Q & A: Hydroxychloroquine: A Potential Ethical Dilemma for Rheumatologists during the COVID-19 Pandemic

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Dr. Earl Silverman (ES): Hi, I'm Earl Silverman, editor-in-chief of *The Journal of Rheumatology*. I hope you all are doing well and are healthy during the coronavirus pandemic.

Today, I'm pleased to be speaking to Dr. Rosie Scuccimarri, current Chair of the Therapeutics Committee of the Canadian Rheumatology Association; Dr. Evelyn Sutton, President of the Canadian Rheumatology Association; and Dr. Mary-Ann Fitzcharles, past Chair of the Therapeutics Committee of the Canadian Rheumatology Association.

They are the authors of an article entitled, "Hydroxychloroquine: A Potential Ethical Dilemma for Rheumatologists during the COVID-19 Pandemic," which is now available as an open access article on the website at www.jrheum.org.

Rosie, Evelyn, and Mary-Ann, I want to thank you for writing your editorial and for joining me and agreeing to discussion this timely editorial.

Dr. Rosie Scuccimarri (RS): Thank you for having us.

Dr. Mary-Ann Fitzcharles (MF): Thank you. Looking forward to it.

ES: Great! First, if you could just briefly summarize the key points of your editorial.

RS: So with the intense media attention on antiviral agents as a potential in the treatment of coronavirus-associated disease or COVID-19, our editorial discusses the challenges and ethical dilemmas that rheumatologists might face in clinical care.

These drugs have been trusted treatments for a range of rheumatic diseases over the past 70 years, especially in the management of systemic lupus and rheumatoid arthritis. For pregnant patients with rheumatic diseases, hydroxychloroquine has been an important drug due to its safety.

When the antimalarials are found to have an *in vitro* potential to reduce activity of this virus, a number of clinical trials are rapidly initiated to test its efficacy and safety for the treatment of COVID-19.

One of the studies that is discussed in our paper by the French group of Gautret and Raoult, they published a small, non-randomized study of 42 hospitalized patients, who showed improved nasal pharyngeal clearance of the virus in the treated groups, which were up with hydroxychloroquine plus

azithromycin, hydroxychloroquine alone compared to placebo. But this study was small with a lot of methodological issues.

With the interest in antimalarials, as rheumatologists, we found ourselves placed with the most common prescriber of an old drug that could have the potential to be a lifesaver in this viral pandemic.

But given the significant media attention, we saw potential for a supply shortage of these drugs. Anticipating this, the question we felt that had to be asked was: who should get treatment?

As rheumatologists, we needed to advocate for the continued availability to treat patients with chronic rheumatic diseases, such as lupus and inflammatory arthritis, where this continuation could lead to disease flare, significant morbidity, and even mortality in patients with lupus.

Until good clinical evidence was available, we recommended that the use of antimalarials to treat COVID-19 be limited to the hospital or intensive care unit settings within the context of a formal research protocol. We felt strongly against the off-label use outside of these settings. We also urged producers and suppliers to be proactive, ensuring sufficient supply.

But despite these strategies, in the event of limited supply, we are concerned that, as rheumatologists, we may have to choose which of our patients should remain on these drugs. This ethical decision would be difficult.

Rheumatic disease patients with life-threatening illnesses, such as lupus or pregnant patients, we felt should have priority to continue treatment, and those with inflammatory arthritis whose diseases are well controlled and receiving additional DMARDs of antimalarials in this case could be considered less essential.

Deprescribing antimalarials would require empathetic discussion with the patient, and it could be framed in the context of a societal contribution with the opportunity to have some influence on the outcome of others.

Whether these steps with truly influence supply, those are unknown. However, what we urge was that any recommendation on who should get treatment be based on the tenets of evidence-based medicine.

ES: Thank you. Any further comments by Dr. Fitzcharles or Sutton?

MF: Perhaps the reality is what prompted us to consider writing an article like this. And I think at this time, we've all been bombarded with a lot of media coverage of COVID, and very, very early in this pandemic, hydroxychloroquine popped up.

And I was prompted to read a little bit more about this when I heard about it in the public media. It was very, very quickly taken up by regulators, governments, political people as well. And my first thought was: well, let's see what is the evidence and, not being a virologist or an infectious disease person, I wondered how on earth hydroxychloroquine could impact this virus.

So that was sort of one of the promptings for us to begin to look at the subject a little more clearly and a bit more closely.

When I started looking at the two studies that have been very, very widely publicized, I was quite impressed by the poor quality of the studies and that this treatment was being advocated on the basis of very feeble evidence.

So, that was when I got together with my two esteemed colleagues and said, “Let's get something going.”

ES: Thank you. Dr. Sutton, any further comments you have?

Dr. Evelyn Sutton (ESutton): I completely agree. Early on there was almost a stampede of people wanting to prescribe this and advocating for it and that was quite alarming. So Dr. Fitzcharles, let us in the charge.

ES: Great, I'm glad you certainly did.

Dr. Fitzcharles, I know you sent me an e-mail with some, over 2000 PubMed hits when you search for it, so are there any updates since you wrote the article or any papers you'd want to highlight or summarize in the writing of your article?

MF: Right, so Earl and colleagues, I think we know that our management of patients must be evidence-based, and therefore we're looking for good, solid evidence.

At this point, we really do not have any good evidence that this drug is working. So where does all of this come from?

First of all, we have a lot of pre-clinical studies. So if you take hydroxychloroquine and you add it to a petri dish that has got bugs in it, it actually works quite well. It prevents viral infectivity of cells.

However, we know that what happens in pre-clinical studies does not necessarily translate into clinical studies, so with that: what evidence do we have in the clinical world?

Rosie mentioned the first study, which came from the group in Marseille and they gave these patients, about 20 patients, both hydroxychloroquine as well as azithromycin, and they reported 100% viral clearance.

When we look at the studies that are being published now, there are some studies looking at viral clearance. There are 1 or 2 studies looking at different doses, and what is the outcome regarding viral clearance, and we've got a retrospective study from the vets in the US, looking at both death as well as ventilation.

The viral clearance, the original study from Marseille, showed wonderful viral clearance. Subsequent studies have been done in Paris, and this was led by Malini, and they took 10 patients and looked at the viral clearance, they gave them exactly the same amount of hydroxychloroquine and azithromycin, they

looked at viral clearance over a period of 5 to 6 days, and in fact they found that 8 out of the 10 patients still had the virus, so they did not clear the virus. This is questioning the first study.

Subsequently, there have been 2 other studies from China, also looking at viral clearance, and one study was quite a big one. They looked at 150 patients, it was an open-label study. They either give them hydroxychloroquine or placebo, and, again, looked at viral clearance over a period of about 28 days. And in fact, there was no difference in viral clearance between the patients on hydroxychloroquine and the controls.

However, the patients that were given hydroxychloroquine did have a reduced CRP, and they did have some attenuation of symptoms during the course of the disease. This is really one of the first studies, even though it was open-label, indicating that maybe patients felt a little better with hydroxychloroquine.

The fifth study is quite interesting. This was a multicenter study. They retrospectively looked at patients in the vets who had COVID and who had either been given hydroxychloroquine or azithromycin or both. They had about 368 patients. About 99 got hydroxychloroquine, 113 got a mixture of hydroxychloroquine and azithromycin, and they looked at deaths.

And there was no difference in the death rate between active groups and the patients that got no drug treatment. So the death rate was the same. They also looked at ventilation rate, and there was also no difference in ventilation rate.

So this is sort of it. Even though it's retrospective, it's sort of beginning to gather some information.

There's been a recent study from Brazil, looking at both high- and low-dose hydroxychloroquine in patients with COVID. And this group had 80 patients, about 40 in each group, low-dose and high-dose, and we know high-dose hydroxychloroquine as chloroquines have got problems, cardiovascular problems, and in this group, the high dose was associated with an increased death rate.

So 40% of the patients in high dose died whereas only 15% in low dose died.

That's what we have at the moment.

There are currently about over 80 RCTs that have been registered and currently ongoing. Most of those RCTs are in China. However, the World Health Organization has established a huge multinational study called the Solidarity Study, where they're going to be looking at various interventions, including antiviral drugs that form subcategories, and of course, hydroxychloroquine is one.

ES: Thank you for that update. At the moment, I'm sure if we spoke next week, there'd be even more trials. And nice to hear that there are RCTs coming, which raises a question, I know there are trials, and this is just my curiosity, really. There are trials going on in Canada, and are any of your hospitals involved in any trials?

ESutton: Yes, I know our hospital in Halifax is involved. I don't know how many across the country, but I think there's quite a few.

MF: Montreal is, as well. McGill is.

interestingly, the very beginning of this pandemic, as patients were coming into the emergency room at McGill, they were put onto hydroxychloroquine immediately. And then it was stopped, so people were very insecure and unsure. But I understand now that it's only administered in the setting of a clinical trial.

ES: Oh, that's good to be hear.

So that brings me to my final question. One of the motivations for writing this article was the possibility of a shortage for patients who are currently on it or you believe with rheumatic disease had an indication during this time, as we see new patients.

Have any of your patients commented to that they've had difficulty in [obtaining] hydroxychloroquine?

We know Canada, we can't get chloroquine, but has anybody commented on the problem of getting hydroxychloroquine?

ESutton: Thanks for that question.

Some patients have been told by their pharmacist in Nova Scotia that that there may be a problem, and they've been limited to only getting a 30-day supply.

And early on, there was a definite drug shortage, particularly in Quebec, and that was due to short burst of off-label prescribing, as Dr. Fitzgerald just described, and some physicians even self-prescribing for themselves and their family in anticipation that they might get sick, and some clinics were even stocking up on hydroxychloroquine.

This actually led to the INESSS, which stands for the Institut national d'excellence en santé et en services sociaux in Quebec to issue a directive to restrict prescriptions of hydroxychloroquine only to patients with lupus or pediatric patients and pregnant women with rheumatoid arthritis.

Since then and through advocacy by the Canadian Rheumatology Association, with meeting with the manufacturers there, the good news is that there is a promise that the producers of hydroxychloroquine and will be able to meet the Canadian market demand, and we anticipate that there will be a resolution in the near future.

There was definitely a problem with distribution early on, but most manufacturers are ramping up their production to support the increased demand for the clinical trials and to meet the need for our patients who've been on it for years.

MF: So just the fact that we do currently have a regulation from the Pharmacist Association in Quebec, and the only way that a patient who does not fulfill those three criteria that Evelyn mentioned, such as a

patient with palindromic rheumatism or rheumatoid arthritis, the only way these patients can access hydroxychloroquine is if the physician makes a special statement to the pharmacist.

So pharmacists in Quebec are stopping prescribing, stopping dispensing hydroxychloroquine to all patients unless they fulfill the three criteria, which Evelyn said: lupus, pregnancy, and under the age of 18.

RS: What was good about this scenario, though, is that the Minister of Health actually asked the association of rheumatologists in Quebec to form a committee to look at which are the most important groups to have the prescription filled for.

I think at least it was a proactive process in regards to what our editorial was actually bringing up, was that we're going to potentially be faced with this issue. And actually in Quebec, rheumatologists were called upon to make that decision with the Ministry of Health and so the life-threatening illness, such as lupus and pregnant patients with the disease who don't have many options in terms of their safety with drugs, were put on that list, and then juvenile idiopathic arthritis. The amount of drug availability was then increased.

At least rheumatologists were placed in a position to help Ministry of Health to make that list. Certainly, it wasn't ideal, because a large group of patients, such as patients with rheumatoid arthritis, was left off that list, but as Mary-Ann had said, we were able to still advocate for the patients who we felt required it by making these special prescriptions for those patients.

ES: Thank you.

So, certainly, I was going to say it was mentioned by Dr. Sutton, that 30-day limitation. Certainly, in Ontario right now, all drugs are limited to 30 days. So, hydroxychloroquine is not unique, certainly in Ontario. Currently, are patients with rheumatoid arthritis in Quebec allowed to get antimalarial treatment?

MF: Yes, they can, as long as the physician has communicated with the pharmacist to say that this drug must be prescribed.

ES: Ok, thank you.

It was excellent and I really want to thank you for the editorial, answering my questions. Are there any other final points any one of you would like to add before we end this?

RS: I just wanted to add that we're all we're all involved with the Canadian Rheumatology Association, and I just wanted to put a plug that they have been quite on the forefront of this issue of putting out position statements. I feel that that has supported the Canadian community overall on this issue.

MF: Good, Rosie. And I think we would like to thank The Journal of Rheumatology for really being so upfront and accelerating the editorial. I must say that I think it went ahead at the speed of light. So I'd like to thank you, Earl, and your team.

ES: Thank you. It's always nice to get compliments, so I'll accept them.

Dr. Sutton, anything from you before we conclude?

ESutton: I echo Rosie's and Mary-Anne's comments, and thank you very much. Appreciate the opportunity to speak with you today.

ES: Thanks! I want to thank you all for the time. I found it very interesting and certainly enlightening.

For those who are listening, please read the full-length editorial entitled, "Hydroxychloroquine: A Potential Ethical Dilemma for Rheumatologists during the COVID-19 Pandemic," by Drs. Rosie Scuccimarri, Evelyn Sutton, and Mary-Ann Fitzcharles.

As well, our other special editorials about the SARS-CoV-2 infection and COVID-19 and its effects and implications for rheumatologists and rheumatology practice as a whole at www.jrheum.com/covid19.

If there are any questions or comments, please message us at Twitter @jrheum or e-mail us at manuscripts@jrheum.com.

I want to thank you all for joining us, Continue to follow the guidelines of your regional and national health authorities, and be sure to maintain social distancing in order to keep you and your family safe.

Thank you.

MF: Thank you.

RS: Thank you so much.