

Author Notes: Hydroxychloroquine in Patients with Rheumatic Disease Complicated by COVID-19: Clarifying Target Exposures and the Need for Clinical Trials

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Hello and thank you for your interest in our study. My name is Stephen Balevic, I am an adult and pediatric rheumatologist at Duke University and a researcher specializing in clinical pharmacology and drug trials.

Over the next few minutes, I would like to present some background on the target HCQ drug levels that have been shown to inhibit the novel coronavirus SARS-COV-2 in-vitro and data from our study investigating whether these drug levels are even obtainable in patients with rheumatic disease. I will conclude with what this means for practicing clinicians as well as current clinical trials.

(Brief Background)

So as we all have experienced, the sars-COV-2 virus has caused substantial morbidity and mortality across the globe. Hydroxychloroquine has been shown to inhibit viral replication through several possible mechanisms.

But because HCQ requires several months to reach steady state, patients receiving long-term treatment eventually achieve higher both blood and tissue concentrations over time, so it is important we think differently about the drug's potential effectiveness with short term vs long-term dosing. However, it is unknown whether our current dosing strategies actually achieve these antiviral concentrations.

So therefore our goal was to compare observed HCQ concentrations in patients with rheumatic disease to those with reported anti-viral activity. And then secondly, we wanted to provide an example of how dosing simulations can be conducted using available pharmacokinetic (or PK) models and how these can guide dosing for clinical trials.

(Target HCQ Concentrations for SARS-CoV-2)

So first I would first like to spend a moment to define the target antiviral concentrations. There have been at least two pivotal in-vitro studies and I will briefly summarize key points from the first study.

The authors took monkey kidney cells and infected them with the sars-COV-2 virus for 2 hours. Afterwards, they added HCQ containing medium at different concentrations and quantified viral replication. This allowed the investigators to determine the EC50; that is the concentration at $\frac{1}{2}$ the maximum viral inhibition. So this is a very common measure of drug potency, but as we will discuss in a moment, may not be the ideal clinical target.

With that in mind, the authors found the EC50 was 6.14 micromolar at 24 hours and 0.72 micromolar at 48 hours. In other words, incubation time and possibly accumulation into cells was important.

Now as clinicians we need to take these molar concentration targets and transform them into something we can actually work with. To do that, we use the molecular weight of HCQ and correct for protein binding. When we crunch these numbers, we come up with a total level in plasma of 0.48 mg/L that corresponds to that 48h EC50 and 4.1 mg/L corresponding to the 24h EC50.

I would also like to point out that though complete viral inhibition occurs at an even higher target of 6.7 mg/L.

It is also important to note that there are differences between plasma or serum and whole blood. We make the case that for SARS-COV-2, actually measuring HCQ concentration in plasma or serum is preferred and highlight this discussion in our manuscript.

(Methods)

Now that we defined target concentrations, we evaluated 3 data sources to determine whether patients with rheumatic disease routinely obtain these targets. These three sources allowed us to characterize average drug levels across a wide range of patients with rheumatic disease.

(Results)

And the results of our first aim is presented in this table. So I will focus your attention to the highest dose group of 400 mg daily, here highlighted in yellow. We have here the average HCQ levels observed in the study along with the standard deviation. We found that the average levels were below the lowest target exposure- so here highlighted in red- in all studies. However, consistent with the wide variability in HCQ pharmacokinetics, we do see that a small proportion of patients can reach or exceed the lowest EC50 target. Now importantly, assuming the highest EC50, all studies had approximately one-tenth or less the required exposure for viral inhibition. Now the study also suggests that no patients were able to achieve concentrations needed for complete viral inhibition.

(Methods)

So then next we leveraged a published pharmacokinetic model of pregnant women with rheumatic disease and conducted dosing simulations using one of several regimens being tested for COVID-19. So for this abstract though, I will focus on just the last two dosage regimens.

(Results)

The results are our dosing simulations are noted in these figures. Just to orient you for a moment, the Y axis here is HCQ concentration and X axis is time in hours. This thick black line in the middle is the median drug concentration for this simulated dose. The dashed lines here are the 95th and 5th percentile. This blue dashed line in the middle is the lowest EC50 target and the red line is the surrogate ceiling for safety. This was derived from the clinical study that did the PK model. So we can interpret this data as follows: so for a pregnant women already on

long-term HCQ at a dosage of 400 mg a day, increasing that dose to 600 mg actually would obtain a peak or CMAX target concentration after the first dose and that is seen here and then average concentrations after the second dose.

However, mothers who continue the standard of care dosing of 400 mg once a day would actually not achieve median concentrations.

So the model also supports that, despite using loading doses of HCQ, no patients are able to obtain the levels needed for the higher EC50 or for complete viral inhibition.

(Conclusions and Discussion)

So then in summary, we found that the average patient with rheumatic diseases, including children, pregnant adults, and non-pregnant adults, are unlikely to obtain total serum or plasma concentrations shown to inhibit SARS-CoV-2 in-vitro.

The data therefore suggests that current HCQ dosing strategies, are unlikely to be effective in the setting of SARS-CoV-2 viremia, so this is where the serum most directly mirrors what they did in the in-vitro studies.

However, it is important to note that our data does not entirely preclude a potential benefit for HCQ in the setting of COVID-19. So first, HCQ may have antithrombotic and anti-inflammatory benefits, and these may be mediated at different target concentrations. Second intracellular lung concentrations may be critical for the drug's potential antiviral effect. Studies in rats suggest the lung concentrations are several hundred times higher than plasma. However, because HCQ accumulates in the lungs over several months, it may be the duration of therapy, as opposed to the dose, that is really key to understanding its potential in COVID-19.

So ultimately, our study really highlights that well-designed clinical trials are urgently needed to characterize the efficacy, mechanism of action, and goal concentrations for HCQ in the target tissues before any specific dosage adjustments can be recommended. I think rheumatologists are well poised to lead these studies.

So with that in mind, on behalf of the authors, I would like to acknowledge our funding sources and thank our collaborators

I have also listed here several key references.

So please check out our article at the Journal of Rheumatology and feel free to e-mail me with any comments or questions. Again, thank you very much for your time and have a great day.