ISSUES IN PUBLIC HEALTH

Access to chloroquine in patients with rheumatic and musculoskeletal diseases attending rheumatology outpatient clinics during the COVID-19 pandemic

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Herbal medicines made from the bark of the *Cinchona* tree, and later quinine, have been widely used for centuries to treat medical conditions such as tropical malaria. More recently, chloroquine (CQ) and its synthetic derivatives have been used as antimalarials and to treat systemic lupus erythematosus, rheumatoid arthritis, and in the past 14 months or so, COVID-19 pneumonia. Anecdotal evidence and the erratic covering through social media of its potential efficacy in the treatment of COVID-19 pneumonia have resulted in the widespread off-label use of CQ in South Africa and worldwide. This study aimed to show that access to CQ as a chronic medication for rheumatic and musculoskeletal diseases was limited during the COVID-19 pandemic, and that this resulted in an increased incidence of flares in these patients, affecting their morbidity and potentially leading to mortality.

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Background

History of chloroquine use

From the middle of the 20th century, chloroquine (CQ) and its synthetic analogues (e.g. sontoquine and primaquine) have been used widely for the prophylaxis and treatment of tropical malaria. Empirical studies showed CQ to be one of the most effective antimalarial agents, and further molecular adaptations led to the development of hydroxychloroquine (HCQ), a less toxic metabolite of CQ.[1,2] During World War II, soldiers using chloroquine as malaria prophylaxis noticed a significant improvement in their skin rashes and inflammatory arthritis. Subsequent studies showed chloroquine and its synthetic analogues to be highly efficacious in the management of autoimmune conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[1,2]

Management of rheumatic and musculoskeletal diseases

In a 4-year study conducted in the 1950s, CQ was used continuously to manage RA.[3] Minimal serious side-effects and a 70% positive outcome were seen in the RA patient population. It was shown that apart from their effective antimalarial activity, CQ and HCQ have immunomodulatory properties that make them ideal for the management of autoimmune diseases. During the 1950s, both CQ and HCQ were therefore identified as disease-modifying anti-rheumatic drugs (DMARDs), and since then they have been used to treat rheumatic autoimmune diseases, specifically SLE.[3] A pivotal study published in 1991 showed that abruptly stopping HCQ treatment in patients with SLE was associated with a doubled risk of having an acute disease flare.[4]

The COVID-19 pandemic

Several studies have shown that CQ has the ability to interfere with viral growth and transmission, including SARS-CoV-2. Both *in vitro* and *in vivo* studies have demonstrated that chloroquine increases endosomal pH, inhibits viral receptor activity, and reduces functionality of the host's angiotensin-converting enzyme 2 receptors.[2] All these mechanisms interfere with virus receptor binding, which makes CQ a potential and relatively safe agent to prevent infection by and transmission of SARS-CoV-2.[5] For this reason, CQ was included in COVID-19 pneumonia clinical trials in China and showed promising results.[6] An open-label non-randomised clinical trial by Gautret *et al.*[7] in 2020 showed that HCQ has the ability to reduce viral load in patients infected with COVID-19, especially when combined with azithromycin. However, a meta-analysis published in September 2020 concluded that there was no convincing evidence that CQ or HCQ improved clinical outcomes in COVID-19 pneumonia.[8]

Impact of limited access to CQ in South Africa

The national lockdown in South Africa (SA) starting in March 2020 included a necessary de-escalation of clinical services, closure of outpatient departments and limited access to secondary and tertiary medical services for patients, including those with chronic rheumatic and musculoskeletal diseases (RMDs). At the same time, with the speculation and excessive social media coverage regarding anecdotal evidence of a potential beneficial role of CQ in COVID-19 treatment, shortages of CQ and HCQ were anticipated. Discontinuation of CQ for reasons such as limited availability or limitations in access

to healthcare services may lead to acute disease flares, increased morbidity, and potentially increased mortality.

Objectives

Morbidity and mortality due to the COVID-19 pandemic, and its global impact, are not limited to COVID-19 infections, but affect a wider patient population, including those with chronic RMDs. The objective of this study was therefore to show that access to CQ during the COVID-19 pandemic was limited, leading to an increased incidence of flares in patients with chronic RMDs and affecting their morbidity and potentially causing mortality.

Methods

An audit was conducted in the Division of Rheumatology, Tygerberg Hospital, Cape Town, SA, between 15 November and 15 December 2020. All patients attending the clinic with an underlying RMD who had been using CQ for a minimum of 6 months were included. A questionnaire was completed, including details of the healthcare facility where the patient routinely collected their chronic medication, and details of problems in accessing chronic medication during the 12 months preceding their appointment. A flare of the underlying condition was based on clinical assessment by the treating clinician and application of relevant disease activity indices. Hospitalisation and mortality related to a flare were documented. The audit was approved by the Health Research Ethics Committee of Stellenbosch University (ref. no. N20/11/072_COVID-19) and complied with the ethical guidelines and principles of the International Declaration of Helsinki.

Results

Of a total of 342 consecutive outpatients screened, 177 had used CQ for a minimum of 6 months and were included in the audit. The majority of these patients (91%) were female, and the mean (standard deviation) age was 48 (13.4) years. The spectrum of RMD diagnoses is summarised in Fig. 1.

Our patients attended 56 different community healthcare centres (CHCs) prior to their outpatient appointment. These included 22 different rural clinics as far away as Beaufort West, Nieuwoudtville and Villiersdorp. Only 6 patients (3%) routinely collected their medication from Tygerberg Hospital, and 5% collected it from a private pharmacy. The most frequent CHCs visited were within the Khayelitsha Health District (total of 6 different clinics attended by 22 patients (12%)) and in Delft (*n*=16 patients; 9%), Elsiesrivier (*n*=11; 6%) and Kleinvlei (*n*=10; 6%).

Limited access to CQ was reported by 80% of patients (*n*=142) for a median (interquartile range) period of 4 (1 - 6) months, maximum 11 months. Shortages were most frequently reported during July (72%), August (77%) and September 2020 (76%), coinciding with the first peak of the pandemic in SA. Access to CQ was significantly more limited than access to other conventional synthetic DMARDs (*n*=8), immunosuppressive therapy (including prednisone) (*n*=10), and other chronic medication (Table 1). Most participants (96.6%) reported that CQ was not available at their local CHC. Three patients were unable to attend their CHC, while 2 patients had incorrect prescriptions. Fifty-two patients (29%) made use of alternative means to obtain their medication, including buying medication from a private pharmacy, borrowing from a family member or friend, or returning to Tygerberg Hospital to collect medication.

In 69 cases (39%), the treating clinician reported the patient to have had a flare, based on clinical assessment and relevant disease activity indices (Fig. 2). In the majority of cases (86%; *n*=59/69), the

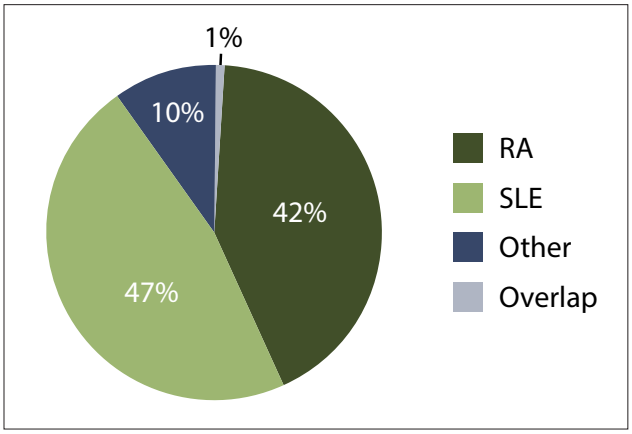

Fig. 1. Spectrum of rheumatic and musculoskeletal conditions of patients included in the audit (N=177). (RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; Other = dermatomyositis (n=3), systemic sclerosis (n=2), primary Sjogren's syndrome (n=4); undifferentiated connective tissue disease (n=5), psoriatic arthritis (n=2), sarcoidosis (n=1), polymyalgia rheumatica (n=1); Overlap = RA and SLE/systemic sclerosis (n=2).

Table 1. Limited access to chronic treatment reported in patients attending rheumatology outpatient department (*N*=177)

Treatment access limited	*n* (%)
Chloroquine	142 (80.2)
Methotrexate*	7 (4.0)
Sulfasalazine	1 (0.6)
Leflunimide*	1 (0.6)
Azathioprine	1 (0.6)
Prednisone	9 (5)
PPI	22 (12.4)
Vitamin D	40 (22.6)
Calcium carbonate	12 (6.8)
Antihypertensive treatment	4 (2.3)

PPI = proton pump inhibitor.
*Some patients had limited access to a combination of conventional synthetic disease-modifying antirheumatic drugs.

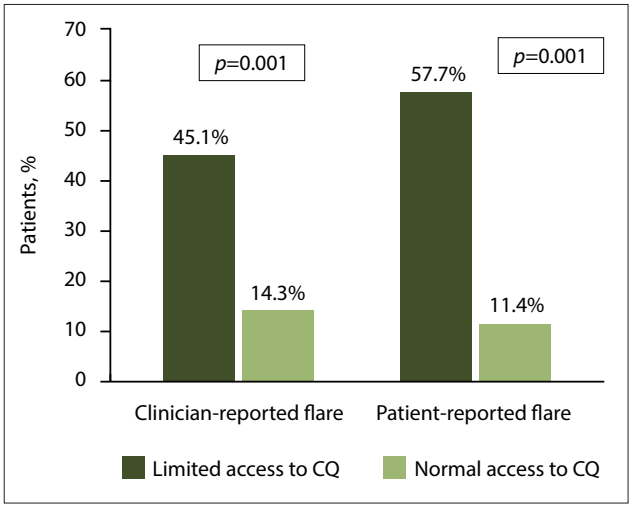

Fig. 2. Percentage of patients with limited v. normal access to CQ and reported flares of their rheumatic and musculoskeletal disease. (CQ = chloroquine.)

Table 2. Spectrum of rheumatic diseases where limited access and a flare was reported (*N*=177)

	RA (*N*=74), *n* (%)	SLE (*N*=83), *n* (%)	Other (*N*=18), *n* (%)	Overlap (*N*=2), *n* (%)
Limited access to CQ	58 (78.3)	40 (48.2)	16 (88.9)	1 (50.0)
Clinician-reported flare	40 (54.1)	20 (24.1)	8 (44.4)	1 (50.0)

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; Other = dermatomyositis (*n*=3), systemic sclerosis (*n*=2), primary Sjogren's syndrome (*n*=4), undifferentiated connective tissue disease (*n*=5), psoriatic arthritis (*n*=2), sarcoidosis (*n*=1), polymyalgia rheumatica (*n*=1); Overlap = RA and SLE/systemic sclerosis (*n*=2); CQ = chloroquine.

flare was attributed to limited CQ access. Of the 69 patients who had a flare, 93% (*n*=64) had limited access to CQ. The various RMDs with limited CQ access and clinician-reported flares are depicted in Table 2.

A single patient was hospitalised for a flare of lupus nephritis.

Discussion

The off-label use of a drug can be a commendable gesture in a setting where there is some scientific evidence to support this decision by a clinician. The patient should be well informed about the decision, and signed consent should be obtained.[9] However, off-label use of a drug without compelling scientific evidence is discouraged by the US Food and Drug Administration.[10] Reasons for this include inability to recruit patients already on the drug for randomised controlled trials, as they might be assigned to a placebo; hesitancy of drug companies to invest in a drug that is already used for the indication; and the increased number of side-effects that are seen with off-label prescribed drugs as opposed to on-label prescriptions.[11]

The off-label use of CQ during the first wave of the COVID-19 pandemic in SA led to an additional disadvantage not described by the Congressional Research Service group in the document that reviewed the advantages and disadvantages of off-label use of drugs in February 2021.[12] This is the shortage of drug supply for patients who are taking the drug for an on-label indication. In our study, shortages of CQ for patients with RMDs were observed as a result of the off-label use of this drug during the first wave of COVID-19 in SA beginning in March 2020.

One of the World Health Organization's Millennium Development Goals is to achieve universal health coverage.[13] This principle recognises the availability and affordability of health services and prescription drugs as a basic human right. The limited availability of CQ for patients with chronic RMDs during the first wave of COVID-19 in SA can therefore be considered a violation of a basic human right.[13] Such violations should be taken into consideration in the near future as the COVID-19 pandemic continues and other sets of drugs are considered for off-label use.

Globally the COVID-19 pandemic has affected governments in various areas, including healthcare systems and the economy.[14] Off-label prescription of CQ led to shortages of this drug for patients with RMDs in many countries. In European countries, there was estimated to be a 49% shortage of CQ for patients with RMDs.[15] In Canada, a range of 50 - 79% in the different provinces was estimated.[16] In the USA, HCQ non-compliance among patients with RMDs was found to be multifactorial and estimated at 20 - 50%.[17] In 15 Arabic countries in the Middle East and North Africa, 47% of patients were affected by limited access to HCQ.[18]

The off-label use of CQ and HCQ for the treatment of COVID-19 in Africa has been an ongoing concern and has been observed in many countries across the continent. However, the magnitude and the impact of this problem have not been established.[19] Our audit delineates the challenges of CQ acquisition and consequences of lack of the drug during the COVID-19 pandemic in a cross-sectional cohort of patients with RMDs in Cape Town, SA. We found a significantly higher proportion of patients with limited CQ access in comparison with reports from the USA and North Africa, with disease flares reported by a clinician in 45% of patients v. 14% of those with uninterrupted CQ access (p=0.001).

Study limitations

Only outpatients were questioned in the audit. Patients hospitalised during the preceding months were not specifically questioned about chloroquine access at the time or included in the analyses. Hospitalisation, significant disease flares and associated mortality may therefore be underestimated in our analyses.

Conclusions

The off-label use of prescription drugs can lead to shortages of the drug for patients who are on the drug for on-label use, as demonstrated in our cohort, where a shortage of CQ followed its off-label use. The shortage of CQ had a significant impact on the disease activity of patients with RMDs. Off-label prescription of a widely used drug such as CQ should therefore be implemented cautiously by clinicians, especially during pandemics, as this may lead to poor outcomes for the subset of patients already on the drug in question.

Declaration. None.

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