Research article

Treatment of chronic inflammatory joint disease in Zanzibar: impact of the Covid-19 pandemic

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Abstract

Background: The Covid-19 pandemic has had a major impact on economies and health globally. It has also affected the availability of drugs such as hydroxychloroquine, commonly used in rheumatic disorders.

Objective: The aim of this study was to describe the impact of the Covid-19 pandemic among patients with chronic inflammatory joint disease.

Methods: A study on chronic inflammatory joint disease in Zanzibar was undertaken in July 2019 and is ongoing. So far, 38 participants have been recruited and were included in the present study. These participants were contacted for phone interview regarding information on self-reported disease activity, joint pain and swelling. Patients were also asked about adherence to medication, Covid-19 symptoms, household expenditure and quality of life during the pandemic.

Results: At baseline, 38 patients, mostly females (92%), had been enrolled. The mean age was 45 years and mean disease duration was 3.5 years. Majority had moderate and severe disease activity (58%). For this study, 33 patients were reached for interview. The majority reported joint pain (91%) and swelling (52%). Twenty four (73%) noted their disease activity to be better than before joining the ongoing study. Only 13 (39%) reported symptoms of Covid-19. Adherence was generally lower during the pandemic (52%) compared to baseline (58%) although this was not statistically significant. About a third of participants were unable to quantify their expenditure. Of the remainder, 13 (39%) participants reported a decrease.

Conclusion: The pandemic had a negative impact on patients due to lack of funds to purchase drugs and unavailability of drugs such as hydroxychloroquine which is cheaper compared to alternatives. We believe that the overall improvement in disease activity may be attributed to management that had been commenced prior to the pandemic.

Key words: Arthritis, COVID-19, Health expenditure, Zanzibar, Medication adherence

Introduction

Chronic Inflammatory Joint Diseases (CIJD) reduce health-related quality of life substantially due to pain and immobility, among others[1,2]. The prevalence is estimated to be 0.13-2.5%[3]. Coverage of effective Disease Modifying Anti Rheumatic Drugs (DMARDs) are low in African countries[2]. By large, rheumatic disorders have so far been neglected in low-income health systems, and many patients remain undiagnosed and untreated[4]. The Covid-19 pandemic has influenced health systems and economies all over the world, and there is now growing concern that this leads to disinvestments of essential non-Covid-19 services like DMARDs in rheumatic disease[5,6]. Therefore, there is a need to learn more about how Covid-19 indirectly affects patients with CIJD.

Evidence has shown that DMARD therapy in sufficient dosage significantly improves patient outcomes[7]. However, most studies that evaluate effect of DMARDs are conducted in settings with optimal access to drug therapy where patients can be reviewed regularly in the health system. This is not the case in many low-income countries. Additionally, the modes of routine care and patient reviews have had to undergo significant changes in such settings during the Covid-19 pandemic. Not much is known about how DMARDs influences patient outcomes in low-income settings like Zanzibar. A study in Egypt reported an increase in disease flares among patients with CIJD in the cities with more Covid-19 cases[8].

Covid-19 continues to affect people worldwide and the World Health Organisation estimates that over 65 million people had been infected and over 1.5 million had died by December 2020. Although it is difficult to make sound predictions about the disease[9], it is well known that it causes increased mortality for the elderly and those with underlying

health conditions[10]. Furthermore, many countries, including Zanzibar, have implemented restrictive public health policies like home office, home school, quarantine, closing restaurants and public transport regulations[11]. These restrictive policies have many negative societal and indirect health effects. There is an urgent need for the development of an effective vaccine to stop infections. Until then, it is important to maintain public health measures and protect the vulnerable from acquiring the disease, but also to get a better understanding of indirect health effects of Covid-19 on other diseases and their management in the health system[12].

In this case study we describe patient characteristics, disease activity, anti-rheumatic treatment as well as socio-economic factors in patients with CIJD in Zanzibar before and during the Covid-19 pandemic.

Materials and methods

Design: A mixed-methods descriptive study was undertaken. The first part is the quantitative component comparing findings at baseline and during the Covid-19 pandemic. The second part is qualitative and selected patient cases are presented to illustrate personal experiences and how the Covid-19 pandemic had affected them regarding their disease and its management.

Setting: The Zanzibar islands (Unguja and Pemba) are a semi-autonomous region of Tanzania, with a population of about 1.46 million[13]. The main referral hospital, Mnazi Mmoja Hospital, is based at Unguja island. This is currently the only hospital with rheumatology care, and where DMARDs are prescribed. A research project on treatment and diagnostics of patients with Rheumatoid Arthritis (RA), psoriatic arthritis and ankylosing spondylitis was initiated in 2019. Enrolled patients were closely monitored and included in a follow-up study. Before the pandemic, the included patients had started to improve vastly because of intensified treatment and follow-up that had already been initiated.

Study population: From September 2019, all patients with a clinical diagnosis of RA, psoriatic arthritis or ankylosing spondylitis were informed of the study and invited to participate. At the time of this write-up 38 patients had been recruited.

Inclusion criteria: Patients aged ≥18 years with a clinical diagnosis of RA, ankylosing spondylitis or psoriatic arthritis were included. Written and informed consent was obtained from all included patients. Prior to the phone interview, informed consent was acquired.

Quantitative data: The following data were registered at the first visit (the baseline visit): age, year since first symptoms, year of diagnosis, medication used in management, comorbid illnesses, tender and swollen joint count, lab results for complete blood count, liver function tests, erythrocyte sedimentation rate, chest X-ray reports and hand X-ray reports. Baseline disease activity score -28 (DAS 28) and Clinical Disease Activity Index (CDAI) were also registered. Questionnaires were completed for medication adherence, income and total household expenditure.

Data on total household expenditure was collected using specific questions on health and non-health expenditures of households in Tanzanian shillings. For the first three clinic visits, patients were asked to quantify how much they had spent on reaching the hospital, acquiring treatment and care, payment for alternative medicine and caretakers. They were also asked about total household expenditure on household items, food, clothing, utilities, transport, education, rent, healthcare, insurance, repairs and loans.

At the first visit, patients are informed of the diagnosis, educated on their disease, its progression and management. Key messages include chronicity of the disease, information concerning medical treatment and precautions in relation to pregnancy, as well as restriction of steroids and non-steroidal anti-inflammatory drugs to prescribed use. Medication was prescribed according to a pre-defined treatment protocol in adherence to internationally recommended guidelines which recommend early and targeted therapies using DMARDs[14].

Interview data: For the present study, all patients were contacted by phone for interview. Six of the interviews were conducted face-to-face. Patients were asked to describe their symptoms during the Covid-19 pandemic as compared to baseline. They were asked whether they had any painful or swollen joints, and whether they felt their disease had improved, stayed the same or deteriorated. Medication adherence was also investigated, and the following questions were addressed: When was the last time they took their DMARD, and was it taken on time as prescribed, or did they ever forget to take it? Did they ever run out of their medication, or experience difficulties obtaining it at their local pharmacy in terms of availability? Had there been difficulties obtaining funds to purchase their medication during the pandemic?

For Covid-19 symptoms, we used a questionnaire with a variety of symptoms categorised as systemic, respiratory, neurological, and gastrointestinal. Patients answered yes or no to whether they or any of their immediate family members had experienced any of these symptoms within the last month.

Concerning the household expenditure, participants were asked about monthly expenditure on the various parameters similar to that of the baseline visit. They were asked to give as exact figures as possible, and these were used for comparison.

Qualitative cases: Patients accounts and experiences are described to illustrate their personal experiences during the pandemic. The choice was of critical cases of patients who had undergone difficulties in managing their disease because of the pandemic. This was either from loss of income or unavailability of hydroxychloroquine.

Statistical analysis: Descriptive statistics were used for the presentation of patient baseline characteristics. Data from the interviews, self-reported disease activity and adherence are presented as percentages. Total household expenditure before and after the Covid-19 pandemic was assessed using the paired T-test.

Ethics: Ethical approval was obtained both from the Zanzibar Health Research Institute (ZAHRI) and Norway Research Ethics Committees (2019/472/REK vest), respectively.

Results

Thirty eight patients were included in the study (mean age 45 years, 92% women). Patient characteristics registered at the baseline visit (when the patient was included in the study) are presented in Table 1.

Table 1: Patient characteristics at baseline (n=38)

Characteristic	No. (%)
Gender (% women)	92
Age (mean, SD)	45 (13)
Disease duration (mean, SD years)	3.5 (3)
Time to diagnosis (mean, SD years)	2.6 (3)
Disease activity at baseline (n, %) *	
Remission	3 (8)
Low	12 (33)
Moderate	16 (41)
Severe	7 (17)
Medication at baseline (n, %)	
No DMARD	12 (28)
Methotrexate (MTX)	21 (58)
Hydroxychloroquine (HCQ)	1 (1)
MTX + HCQ	4 (11)
Prednisolone	18 (50)
Comorbidity (n, %)	
Hypertension	4 (11)
Malignancy	1
Diabetes mellitus	2
Education	
No formal education	7 (19)
Incomplete primary school	4 (11)
Primary school	2 (6)
Completed O-levels	18 (44)
Completed tertiary education	7 (19)

Self-reported disease activity, medication adherence and Covid-19 symptoms: Overall, there were 33 interview respondents, an equivalent of 86% response rate of whom 30 (90%) were women. The findings from the interviews regarding self-reported disease activity, medication adherence and Covid-19 symptoms are summarised in Table 2. The majority of patients (91%) reported some level of pain in the joints while 52% reported swelling of at least one joint. Medication adherence was overall low (52%), and 45% reported difficulties obtaining funding for their medication (Table 2). Assessment of adherence at baseline showed it to be 58% in the same cohort of patients.

Table 2: Covid-19 phone interview response (n=33)

Response	No. (%)
Self-reported disease activity (n, %)	
Pain*	30 (91)
Swelling**	17 (52)
Disease activity	
Worse	9 (27)
Better	24 (73)
Self-reported medication adherence (n, %)	
Adherent	17 (52)
Difficulties obtaining medication (availability)	12 (36)
Difficulty acquiring funds for medication	15 (45)
Self-reported Covid-19 symptoms (n, %)	13 (39)

*Self-reported pain in any joint
** Self-reported swelling in any joint

Total household expenditure: Changes in household economy are presented in Table 3. Of the 33 participants, 13 reported a reduction in total household expenditure and the monthly household expenditure decreased from 668,700 to 502,900 Tanzanian shillings on average per month, equivalent to 288 and 216 US dollars, respectively. This was predominantly reported as a cutting down purchases on clothing and household items. Seven patients had a reduction in expenditure on food items from baseline mean of 408,600 to 287,500 Tanzanian shillings (USD 176-123) per month during the pandemic. Analysis of the change in expenditure showed the difference to be non-significant (P-value 0.08). Ten patients (30%) were unable to quantify their total household expenditure during the interview. This was either because they had moved during the pandemic to live with relatives or because they were not heads of the households.

Table 3: Change in total household expenditure during Covid-19 (n=33)

Expenditure	No. (%)
Household expenditure (n, %)	
No change	10 (30)
Increased	0
Decreased	13 (39)
Unable to quantify	10 (30)

Patient cases

Case 1

A patient in her 20s had been treated with methotrexate for RA in the last 10 years and her disease activity was low during that period. She was enrolled in this study in September 2019. Two months after enrolment, she switched to hydroxychloroquine (HCQ) therapy in preparation for pregnancy. During the pandemic, the drug was unavailable at all government hospital pharmacies and could only be purchased at a few privately owned pharmacies. It had been indicated that HCQ was a potential treatment for Covid-19 leading to subsequent massive over-the counter purchases of HCQ in Zanzibar and stockpiling by individuals, leading to stock outs at the pharmacies supplying it. Her income had not been affected.

The patient was advised to switch to sulfasalazine, which she could unfortunately not take because of an allergy to sulphur. She was then offered azathioprine as an alternative; however, this proved to be unattainable because of lack of availability. She was fortunate enough to receive HCQ as donation, but due to drug scarcity and the need to extend her supply, the patient took it once a day instead of her prescribed twice daily dose. This led to worsening disease activity to moderate. She was also taking prednisolone 5mg once daily sporadically during episodes of severe joint pains. Fortunately, over the remainder of her pregnancy, the patient has received further donations of hydroxychloroquine and has delivered a healthy baby boy. We hope she will continue receiving the drugs from well-wishers so that she will be able to continue breastfeeding her baby.

Case 2

This was a patient with symptoms of RA since 2004 and diagnosis was set in 2019 and methotrexate dose titrated to 25mg weekly. At baseline, disease activity score -28 (DAS28) was 3.56/ Clinical Disease Activity Index (CDAI) 16.5 indicating moderate disease activity. Resulting from dose adjustment she reached remission on follow-up. In late February 2020, she requested a switch to a pregnancy-safe drug due to plans of conception. She was therefore switched to HCQ and planned for routine follow up. Unfortunately, she presented in mid-March reporting a lack of availability of HCQ in the pharmacies for the same reasons as the patient in case 1. Sulfasalazine was prescribed as an alternative, but due to costs (0.30 USD/ 500mg tablet) it was not considered a feasible option for this patient. The patient is unemployed and depends on her brother for her health care expenses. She has been restarted on methotrexate and postponed conception until second line drugs are either available or affordable.

Case 3

A middle-aged patient was diagnosed with RA in 2018 after having had symptoms for 6 years. At the time of enrolment, she had moderate disease activity with severe joint deformity, especially of the hands, and was treated with both methotrexate and HCQ at doses of 25mg weekly and 200mg twice daily, respectively.

The patient sells snacks and sweets to schoolchildren to supplement her income (<200 USD/month) to purchase her medication. Upon school closure due to the Covid-19 outbreak her income was drastically reduced, and she was unable to afford both methotrexate and HCQ. When she presented to the hospital with these concerns, her disease activity was moderate. Fortunately, methotrexate is available at the government hospital pharmacy as an injectable and was provided to her. Hydroxychloroquine however was not. After two injections, she expressed the inconvenience of having to come to the hospital every week for her medication and opted to source methotrexate via her own means. She continues to take methotrexate as a single drug with low dose steroids for disease control. Patient is adherent to medication and has low disease activity.

Discussion

In this descriptive study the major findings were poor adherence to prescribed drug treatment and a reduction in total household expenditure during the Covid-19 pandemic. We found that more than 50% of patients interviewed were not adherent to the prescribed DMARDs, due to either loss of funding or availability of the drug. One expects that upon diagnosis and initiation of treatment patients would become more adherent especially with regular follow up. Although we cannot determine causality, it is likely that this is associated with the pandemic, as the cases illustrate.

Similarly, a study done in Egypt by Abualfadl *et al*[8] found disruptions among patients with RA in obtaining their medication. Adherence at baseline was 58%, but there is reason to believe it would be even higher after study-onset as the patients received information regarding the importance of drug treatment. Thus, the observed reduction during the pandemic is counter to what would be expected, and the most likely explanation is the pandemic.

A disruption or down-scaling of DMARD treatment will, in time, result in worsening of RA disease activity[15].

This was not seen in our study. In fact, the majority of patients reported improvement in disease activity. This self-reported improvement in disease activity is probably due to initiation or up-scaling of DMARD therapy during the original study. As the treatment effect of most DMARDs, and hydroxychloroquine in particular, is protracted, ranging from 3 to 6 months, possible adverse effects of disrupted treatment on disease activity could not be expected during the short time-span of this study and the pandemic.

There is significant out of pocket expenditure for healthcare among households in African countries[16]. The pandemic also led to disturbing reports on decline in total household expenditure[17] and is likely to be at least partly responsible for the reported difficulty in acquiring funds for medications, as reported by 45% of our patients. As the pandemic continues with resulting fall in national economies and resulting drop in household incomes, we fear that loss of follow-up and disruption or down-scaling of DMARDs will subsequently lead to increased disease activity.

Hydroxychloroquine and chloroquine in general have been banned for use in malaria in Tanzania since the development of resistance by malaria parasites in the year 2001[16]. Its use for RA is neither registered in the pharmacies nor is it in the Zanzibar treatment guidelines. It is however of significance, particularly in younger women, as it may be taken during pregnancy and lactation. With the announcement of hydroxychloroquine as a potential drug in the treatment of Covid-19, many individuals purchased the little that was available in the pharmacies for stockpiling, in the event that they or their families might require the drug. Attempts to re-purchase them resulted in a drastic hike of the price, making it non-feasible as a treatment option. These events rendered patients on hydroxychloroquine left with the option of sulfasalazine as a second line for those who could afford it. It is almost twice the price of HCQ. Leflunomide is not available on the island. The drastic shortage of HCQ that was seen in Zanzibar is similar to what was reported across several African countries by the African League Against Rheumatology (AFLAR) survey that found over 60% of rheumatologists experienced shortages of HCQ and almost a quarter had to switch from HCQ to other therapies[18].

Tanzania did not conduct community-wide testing for Covid 19. We assessed for Covid-19 infection using a symptoms questionnaire. In our study, 13 patients reported Covid-19 symptoms. Although there are multiple Covid-19 symptom questionnaires in use, no studies have verified their sensitivity and specificity for diagnosis. Furthermore, there is no study looking at the combination of symptoms and their sensitivity in predicting Covid-19 infection[19,20]. Therefore, even if a participant had symptoms, we have no way to verify whether they truly had Covid-19.

The study limitations included the insufficient sample size and subsequent lack of statistical power to evaluate the impact of Covid-19 in this patient group taking into consideration the challenges inflicted by the pandemic. The time span was also too short for the assessment of the effect of in-adherence to DMARD therapy. This report, describing three cases and a small study cohort, does, however, provide an illustration of the challenges inflicted on patients with inflammatory joint disease by Covid-19, in Zanzibar. Final results from the ongoing inflammatory arthritis study will be published in forthcoming articles.

Study strengths include the use of mixed methods on a prospective cohort in order to clearly highlight patient experiences during the pandemic.

Conclusion

Covid-19 has had a major impact on the global economy. On a more individual level, the majority of patients in this study were adversely affected with a drop in total household expenditure during the Covid-19 pandemic, probably reducing drug adherence. Because RA does not present as an acute and life-threatening medical need, patients may opt to skip medication and bear their pain to meet basic needs. This does not lead to catastrophic health expenditure but does in the long-term lead to adverse outcomes on morbidity and mortality. Patients who were on hydroxychloroquine therapy were also directly affected because of the lack of availability of medication and no cheaper alternative. Many will have to revert to monotherapy and steroid bridging until a sustainable solution is acquired, with subsequent expected side effects.

References

1. Wysocka-Skurska I, Sierakowska M, Kułak W. Evaluation of quality of life in chronic, progressing rheumatic diseases based on the example of osteoarthritis and rheumatoid arthritis. *Clin Interv Aging* [Internet]. 2016 Nov 28 [cited 2020 Dec 6];Volume **11**:1741–50. Available from: https://www.dovepress.com/evaluation--of-quality-of-life-in-chronic-progressing-rheumatic-diseas-peer-reviewed-article-CIA.
2. Katchamart W, Narongroeknawin P, Chanapai W, Thaweeratthakul P. Health-related quality of life in patients with rheumatoid arthritis. *BMC Rheumatol.* [Internet]. 2019; **3**(1):34. Available from: https://doi.org/10.1186/s41927-019-0080-9.
3. Usenbo A, Kramer V, Young T, Musekiwa A. Prevalence of arthritis in Africa: A systematic review and meta-analysis. *PLoS One* [Internet]. 2015 Aug **4**;10(8):e0133858–e0133858. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26241756.

4. Kumar B. Global health inequities in rheumatology. *Rheumatology* [Internet]. 2017 Jan 1; **56**(1):4–5. Available from: https://doi.org/10.1093/rheumatology/kew064.
5. Blanchet K, Alwan A, Antoine C, Cros MJ, Feroz F, Amsalu Guracha T, *et al*. Protecting essential health services in low-income and middle-income countries and humanitarian settings while responding to the COVID-19 pandemic. *BMJ Glob Health* [Internet]. 2020 Oct 1; **5**(10):e003675. Available from: http://gh.bmj.com/content/5/10/e003675.abstract.
6. Davids R, Ahmed N. iMedPub Journals Cry the Beloved Non-COVID Country : A Review of South African Health Care ' s Response to COVID Pandemic Abstract. 2020;1–5.
7. Hunt L, Buch M. The "therapeutic window" and treating to target in rheumatoid arthritis. *Clin Med* [Internet]. 2013 Aug; **13**(4):387–390. Available from: https://pubmed.ncbi.nlm.nih.gov/23908511.
8. Abualfadl E, Ismail F, Shereef RRE, Hassan E, Tharwat S, Mohamed EF, *et al*. Impact of COVID-19 pandemic on rheumatoid arthritis from a Multi-Centre patient-reported questionnaire survey: influence of gender, rural–urban gap and north–south gradient. *Rheumatol Int* [Internet]. 2020; *2019*(0123456789). Available from: https://doi.org/10.1007/s00296-020-04736-9.
9. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, *et al.* Living with the COVID-19 pandemic: act now with the tools we have. *Lancet*. 2020; **396**(10259):1314–16.
10. Koff WC, Williams MA. Covid-19 and immunity in aging populations — A new research agenda. *N Engl J Med* [Internet]. 2020 Apr 17; **383**(9):804–805. Available from: https://doi.org/10.1056/NEJMp2006761.
11. Freudenthal R, Horowitz M, Jadhav S, Moncrieff J. Lack of safeguards in response to restrictive public health measures. *Lancet* [Internet]. 2020; **396**(10260):e70. Available from: http://dx.doi.org/10.1016/S0140-6736(20)32118-8.
12. Clark A, Jit M, Warren-Gash C, Guthrie B, Wang HHX, Mercer SW, *et al.* Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. *Lancet Glob Heal.* 2020; **8**(8):e1003–17.
13. Government O of TC, Statistician Z. Survey Zanzibar Households 2014/15. 2016;(3):232. Available from: https://www.ocgs.go.tz/php/ReportOCGS/HBS 2014_2015 FINAL.pdf.
14. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014; **73**(3):492–509.
15. Siri Lillegraven, Nina Sundlisater, Anna-Birgitte Aga, Joe Sexton, Inge Christoffer Olsen, *et al*. Tapering of conventional synthetic disease modifying anti-rheumatic drugs in rheumatoid arthritis patients in sustained remission: Results from a randomized controlled trial [abstract]. *Arthritis Rheumatol.* 2019; **71** (Suppl 10).
16. Mohammed A, Ndaro A, Kalinga A, Manjurano A, Mosha JF, Mosha DF, *et al.* Trends in chloroquine resistance marker, Pfcrt-K76T mutation ten years after chloroquine withdrawal in Tanzania. *Malar J*. 2013; **12**(1):1–7.
17. Baker SR, Farrokhnia RA, Meyer S, Pagel M, Yannelis C. How Does household spending respond to an epidemic? Consumption during the 2020 COVID-19 pandemic. *Rev Asset Pricing Stud* [Internet]. 2020 Dec 1; **10**(4):834–62. Available from: https://doi.org/10.1093/rapstu/raaa009.
18. Akintayo RO, Akpabio A, Kalla A, Dey D, Migowa A, Olaosebikan H, *et al.* COVID-19 and the practice of rheumatology in Africa: big changes to services from the shockwave of a pandemic. *Ann Rheum Dis* [Internet]. 2020 Jul 1;annrheumdis-2020-218273. Available from: http://ard.bmj.com/content/early/2020/07/01/annrheumdis-2020-218273.abstract.
19. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MMG, *et al.* Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev.* 2020; **7**(7):CD013665. doi: 10.1002/14651858.
20. Callahan A, Steinberg E, Fries JA, Gombar S, Patel B, Corbin CK, *et al*. Estimating the efficacy of symptom-based screening for COVID-19. npj *Digit Med* [Internet]. 2020; **3**(1):8–10. Available from: http://dx.doi.org/10.1038/s41746-020-0300-0.