Possible Consequences of a Shortage of Hydroxychloroquine for Lupus Patients Amid the COVID-19 Pandemic

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As the COVID-19 pandemic took hold in North America, rheumatology clinics across the continent were inundated with phone calls from lupus patients understandably fearful of COVID-19. One of the most common questions from patients was whether they should stop taking their lupus medications. Since the beginning of the epidemic, turned pandemic, our immune compromised lupus patients have been overwhelmed with warnings of their higher risk of severe illness (1, 2). These statements are based on general knowledge of increased infection risk in lupus patients, extrapolation from other viral illnesses, and expert opinion. However, adding to the confusion, there is no specific information on lupus per se or on any of the commonly used immunosuppressive drugs for lupus (3). Even summary statements from those countries farther along the track of this pandemic broadly reference "patients with serious underlying disease" as being at high risk of poor outcomes without particulars (4, 5). Moreover, some very recent articles focus on the possible benefits of immunosuppressive drugs, both synthetic and biologic, to fight COVID-19, including early rumblings about the potential positive impact of chloroquine and hydroxychloroquine (HCQ) (6, 7). Then, on Thursday, March 19th, President Trump, in a White House briefing, stated that antimalarials "showed tremendous promise" and "could be a game- changer". Suddenly, the rumblings became a roar. The questions about stopping HCQ turned into 'I can't get HCQ, my pharmacy is out' from lupus patients trying to access refills. All over Canada and the US, news organizations were publishing stories of patients worried about drug supply, pharmacies documenting shortages, hospitals trying to stock up, drug companies promising to ramp up production, and governments securing supply to treat COVID-19 patients (8, 9), and even physicians stocking up for personal use(10) .

The benefits of antimalarials are proven for lupus patients. In addition to managing skin and joint manifestations of lupus, antimalarials are known to prevent flares and reduce overall disease activity, reduce accrual of irreversible organ damage, reduce cardiovascular complications and thrombosis, and improve survival (11-13). These comprehensive benefits have led to sweeping statements by lupus experts, recommending treatment with antimalarials "starting as soon as the diagnosis is made and maintained indefinitely (unless toxicity develops), regardless of the subsequent course of lupus, including pregnancy and any additional medications needed" (11). With antimalarials now touted as being one of the premier weapons against the global COVID-19 pandemic, and dozens of clinical trials starting up worldwide, along with off-label use outside clinical trials, demand has skyrocketed. What effect could a shortage of HCQ have on lupus patients who rely on the drug to manage and stabilize their disease?

The first effect will undoubtedly be an increase in worry, anxiety, and illness uncertainty. Illness uncertainty is defined as the experience of living with continuous uncertainty from a chronic illness requiring ongoing management or with a possibility of recurrence (14-16), and is already an important concept in lupus (15, 17). As expected, high uncertainty is associated with high emotional distress, anxiety, and depression [5], and in lupus is shown to be inversely related to health related quality of life (17). No doubt the entire world is experiencing high levels of uncertainty at present. Mental health concerns are already rising, with talk of a parallel epidemic of fear, anxiety and depression (18, 19).

Lupus patients already have very high levels of comorbid anxiety and depression, which are associated with worse lupus outcomes and higher symptom burden (20). Further, there is mounting evidence that psychological stress, as seen in depression and anxiety, may contribute to inflammation in SLE. The mechanisms connecting emotional stress to immune dysfunction have been previously described: stress alters immune function via changes to the hypothalamic pituitary adrenal axis, which controls the stress response and cortisol secretion. Chronic exposure to cortisol downregulates glucocorticoid receptors, leading to reduced sensitivity of immune cells to cortisol's inhibitory actions and consequently a state of chronic immune dysregulation (21, 22). In a study comparing 153 women with SLE to controls; serum TNF alpha levels were independently associated with both disease activity as measured by the SLEDAI, and mood disorders (23). Pawluk et al followed 41 female SLE patients for six months, and found that higher levels of daily stress were associated with increased disease activity as measured by the European consensus lupus activity measurement, and CH50 levels (24). Another study of stressors over six month period in 46 lupus patients found that a high percentage of lupus patients reported a worsening in their clinical symptomatology due to the effects of daily stress; a subset of these with more prolonged symptoms had reductions in complement levels and increased levels of dsDNA antibodies (25). A second small study found that high levels of perceived stress in lupus patients were associated with increases in SLEDAI score 4 to 5 months later (26). Could we then expect to see a surge of lupus flares as this pandemic progresses, related to the stress both of the pandemic and the disease, and compounded by fears of a HCQ shortage? Will it necessitate increased immunosuppressive medications, with an even higher risk for our lupus patients?

There is a known risk of flare related to HCQ withdrawal. This was clearly demonstrated in the landmark study by the Canadian Hydroxychloroquine Study Group, where a randomized controlled trial of withdrawal of HCQ in patients with inactive lupus showed a 2.5 times higher risk of flare, as well as a shorter time to flare(27). The extension of this study also demonstrated increased risk of major flares requiring hospitalization after HCQ withdrawal (28). A more recent study similarly showed higher flare rates and a shorter duration to flare in lupus patients discontinuing HCQ, and found an even higher risk of flare in those who have taken it for less than a year prior to discontinuation(29). Low blood concentrations of HCQ have been associated with flares of SLE in the following months (30, 31), with nonadherence a major determinant of low blood concentrations (31, 32). Studies show that HCQ provides protection from flares for 3 to 6 months following withdrawal; thus we know that some missed doses, or even a week or two off HCQ won't matter. However if the pandemic goes on for months as predicted by many, and with it the shortage of HCQ, then serious lupus flares will almost certainly result. Another unanswered question is the impact of dose reductions on the risk of lupus flares. Some patients may have to reduce their dose to maintain some level of protection in the face of shortages. Indeed in Italy, where all hospitalized COVID-19 patients are treated with HCQ and the resultant shortage at outpatient pharmacies is widespread, lupus patients are advised to reduce their doses to maintain some degree of coverage (personal communication). Optimal doses of HCQ are not known (33), and multiple factors impact on individual variations in blood concentration (34-36). However, there is a clear correlation between daily dose, blood concentration, and increased disease activity with risk of flare. Long-term dose reduction for some patients may carry a risk of serious flares similar to withdrawal.

One final and ironic possibility: is it possible that one outcome may be improved adherence to HCQ by lupus patients? Part of what makes HCQ such an attractive prospect as a treatment for COVID-19 was summarized by Dr. Raoult, the author of the French study at the heart of the current furor: "It is difficult

to find a product that has a better established safety profile….Furthermore its cost is negligible" (37). For years, rheumatologists have been trying to convince lupus patients of essentially the same thing. The risk benefit ratio for HCQ is excellent, and the potential benefits significant. Yet adherence to HCQ is universally low. An early study aimed at demonstrating the relationship between blood concentrations of HCQ and clinical efficacy in lupus patients (30) found undetectable blood HCQ concentrations in a number of the patients, leading to the realization of severe nonadherence in a subset of these patients (32). Since then multiple studies have shown high levels of very poor adherence, generally ranging from 20-50% of patients (38-42). Common reasons for poor adherence cited by patients include fear of adverse effects and lack of understanding of the benefits (32, 43). Is it possible that part of the mad scramble at pharmacies for HCQ comes from our "legacy" patients who suddenly want to fill their previously neglected HCQ prescription? Will the positive light currently shining on antimalarials help to convince lupus patients of the benefits? Will we see improved adherence? Only time will tell.

In the interim, rheumatologists caring for lupus patients will need to provide reassurance if a few doses are missed and evidence based guidance on the use of HCQ for COVID-19, while joining the chorus of healthcare providers, patients, and advocacy groups urging protection of HCQ supply for lupus patients.

References

1. Center for Disease Control and Prevention. Coronavirus disease 2019 (covid-19): People who are at higher risk.; 2020 [Internet. Accessed March 25 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/people-at-higher-risk.html.
2. American College of Rheumatology. Covid-19 frequently asked questions. 2020 [Internet. Accessed March 23 2020]. Available from: https://www.rheumatology.org/announcements
3. Figueroa-Parra G, Aguirre-Garcia GM, Gamboa-Alonso CM, Camacho-Ortiz A, Galarza-Delgado DA. Are my patients with rheumatic diseases at higher risk of covid-19? Annals of the rheumatic diseases 2020 Mar 22. (E-pub ahead of print).
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in china: Summary of a report of 72314 cases from the chinese center for disease control and prevention. Jama 2020 Feb 24. (E-pub ahead of print).
5. Italian Society of Infectious and Tropical Diseases. Guidelines for the treatment of people with covid-19 disease. 2020 [Internet. Accessed March 25 2020]. Available from: https://www.acep.org/globalassets/images/italian-guidelines-for-covid-19-google-translate.pdf.

6. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. Covid-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmunity reviews 2020 Mar 25. (E-pub ahead of print).
7. Khan S, Siddique R, Shereen MA, Ali A, Liu J, Bai Q, et al. The emergence of a novel coronavirus (sars-cov-2), their biology and therapeutic options. Journal of clinical microbiology 2020 Mar 5. (E-pub ahead of print).
8. Griffin R. Hospitals stockpile drug trump says could treat covid-19. Bloomberg.com [serial on the Internet]. 2020 [Internet. Accessed March 25 2020]. Available from:: https://www.bloomberg.com/news/articles/2020-03-20/hospitals-stockpile-malaria-drug-trump-says-could-treat-covid-19.
9. U.S. Department of Health and Human Services. HHS accepts donations of medicine to strategic national stockpile as possible treatments for covid-19 patients: FDA issues emergency use authorization for donated hydroxychloroquine sulfate, chloroquine phosphate. [Internet. Accessed March 30 2020]. Available from: https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html
10. Sawa T. Doctors face sanctions for prescribing unproven covid-19 drugs to friends and family, regulators warn. CBC.ca [Internet. Accessed March 27 2020] Available from: https://www.cbc.ca/news/health/sanctions-canadian-doctors-experimental-drugs-1.5511244.
11. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: A systematic review. Annals of the rheumatic diseases 2010;69:20-8.
12. Costedoat-Chalumeau N, Leroux G, Piette JC, Amoura Z. Why all systemic lupus erythematosus patients should be given hydroxychloroquine treatment? Joint bone spine 2010;77:4-5.
13. Petri M. Lupus in baltimore: Evidence-based 'clinical pearls' from the hopkins lupus cohort. Lupus 2005;14:970-3.
14. McCormick KM. A concept analysis of uncertainty in illness. Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing 2002;34:127-31.
15. Cleanthous S, Newman SP, Shipley M, Isenberg DA, Cano SJ. What constitutes uncertainty in systemic lupus erythematosus and rheumatoid arthritis? Psychology & health 2013;28:171-88.
16. Johnson Wright L, Afari N, Zautra A. The illness uncertainty concept: A review. Current pain and headache reports 2009;13:133-8.
17. Delis PC. Uncertainty and quality of life in systemic lupus erythematosus: A cross-sectional study. Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses 2019;44:2-10.
18. Urback R. Covid-19 could spark a mental-health tsunami. The Globe and Mail. 2020 March 24. [Internet. Accessed March 24 2020.] Available from: https://www.theglobeandmail.com/opinion/article-covid-19-could-spark-a-mental-health-tsunami/
19. Yao H, Chen JH, Xu YF. Patients with mental health disorders in the covid-19 epidemic. The Lancet Psychiatry 2020;7:e21.
20. Tisseverasinghe A, Peschken C, Hitchon C. Anxiety and mood disorders in systemic lupus erythematosus: Current insights and future directions. Current rheumatology reports 2018;20:85.
21. Morand EF. Systemic lupus erythematosus: Stress and the onset of sle. Nature reviews Rheumatology 2018;14:127-8.
22. Tosevski DL, Milovancevic MP. Stressful life events and physical health. Current opinion in psychiatry 2006;19:184-9.
23. Postal M, Lapa AT, Sinicato NA, de Oliveira Pelicari K, Peres FA, Costallat LT, et al. Depressive symptoms are associated with tumor necrosis factor alpha in systemic lupus erythematosus. Journal of neuroinflammation 2016;13:5.

24. Pawlak CR, Witte T, Heiken H, Hundt M, Schubert J, Wiese B, et al. Flares in patients with systemic lupus erythematosus are associated with daily psychological stress. Psychotherapy and psychosomatics 2003;72:159-65.
25. Peralta-Ramirez MI, Jimenez-Alonso J, Godoy-Garcia JF, Perez-Garcia M. The effects of daily stress and stressful life events on the clinical symptomatology of patients with lupus erythematosus. Psychosomatic medicine 2004;66:788-94.
26. Jung JY, Nam JY, Kim HA, Suh CH. Elevated salivary alpha-amylase level, association between depression and disease activity, and stress as a predictor of disease flare in systemic lupus erythematosus: A prospective case-control study. Medicine 2015;94:e1184.
27. Group, C.H.S. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. The N EngJ Med 1991;324:150-4.
28. Tsakonas E, Joseph L, Esdaile JM, Choquette D, Senecal JL, Cividino A, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The canadian hydroxychloroquine study group. Lupus 1998;7:80-5.
29. Aouhab Z, Hong H, Felicelli C, Tarplin S, Ostrowski RA. Outcomes of systemic lupus erythematosus in patients who discontinue hydroxychloroquine. ACR open rheumatology 2019;1:593-9.
30. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Hammoud HA, Aymard G, Cacoub P, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. Arthritis and rheumatism 2006;54:3284-90.
31. Mok CC, Penn HJ, Chan KL, Tse SM, Langman LJ, Jannetto PJ. Hydroxychloroquine serum concentrations and flares of systemic lupus erythematosus: A longitudinal cohort analysis. Arthritis care & research 2016;68:1295-302.
32. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Aymard G, Leroux G, Marra D, et al. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. Annals of the rheumatic diseases 2007;66:821-4.
33. Melles RB, Jorge AM, Marmor MF, Zhang Y, Choi HK. Sharp decline in hydroxychloroquine dosing-analysis of 17,797 initiators from 2007 to 2016. Clinical rheumatology 2018;37:1853-9.
34. Jallouli M, Galicier L, Zahr N, Aumaitre O, Frances C, Le Guern V, et al. Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. Arthritis & rheumatology (Hoboken, NJ) 2015;67:2176-84.
35. Lee JY, Vinayagamoorthy N, Han K, Kwok SK, Ju JH, Park KS, et al. Association of polymorphisms of cytochrome p450 2d6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis & rheumatology (Hoboken, NJ) 2016;68:184-90.
36. Yeon Lee J, Lee J, Ki Kwok S, Hyeon Ju J, Su Park K, Park SH. Factors related to blood hydroxychloroquine concentration in patients with systemic lupus erythematosus. Arthritis care & research 2017;69:536-42.
37. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus sars-cov-2. International journal of antimicrobial agents 2020;55:105923.
38. Liu LH, Fevrier HB, Goldfien R, Hemmerling A, Herrinton LJ. Understanding nonadherence with hydroxychloroquine therapy in systemic lupus erythematosus. The Journal of rheumatology 2019;46:1309-15.
39. Costedoat-Chalumeau N, Galicier L, Aumaitre O, Frances C, Le Guern V, Liote F, et al. Hydroxychloroquine in systemic lupus erythematosus: Results of a french multicentre controlled trial (plus study). Annals of the rheumatic diseases 2013;72:1786-92.
40. Feldman CH, Collins J, Zhang Z, Subramanian SV, Solomon DH, Kawachi I, et al. Dynamic patterns and predictors of hydroxychloroquine nonadherence among medicaid beneficiaries with systemic lupus erythematosus. Seminars in arthritis and rheumatism 2018;48:205-13.

41. Lee SG, Park EK, Park JH, Kweon SM, Kim YK, Kim GT. Compliance and persistence with hydroxychloroquine in south korean patients with systemic lupus erythematosus. Lupus 2018;27:753-61.
42. Iudici M, Pantano I, Fasano S, Pierro L, Charlier B, Pingeon M, et al. Health status and concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-adherence in systemic lupus patients with prolonged inactive disease. Lupus 2018;27:265-72.
43. Cabral RTS, Klumb EM, Carneiro S. Patients opinion and adherence to antimalarials in lupus erythematosus and rheumatoid arthritis treatment. The Journal of dermatological treatment 2020;31:264-9.