash and arthritis and preventing lupus disease flares [6]. The 1995 HERA study showed its significant benefit on synovitis, pain, and physical disability of recent-onset rheumatoid arthritis [7]. Despite its relatively delayed onset of action, its benefits in reducing cardiovascular morbidity in patients with RA have been recognized, making it a good second-line disease-modifying anti-rheumatic drug (DMARD) therapy for patients with inadequate response to methotrexate [8].

The surge in demand for hydroxychloroquine as a COVID treatment has severely affected access to this drug, putting additional burden on our patients with SLE and RA [9]. Especially for Filipino patients with SLE who are already with increased baseline (pre-pandemic) anxiety and depression scores [10] and have certain vulnerabilities, such as coping, self-esteem, and social support, increasing the risk for anxiety, [11] the life changes resulting from the pandemic and quarantine, anxiety over their vulnerability to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and lack of supply of hydroxychloroquine and/or methotrexate predispose these patients to disease flare.

This study aimed to investigate self-reported symptoms of disease flares among patients with SLE and RA during the COVID-19 pandemic. Documentation of the health status of our patients during this health crisis will assist the government and the health sector in facilitating care for non-COVID patients whose treatment support may have been inadvertently marginalized at this time when supply of hydroxychloroquine and other common medications for these patients are inaccessible.

Methods

We conducted an online survey through the SurveyMonkey platform. The snowball sampling technique was implemented by sending a link to the questionnaire through various online channels.

Patients

Patients with RA or LE were recruited to participate in the survey through a public invitation in social media and through their rheumatology patient groups. A link of the questionnaire was sent through email addresses and social media accounts. Respondents were encouraged to share the link to as many people as possible. Only respondents who disclosed a diagnosis of either RA or LE in the screening question were allowed to complete the survey.

Main outcome variable

The presence of any of the following symptoms was determined through the questionnaire: fever, chills, headaches, myalgia, cough, difficulty breathing, chest pain, coryza, sore throat, dizziness, nausea, vomiting,

diarrhea, rash, oral ulcer, joint pain with or without swelling, bubbly or foamy urine, leg or facial edema, bleeding, or convulsion.

Study factors

We collected data on SLE and RA patients' sociodemographic characteristics, availability of medications, and health service utilization.

Procedures

We conducted this study in accordance with the Declaration of Helsinki as approved by the UP Manila Research Ethics Board (UPMREB 2020–198–01). We ensured that all information given was kept confidential and anonymous.

Statistical analysis

We used IBM SPSS Statistics 24.0. Percentages were calculated for sociodemographic variables, access to medicines, physical symptoms, and health service utilization variables. We used the Chi-square test of independence to test the association between the symptoms experienced and the supply of medicines (hydroxychloroquine and methotrexate) during the pandemic. The level of significance was set at 0.05.

Results

Population Characteristics

The survey was conducted in the third week of May 2020. There were 512 participants; most of them were females (96%), aged 20–50 years old, and residents of the island of Luzon, including the National Capital Region (Table 1, Appendix 1). The majority had children and a household size of 3–5 persons. Most (77%) had college education; 50% completed university education. Approximately 48.2% were employed; some were health care professionals (45/512, 8.8%). Most had medical insurance (85%). There were more respondents with lupus (405/512, 79.1%) than rheumatoid arthritis (107/512, 20.9%). The majority had a duration of illness of more than two years.

Approximately one-third of the cohort had contact or consultation with their attending physician during the two-month quarantine period prior to the survey. Ninety percent of LE and 50% of RA were prescribed hydroxychloroquine, whereas 10% of LE and 66% of RA were on methotrexate. In total, 82% were on hydroxychloroquine and 23.4% on methotrexate. However, 68.6% and 65%, respectively, had irregular intake of these medicines during the quarantine period due to unavailability.

Self-Reported Symptoms

The majority of respondents (345/521, 66.2%) rated their current health status as good. Twenty-four percent (25.9% of LE and 18.7% of RA) had no symptoms. Among those symptomatic, 25% had one symptom, 19% had

two symptoms, and 12% had three. Most of these symptoms were nonspecific, but some may be related to lupus or RA disease flare (joint pains, muscle pains, edema, foamy urine, rash, oral ulcer, pallor, or bleeding).

The most common symptoms during the two-week period prior to the survey were joint pain, muscle pain, headache, skin rash, and dizziness, with respective percentages of 67.4%, 46.3%, 35.4%, 25.3%, and 15.2%, respectively (Table 2, Appendix 1). There were combined symptoms of joint pain, headache, muscle pain, and rashes in 4.6% (Figure 1, Appendix 1).

Fever, chills, colds, cough, sore throat, difficulty breathing, or diarrhea each occurred in less than 10%. Bubbly or foamy urine, facial or leg edema, pallor, or bleeding was reported in less than 10% of the respondents.

Among those with irregular supply of hydroxychloroquine, there was a higher proportion of joint pains (54.9% versus 41.7%, $p = 0.012$) and rash (24.7% versus 9.8%, $p < 0.001$, Table 3, Appendix 1). In the lupus cohort, those with an irregular supply of hydroxychloroquine had a higher proportion with rash (26.9% versus 10.7%, $p < 0.001$). There was no difference in symptoms between those with regular and irregular supplies of methotrexate.

Discussion

The benefits of hydroxychloroquine for lupus have been previously demonstrated [13–16]. Its use is recommended for all patients with SLE unless contraindicated [6]. In the survey, 90% of patients with SLE were on hydroxychloroquine. In RA, hydroxychloroquine is usually added to the treatment regimen when there is an inadequate response to methotrexate monotherapy. It is notable that 50% of our RA respondents are on hydroxychloroquine. Both hydroxychloroquine and methotrexate are slow-acting drugs with prolonged clinical effects. For hydroxychloroquine, the latter is due to its long plasma terminal elimination half-life (approximately 40–60 days), which reflects a high volume of distribution [14]. For methotrexate, the half-life is less than 10 hours, but its active polyglutamated form may remain in tissues for extended periods and explain the prolonged effects [17].

Patients with chronic autoimmune rheumatic diseases such as SLE and RA require long-term use of combination treatments for disease control. Regular monitoring for adverse effects of drugs and episodes of disease flares are needed for careful calibration of their medications. In most instances, premature discontinuation of disease-modifying drugs leads to a flare or aggravation of disease activity [19,20]. When adequate disease control is achieved, a few studies have shown that withdrawal of these disease-modifying drugs is possible without rebound disease flare [22,23]. There are, however, limited data on the effects and safety of unplanned discontinuation of these drugs on disease activity.

In approximately 55% of our cohort of lupus and RA, the discontinuation of disease-modifying drugs was forced and abrupt due to scarcity of supply during the pandemic. More respondents with missed doses of hydroxychloroquine experienced joint pain and rashes. While almost 75% reported one or more symptoms, only 37% were able to consult their attending physicians. Drug unavailability and inability to reach out to their doctors were therefore additional challenges that they had to deal with during the quarantine period. Changes in school and job workload, financial difficulty, changing patterns of family dynamics and other human interactions were significant life changes to which they had to cope with as well. The feeling of helplessness may fully mediate anxiety, depression, and perceived stress among patients with SLE [24]. Daily stress and stressful life events such as these have been associated with flares of SLE [25].

The study has several limitations. The use of an online survey has limited the subjects to those with access to the internet. There were only a few respondents from the Visayas and Mindanao where there were more reports of constraints in the supply of the medicines of concern. We do not have data on disease activity prior to the pandemic. Due to the study design, the self-reported symptoms cannot be definitely attributed to rheumatic disease flare. We did not look at factors other than supplies of hydroxychloroquine and methotrexate that may affect the occurrence of symptoms. There is no documentation of the length of time when hydroxychloroquine and/or methotrexate were unavailable. Standardized patient reported outcome measures, such as the Medical Outcomes Study Short Form–36 and Lupus Quality of Life, were not used in this study, as it was deemed difficult to deploy these measures through a survey disseminated through social media.

Conclusion

In our cohort of 512 patients with lupus erythematosus or rheumatoid arthritis, 75% had at least one symptom, the most common being joint pain, muscle pain, headache, and rash. Among those prescribed the drug, 68% and 65% had irregular supplies of hydroxychloroquine and methotrexate, respectively, during the two-month period of enhanced community quarantine in the Philippines. There were more patients with joint pains or rash, which may indicate disease flare, among those with irregular supply of hydroxychloroquine.

Declarations

Compliance with ethical standards

The study was conducted in accordance with the Declaration of Helsinki as approved by the UP Manila Research Ethics Board (UPMREB 2020–198–01).

Informed consent

Written informed consent was obtained from all individual participants included in the study.

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Conflicts of interest/Competing interests

EOS, CAT, PWR, HMR, GTZ, and MLT declare that they have no conflicts of interest.

Availability of data and material

The primary author affirms that this manuscript is an accurate and transparent account of the study being reported; and that no important aspects of the study have been omitted. The data are available upon reasonable request.

Authors' contributions

EOS, CAT, PWR, and MLT conceptualized and designed the study. EOS, CAT, HMR, GTZ and MLT acquired the data. PWR analyzed the data. EOS, CAT, and HMR wrote the manuscript. All authors interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version of the paper.

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Tables

Table 1 Characteristics of the Respondents

Variable	n (%)	Variable	n (%)
Female	489 (95.5)	Marital Status	
Age Group		Single	237 (46.3)
12-21	26 (5.1)	Married	246 (48)
22-30	132 (25.8)	Divorced/separated	17 (3.3)
31-40	156 (30.5)	Widowed	12 (2.3)
41-49	113 (22.1)	Parental Status	
50 +	85 (16.6)	Not applicable	145 (28.3)
Educational Attainment		No children	90 (17.6)
Below undergraduate	197 (38.5)	Has child < 16 y. o.	133 (26)
University: Bachelor	272 (53.1)	Has child > 16 y. o.	84 (16.4)
University: Master or PhD	43 (8.4)	Has children > 16 y.o. & < 16 y.o.	60 (11.7)
Location		Employed	247 (48.2)
National Capital Region	220 (43.0)	Health Care Professional	45 (8.8)
Luzon	214 (41.8)	Diagnosed Illness	
Visayas	53 (10.4)	Lupus erythematosus	405 (79.1)
Mindanao	21 (4.1)	Rheumatoid arthritis	107 (20.9)
Oversees	4 (0.8)	Prescribed hydroxychloroquine	420 (82.0)
Household Size		Prescribed methotrexate	120 (23.4)
1-2 persons	70 (13.7)	With at least one comorbidity	315 (61.5)
3-5 persons	308 (60.2)	With at least one symptom	411 (80.3)
6 persons or more	134 (26.2)		

Table 2 Self-reported Symptoms among Respondents

Symptoms	Diagnosed Illness		Total, n (%)
	Lupus erythematosus, n (%)	Rheumatoid arthritis, n (%)	
Joint pain with or without swelling	192 (64.0)	69 (79.3)	261 (67.4)
Muscle pain	141 (47.0)	38 (43.7)	179 (46.3)
Headaches	119 (39.7)	18 (20.7)	137 (35.4)
Rash	86 (28.7)	12 (13.8)	98 (25.3)
Dizziness	49 (16.3)	10 (11.5)	59 (15.2)
Cough	27 (9.0)	11 (12.6)	38 (9.8)
Chest pain	31 (10.3)	6 (6.9)	37 (9.6)
Bubbly or foamy urine	33 (11.0)	2 (2.3)	35 (9.0)
Sore throat	24 (8.0)	9 (10.3)	33 (8.5)
Oral ulcer	27 (9.0)	2 (2.3)	29 (7.5)
Difficulty breathing	24 (8.0)	4 (4.6)	28 (7.2)
Leg edema	23 (7.7)	4 (4.6)	27 (7.0)
Nausea, vomiting, diarrhoea	17 (5.7)	3 (3.4)	20 (5.2)
Facial edema	15 (5.0)	1 (1.1)	16 (4.1)
Runny nose	10 (3.3)	5 (5.7)	15 (3.9)
Persistent fever (>38°C for at least 1 day)	8 (2.7)	3 (3.4)	11 (2.8)
Chills	9 (3.0)	1 (1.1)	10 (2.6)
Bleeding	3 (1.0)	1 (1.1)	4 (1.0)
Persistent fever and cough or difficulty breathing	2 (0.7)	0 (0.0)	2 (0.5)
Pallor	2 (0.7)	0 (0.0)	2 (0.5)

Table 3 Association of Self-reported Symptoms with the Supply of Hydroxychloroquine

Symptoms	Supply of Hydroxychloroquine								
	Lupus Erythematosus			Rheumatoid Arthritis			Total		
	With	Without	p-value	With	Without	p-value	With	Without	p-value
Joint pain with or without swelling	50 (41.32)	126 (51.43)	0.069	5 (45.45)	32 (74.42)	.065~	55 (41.67)	158 (54.86)	.012*
Muscle pain	36 (29.75)	96 (39.18)	0.077	4 (36.36)	18 (41.86)	.741~	40 (30.3)	114 (39.58)	0.067
Headaches	30 (24.79)	81 (33.06)	0.106	2 (18.18)	9 (20.93)	.840~	32 (24.24)	90 (31.25)	0.142
Rash	13 (10.74)	66 (26.94)	.000*	0 (0)	5 (11.63)	.235~	13 (9.85)	71 (24.65)	.000*
Dizziness	10 (8.26)	36 (14.69)	0.081	4 (36.36)	3 (6.98)	.010~,*	14 (10.61)	39 (13.54)	0.400
Cough	6 (4.96)	16 (6.53)	0.552	1 (9.09)	4 (9.3)	.983~	7 (5.3)	20 (6.94)	0.524
Chest pain	9 (7.44)	21 (8.57)	0.710	2 (18.18)	2 (4.65)	.126~,^	11 (8.33)	23 (7.99)	0.904
Bubbly or foamy urine	6 (4.96)	21 (8.57)	0.214	0 (0)	1 (2.33)	.610~,^	6 (4.55)	22 (7.64)	0.238
Sore throat	4 (3.31)	19 (7.76)	0.099	4 (36.36)	4 (9.3)	.024~,*	8 (6.06)	23 (7.99)	0.484
Oral ulcer	8 (6.61)	16 (6.53)	0.977	0 (0)	2 (4.65)	.466~,^	8 (6.06)	18 (6.25)	0.940
Difficulty breathing	7 (5.79)	14 (5.71)	0.978	1 (9.09)	1 (2.33)	.289~,^	8 (6.06)	15 (5.21)	0.722
Leg edema	5 (4.13)	14 (5.71)	0.521	2 (18.18)	2 (4.65)	.126~,^	7 (5.3)	16 (5.56)	0.916
Nausea, vomiting, diarrhoea	7 (5.79)	9 (3.67)	0.353	0 (0)	2 (4.65)	.466~,^	7 (5.3)	11 (3.82)	0.486
Facial edema	4 (3.31)	10 (4.08)	.716~	0 (0)	1 (2.33)	.610~,^	4 (3.03)	11 (3.82)	.686~
Runny nose	4 (3.31)	6 (2.45)	.636~	2 (18.18)	2 (4.65)	.126~,^	6 (4.55)	8 (2.78)	.349~
Persistent fever (>38°C for at least 1 day)	3 (2.48)	5 (2.04)	.787~	0 (0)	1 (2.33)	.610~,^	3 (2.27)	6 (2.08)	.901~
Chills	2 (1.65)	6 (2.45)	.624~	0 (0)	1 (2.33)	.610~,^	2 (1.52)	7 (2.43)	.548~

Bleeding	1 (0.83)	1 (0.41)	.610~,^	0 (0)	1 (2.33)	.610~,^	1 (0.76)	2 (0.69)	.943~,^
Persistent fever and cough or difficulty breathing	0 (0)	1 (0.41)	.482~,^	0 (0)	0 (0)		0 (0)	1 (0.35)	.498~,^
Pallor	1 (0.83)	1 (0.41)	.610~,^	0 (0)	0 (0)		1 (0.76)	1 (0.35)	.571~,^

*Significant at level 0.05.

^ The minimum expected count less than 1. Results may be invalid.

~ More than 20% of cells have expected counts less than 5. Results may be invalid.

Figures

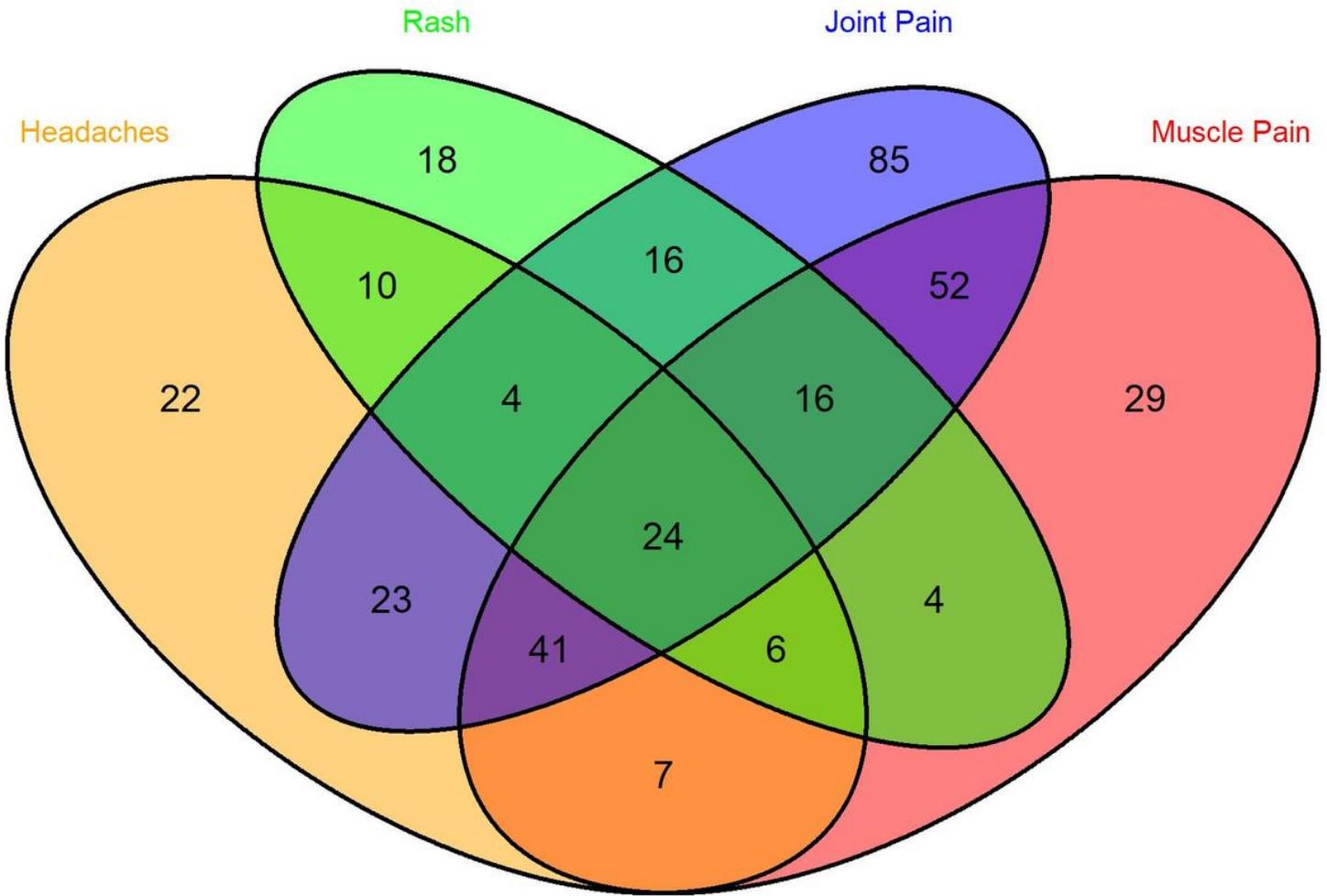


Figure 1

Combinations of the most common self-reported symptoms among respondents (numbers denote frequency of reported symptoms)