Chloroquine and hydroxychloroquine – safety profile of potential COVID-19 drugs from the rheumatologist's perspective

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Abstract

Introduction and objective. The COVID-19 pandemic causes vital concerns due to the lack of proved, effective, and safe therapy. Chloroquine and hydroxychloroquine seem to be useful, but recently serious concerns regarding their adverse events have risen. The aim of the study was to broaden the general perspective of chloroquine and hydroxychloroquine use in COVID-19 treatment, based on an analysis of their current safety profile among patients with rheumatic diseases.
Materials and method. The study was based on a group of 152 patients with rheumatic diseases, aged 20–78 years, treated either with chloroquine or hydroxychloroquine. Analyzed data included age, gender, comorbidities, type of drug, dosage, treatment duration, and reported adverse events. Cases of drug withdrawal related to adverse events were also recorded.
Results. The dosage was consistent in both groups: 250 mg of chloroquine or 200 mg of hydroxychloroquine daily. 77.6% of patients did not experience any adverse reactions to the treatment. Hydroxychloroquine showed better safety profile, with 10.9% of patients reporting side-ffects, compared to 28.9% in patients treated with chloroquine. The overall incidence of ophthalmic complications was 6.6%. For both drugs, no statistically significant correlation between adverse events and age, chronic heart or liver disease, or hypertension was found.
Conclusions. Chloroquine and hydroxychloroquine at lower doses, as used in rheumatic diseases, prove to be relatively safe. Data from the literature show that high dosage as recommended in COVID-19 treatment may pose a risk of toxicity and require precise management, but prophylactic, long-term use of lower, safe doses might be a promising solution.

Key words

adverse events, chloroquine, hydroxychloroquine, COVID-19, SARS-CoV-2

INTRODUCTION

The COVID-19 pandemic causes vital concerns due to a lack of proved, effective, and safe therapy. Only a few known drugs seem to be useful, among them chloroquine and its hydroxyl analog, hydroxychloroquine – both of them old, cheap, and well-known medications [1].

Chloroquine was synthesized primarily as an anti-malarial agent and has been known since 1934. Later, when its immunomodulatory properties were revealed, it was also introduced in the treatment of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, among others [2, 3, 4]. As an anti-malarial agent, it was gradually losing its significance due to rising resistance of Plasmodium falciparum, but in the meantime, its anti-viral activity began to play a role. Apparently, chloroquine exerts an inhibiting influence on several viruses, including flaviviruses, retroviruses, and coronaviruses [2]. It is known to increase endosomal pH required for virus/cell fusion, it also seems to exert an inhibitory effect on nucleic acid replication, glycosylation of viral proteins, virus assembly, transport of new virus particles, virus release, and other processes [5, 6, 7, 8]. Its effective concentration $(EC)_{90}$ value against the SARS-CoV-2 in Vero E6 cells was found to be 6.90 μM [5, 6, 9]. In theory, this should be achievable at the daily chloroquine dose of 500 mg, due to its wide distribution in tissues [5, 6, 10]. Additionally, the immunomodulatory effect of chloroquine includes suppression of tumour necrosis factor α (TNFα) and interleukin 6 (IL6), which are involved in inflammatory complications in several viral diseases [2, 3]. This action is expected to be helpful in controlling cytokine storm [8].

Hydroxychloroquine shares the same mechanism of action as chloroquine [8], and their long-term use in anti-malarial prophylaxis and in rheumatic diseases suggests they are relatively safe during administration for periods of up to few years [2, 3].

Recently, serious concerns regarding severe adverse events with anti-malarial drugs has raised doubts and caused reluctance in using chloroquine and hydroxychloroquine in COVID-19. However, studies among patients with a new coronavirus infection treated with these medications are scanty and more information is urgently needed. In Poland, anti-malarials have been used for decades as

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immunomodulatory drugs in some cases of rheumatic diseases. This treatment is generally considered as quite effective, and of a rather satisfying safety profile [11]. It also seems to have a protective effect against major infections [12] and adds metabolic and cardiovascular benefits [13].

OBJECTIVE

The purpose of the study was to broaden the general perspective of chloroquine and hydroxychloroquine use in COVID-19 treatment, based on an analysis of their current safety profile among patients with rheumatic diseases.

MATERIALS AND METHOD

The study was based on a retrospective analysis of medical data collected between 2018 – 2020. The cohort covered 152 adult patients with various rheumatic diseases, aged 20 – 78 years, treated either with chloroquine or hydroxychloroquine. This included 67 patients with systemic lupus erythematosus, 29 with rheumatoid arthritis, 22 with Sjogren's syndrome, 18 with systemic sclerosis, and 16 with other diseases, such as mixed connective tissue disease, undifferentiated connective tissue disease and polymyositis (Tab. 1). Collected data included age, gender, type of the drug, dosage, treatment duration, and concomitant chronic organ dysfunctions, divided into four subgroups: chronic kidney, heart or liver disease, and arterial hypertension (Tab. 2). Reported adverse effects were subsequently divided into two categories: serious and mild; cases of drug withdrawal related to adverse events were also recorded (Tab. 3).

Table 1. Characteristics of the study group including the diagnosis of rheumatic disease

	All (152)	CQ (97)	HCQ (55)	P-value for 2-tailed z-test
Rheumatoid arthritis	29 / 19.1%	19 / 19.6%	10 / 18.2%	P = 0.83
Systemic sclerosis	18 / 11.8%	10 / 10.3%	8 / 14.5%	P = 0.44
Sjogren's syndrome	22 / 14.5%	16 / 16.5%	6 / 10.9%	P = 0.35
Systemic lupus erythematosus	67 / 44.1%	42 / 43.4%	25 / 45.5%	P = 0.79
Other	16 / 10.5%	10 / 10.3%	6 / 10.9%	P = 0.90

CQ – chloroquine subgroup; HCQ – hydroxychloroquine subgroup; other – mixed connective tissue disease/ undifferentiated connective tissue disease/ polymyositis

The IBM SPSS Statistics 26 was used for the statistical analyses. *P*-value below 0.05 was considered as statistically significant. The Shapiro-Wilk test was performed to test the normality of data distributions. In order to compare the mean values for the data with normal distribution, the student's t-test was used, while in the absence of normal distribution, the Mann-Whitney U test was applied. To compare two population proportions, z-test was used. Due to the lack of the normal distribution of data subject to further analysis, the Spearman correlation was used to verify mutual relations.

The study was carried out in accordance to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

The analyzed subgroups of patients treated either with chloroquine or hydroxychloroquine did not differ significantly, except for the duration of treatment (Tab. 2). The treatment duration ranged from 1 – 264 months and was longer for chloroquine. The dosage was consistent for both drugs: 250 mg daily of chloroquine and 200 mg daily of hydroxychloroquine, respectively.

In the study, 77.6% of patients did not experience any side-effects from treatment. Hydroxychloroquine showed a better safety profile than chloroquine, with 10.9% of patients reporting adverse events, compared to 28.9% for chloroquine patients – the difference was statistically significant. Some patients reported more than one side-effect during treatment. Adverse events classified as serious, i.e., ophthalmic complications and acute allergic reactions, were present in 6.6% and 0.7%, respectively, in all the patients (Tab. 3). Additional analysis revealed that in 69 patients treated with chloroquine without adverse reactions, the mean therapy duration was 37.54 months, while for 49 of those treated with hydroxychloroquine, it was 16.12 months.

The correlations of clinical parameters with observed adverse events are presented in Table 4. This analysis revealed a significant relationship in the chloroquine subgroup – the longer the therapy duration, the fewer side-effects were noted. In the subgroup of patients treated with hydroxychloroquine, a statistically significant association was found between severe adverse events with male gender and chronic kidney disease. However, it must be stated that only one case was found of a severe side-effect which occurred in a male patient with chronic kidney disease; therefore, interpretation of this result should be cautious. No statistically significant correlation were found in either drug between the observed adverse events and age, chronic heart or liver disease, or hypertension.

DISCUSSION

The mechanism of SARS-CoV-2 infection involves the binding of the virus to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2). In the human body, ACE2 is widely expressed, especially in lungs, intestines, brain, heart, kidneys and liver [14]. This is consistent with clinical manifestation of COVID-19, as its major form of presentation – pneumonia – may be accompanied by gastrointestinal or neurological symptoms, and in patients with severe disease, also acute heart, kidney or liver dysfunctions have been observed [15, 16].

In clinical trials, chloroquine seemed to inhibit the exacerbation of pneumonia, improve lung imaging findings, promote a virus-negative conversion, and shorten the disease in patients with COVID-19 [17]. It was one of the first medications recommended in February 2020 by Chinese officials to treat new coronavirus infection. Initially, chloroquine phosphate was suggested to be used at a dose of 500 mg twice daily for 10 days in patients with mild, moderate, or severe pneumonia cases [5, 18, 19]. Precautions included blood count testing (to search for anaemia, thrombocytopenia, and leukocytopenia), serum electrolyte evaluation, as well as liver and kidney tests with routine electrocardiography due to the risk of QT

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Table 2. Clinical characteristics of patients treated with chloroquine (CQ) and hydroxychloroquine (HCQ)

	All	CQ	HCQ	P-value
No. of patients	152	97 / 63.8%	55 / 36.2%	-
Age [years] (SD)	47.30 (15.340)	48.71 (16.145)	44.82 (13.593)	$P = 0.13$[a]
95% CI for Age	(44.84,49.76)	(45.46,51.97)	(41.14,48.49)	-
Men [No / %]	21 / 13.8%	14 / 14.4%	7 / 12.7%	$P = 0.77$[b]
Women [No / %]	131 / 86.2%	83 / 85.6%	48 / 87.3%	$P = 0.77$[b]
Therapy duration [months] (SD)	29.74 (42.823)	37.54 (50.841)	16.12 (15.799)	$P = 0.03$[cs]
95% CI for therapy duration	(22.69,36.39)	(26.93,47.37)	(11.85,20.39)	-
Concomitant chronic organ dysfunctions	80 / 52.6%	56 / 57.7%	24 / 43.6%	$P = 0.09$[b]
Kidney [No / %]	42 / 27.6%	32 / 33%	10 / 18.2%	$P = 0.051$[b]
Heart [No / %]	23 / 15.1%	16 / 16.5%	7 / 13.0%	$P = 0.53$[b]
Liver [No / %]	4 / 2.6%	2 / 2.1%	2 / 3.6%	$P = 0.56$[b]
Hypertension [No / %]	58 / 38.2%	41 / 42.3%	17 / 30.9%	$P = 0.16$[b]

[a] 2-tailed t-student test; [b] 2-tailed z-test; [c] 2-tailed U Mann-Whitney test; [s] statistically significant difference.

Table 3. Occurrence of adverse events in patients treated with chloroquine (CQ) and hydroxychloroquine (HCQ)

	All (152)	CQ (97)	HCQ (55)	P-value for 2-tailed z-test
Without adverse events [No / %]	118 / 77.6%	69 / 71.1%	49 / 89.1%	$P = 0.01$[s]
All adverse events [No / %]	34 / 22.4%	28 / 28.9%	6/ 10.9%	$P = 0.01$[s]
Serious adverse events:				
Ophthalmic	10 / 6.6%	9 / 9.3%	1 / 1.8%	$P = 0.08$
Acute allergic reactions	1 / 0.7%	1 / 1%	0 / 0%	$P = 0.44$
Mild adverse events:				
Mental disorders	4 / 2.6%	3 / 3.1%	1 / 1.8%	$P = 0.47$
Malaise	5 / 3.3%	4 / 4.1%	1 / 1.8%	$P = 0.44$
Photosensitivity	3 / 2%	3 / 3.1%	0 / 0%	$P = 0.19$
Neurological	4 / 2.6%	4 / 4.1%	0 / 0%	$P = 0.12$
Hair loss	1 / 0.7%	1 / 1%	0 / 0%	$P = 0.44$
Gastrointestinal	6 / 3.9%	5 / 5.2%	1 / 1.8%	$P = 0.31$
Skin changes/rash	2 / 1.3%	0 / 0%	2 / 3.6%	$P = 0.06$
Decision of drug withdrawal due to adverse events	29 / 19.1%	24 / 24.7%	5 / 9.1%	$P = 0.01$[s]

Ophthalmic – ophthalmic complications; mental disorders – sleep and mood disturbances; neurological – headache/vertigo/tinnitus; gastrointestinal – nausea/ vomiting/ diarrhoea/ abdominal pain; [s] statistically significant difference.

Table 4. Correlations of adverse events in patients treated with chloroquine and hydroxychloroquine with clinical parameters – age and gender of patients, therapy duration and concomitant chronic organ dysfunctions

	Chloroquine			Hydroxychloroquine		
	All adverse events	Mild adverse events	Serious adverse events	All adverse events	Mild adverse events	Serious adverse events
Age	$r = 0.09$ $P = 0.38$	$r = -0.10$ $P = 0.92$	$r = 0.04$ $P = 0.68$	$r = -0.06$ $P = 0.65$	$r = -0.06$ $P = 0.65$	$r = -0.01$ $P = 0.93$
Gender	$r = 0.07$ $P = 0.51$	$r = 0.15$ $P = 0.16$	$r = -0.05$ $P = 0.60$	$r = -0.22$ $P = 0.11$	$r = -0.07$ $P = 0.62$	$r = -0.36$ $P = 0.01$[s]
Therapy duration	$r = -0.26$ $P = 0.01$[s]	$r = -0.40$ $P < 0.001$[s]	$r = 0.06$ $P = 0.58$	$r = -0.26$ $P = 0.054$	$r = -0.26$ $P = 0.06$	$r = -0.06$ $P = 0.66$
Heart diseases	$r = 0.09$ $P = 0.41$	$r = 0.17$ $P = 0.09$	$r = -0.15$ $P = 0.14$	$r = 0.04$ $P = 0.78$	$r = 0.07$ $P = 0.63$	$r = -0.05$ $P = 0.70$
Kidney diseases	$r = -0.06$ $P = 0.56$	$r = -0.10$ $P = 0.32$	$r = 0.05$ $P = 0.62$	$r = 0.14$ $P = 0.32$	$r = 0.02$ $P = 0.91$	$r = 0.29$ $P = 0.03$[s]
Liver diseases	$r = 0.07$ $P = 0.51$	$r = -0.08$ $P = 0.46$	$r = 0.19$ $P = 0.06$	$r = -0.07$ $P = 0.62$	$r = -0.06$ $P = 0.66$	$r = -0.03$ $P = 0.085$
Arterial hypertension	$r = -0.04$ $P = 0.71$	$r = -0.10$ $P = 0.35$	$r = 0.05$ $P = 0.61$	$r = 0.02$ $P = 0.90$	$r = -0.08$ $P = 0.59$	$r = 0.20$ $P = 0.14$

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interval prolongation. Also, other drugs known to prolong QT interval (eg., quinolones, macrolides, ondansetron) and various anti-arrhythmic, anti-depressant, or anti-psychotic medications were recommended to be avoided in concurrent administration [5]. These guidelines were later modified to shorten the duration of treatment to 7 days, and to lower the dosage in patients with less than 50 kg weight to 500 mg twice daily for the first 2 days, and 500 mg once daily from day three to day seven [18, 19].

Chloroquine has generally good tolerability when used at doses 250–500 mg daily, but side-effects become more frequent when higher doses are administered [3, 10]. Its adverse events involve retinopathy, cardiomyopathy, with QT interval prolongation, liver dysfunction, skin changes, gastrointestinal symptoms, abnormal blood count, and mental disorders [3, 5, 18, 19]. Chloroquine's lethal dose in adults is near 5g. As it has a large volume of distribution and a tendency to accumulate in the human body, the dose of 500 mg twice daily may result in levels close to toxicity. If the severe general condition of some COVID-19 patients is taken into consideration, those with organ damage, including heart, kidneys, and liver, which are also potentially at risk during chloroquine administration, its large doses may be an excessive burden on the body. Furthermore, concurrent drugs must be carefully monitored due to the risk of life-threatening interactions. An example could be a combined use of azithromycin with chloroquine or hydroxychloroquine, as all these medications are known to prolong QT interval, and their interactions may cause serious cardiac threat [5, 20, 21]. In the current study, no heart dysfunctions during treatment were noted (including arrhythmia); however, it should be emphasized that the analyzed patients were treated with lower doses compared to those recommended in COVID-19 treatment.

Hydroxychloroquine, when compared to chloroquine, has a lower level of tissue accumulation and is less toxic [7]. The results obtained in the current study confirm its better safety profile and fewer adverse events. As it seems to require lower doses in anti-viral treatment, it might be considered as an alternative to chloroquine [19].

On 31 March 2020, the Polish Association of Epidemiologists and Infectiologists suggested the use of chloroquine in COVID-19 treatment at a dose of 250 mg twice daily for 7–10 days, or hydroxychloroquine with a loading dose of 400 mg twice daily, followed by 200 mg every 12 hours for 10 days. These recommendations allow lower doses of both drugs but require concurrent additional antiviral treatment (lopinavir/ritonavir or remdesivir) [22]. The above guidelines are subject to subsequent modifications depending on emerging new research results, including alarming, but uncertain reports of increased mortality among severely ill patients receiving large doses of chloroquine in clinical trials (up to 600 mg twice daily) [23].

Interesting and potentially valuable use of discussed drugs could be the prophylaxis against SARS-CoV-2, which is suggested in recent publications [3, 9, 24, 25]. Prophylactic use would require a lower dosage, and it is known that in low doses, these medications are relatively safe even in long-term use, which is confirmed by this study.

In the current study, chloroquine and hydroxychloroquine at doses of 250 mg and 200 mg daily, respectively, were well tolerated. Even though 22.4% of patients experienced adverse reactions during therapy, only 7.3% were classified as serious,

and none of them was life-threatening. Hydroxychloroquine seemed to have a better safety profile, which is consistent with numerous studies, but it's mean duration of treatment was significantly shorter than that of chloroquine. It must be kept in mind that the current studied group consisted of patients with rheumatic diseases, and people with sometimes more than one concomitant chronic condition. If the discussed medications were to be used as prophylaxis against COVID-19 infection in the wider population, even fewer side-effects might be expected. In the presented study, adverse events caused patients to discontinue the therapy in 24.7% of cases in the chloroquine subgroup and in 9.1% for the hydroxychloroquine subgroup. This seems quite often, especially for chloroquine treatment, but it must be stated that it was not always the medical specialist's decision. Sometimes, even with quite mild side effects of the therapy, the patients themselves were withdrawing the medications. Ophthalmic adverse events were observed in 9.3% of patients during chloroquine treatment, 1.8% in hydroxychloroquine therapy, and 6.6% for the whole group, which is comparable with the results of Spinelli et al. [26]. In the presented study, it is important that the adverse events were not dependent on age and comorbidities. This data suggests that even older patients and those with chronic heart or liver diseases, as well as patients with hypertension, should not be at a higher risk for side-effects of chloroquine or hydroxychloroquine if used in low-dose therapy. Moreover, both discussed drugs are also considered relatively safe during pregnancy [27]. Nevertheless, the patients should be monitored during the treatment.

The observed relationship of the longer therapy duration with fewer adverse events during the chloroquine treatment seems to be a consequence of the therapy discontinuation in those patients who experience adverse reactions, or in some cases, also of a gradual decrease in side-effects over time.

As for SARS-CoV-2 infection prophylaxis, the suitable dose might be 250 mg of chloroquine phosphate and 200 mg of hydroxychloroquine daily, as it is used in most patients with rheumatic diseases. Such a prophylactic therapy would be contraindicated in patients with severe renal and hepatic disorders, and could be harmful in individuals treated with other QT interval prolonging medications. Such clinical trials are planned in groups of healthcare workers and other individuals at high risk of SARS-CoV-2 infection [9]. Future results will require careful interpretation, as these drugs are not intended to prevent contact with the virus, but rather the occurrence of the disease in a severe form. Therefore, the presence of antibodies against SARS-CoV-2 in people taking prophylactic doses of chloroquine or hydroxychloroquine should not be a marker of their ineffectiveness. The criteria for effectiveness should be the occurrence of the disease's symptoms and its severity.

A question arises whether sufficient resources of these medications are available for extensive use in the wider population. As the COVID-19 pandemic continues, it has to be realized that the availability of drugs is an important issue.

This study was planned and carried out in response to the growing information about the harmfulness of chloroquine and hydroxychloroquine during the COVID-19 pandemic. Anti-malarial drugs have actually been used for decades and have a theoretically established safety profile; however, they are often abandoned in favour of more modern drugs, and confidence in these medications is diminishing in the

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medical community. Hence, it seems reasonable to bear in mind that they are still used and are relatively safe even in elderly people with chronic diseases. This is particularly important during the ongoing world-wide fight against SARS-CoV-2, as any research in this field contributes to the addition of knowledge and might help in the development of treatment methods.

CONCLUSIONS

Chloroquine and hydroxychloroquine at lower doses, as used in rheumatic diseases, have proved to be relatively safe in long-term use, even in older people with concomitant chronic diseases. However, data from the literature show that a high dosage, as recommended in COVID-19 treatment, require precise management as it may pose a risk of toxicity, especially in patients with additional organ damage or with missed drug interactions. Prophylactic, long-term use of chloroquine or hydroxychloroquine at lower, safe doses might be a promising solution, but require clinical trials. Further research is urgently needed.

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