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By Derek Lowe

CLINICAL TRIALS

Hydroxychloroquine Update, May 4

By Derek Lowe | 4 May, 2020

It's been some days since I posted on the hydroxychloroquine situation versus the coronavirus epidemic, but I have been getting plenty of inquiries. So let's have a look at what's been going on!

Several people have pointed out **this new preprint**, a retrospective look at 568 patients in Wuhan. All of them were confirmed positive and on mechanical ventilation, median age 68, 63% male. 520 of them had standard of care (various antivirals and antibiotics), and in addition 48 patients were treated with 200mg hydroxychloroquine (b.i.d.) They measured hospital stay, mortality, and (interestingly) IL-6 levels as well. And their results were quite striking: mortality was 18.8% in the HCQ group and 45.8% in the others. That's a much larger effect than anyone outside of Marseille has reported, I have to say. Patient IL-6 levels declined significantly in the treatment group, but not in the other cohort. The preprint's Figure 3 also indicates that IL-6 went back up after hydroxychloroquine was discontinued.

That's interesting indeed, and ties a possible mechanism of action to the **same one** that has led to HCQ's use in rheumatoid arthritis and lupus: suppressing cytokine signaling in the immune response. This, however, runs against a lot of the theories advanced by the drug's boosters. You'll note that this mechanism has nothing to do with viral replication, for starters. And there is no azithromycin involved, as opposed to the Marseille protocol – in fact, I would expect Prof. Raoult there to denounce this paper for not following his recommendations (remember, his early results seemed to show that HCQ alone had some effect, but that HCQ plus azithromycin had a much greater one). There was also no zinc involved in this study, and if you've had the courage to look at the comments section here, you have been assured over and over that zinc is necessary for HCQ to have any effect and that people dosing without it are wasting their time. You will also find yourself being assured that it's crucial to give HCQ as early as possible in the disease, and that studies that have shown no effect have failed because only severely ill patients were being treated. But this one has only patients on ventilators, in very bad shape indeed. In fact, if this IL-6 mechanism has something behind it, dosing early could be a bad idea – you probably don't want to turn down cytokine signaling and immune response at first, just later on, when it gets to be a problem.

Thinking about that disease course question, some people have (very vocally) suggested that HCQ be given prophylactically, and a study testing this is underway in the UK. We have, though, a possible source of data already, that is, the many RA and lupus patients who have already been taking the drug. One of the features of my emails has been a reference to **this report** in the Italian press (near the end of the article) that the Italian Rheumatological Society (SIR) has been collecting data on just this question from 1,200 physicians there. The article says that there are 65,000 patients in Italy taking HCQ chronically and that only 20 of them have tested positive for the virus. Now, you'd want to compare that to RA and lupus patients who were *not* taking HCQ, but it would still be quite interesting. If it were true.

But I can't see where that figure comes from. That one Italian press report is the source that everyone else refers back to. And when I look at the SIR itself, I find that it is part of the **COVID-19 Global Rheumatology Alliance**, a worldwide data collection consortium. Their worldwide provider-entered database of coronavirus-positive patients says that it's up to 1072 cases (on the front page) and 777 of those have data broken down

into categories **here**. According to **this map**, 84 of these patients are in Italy (not 20 as stated in the article). The provider registry is just of people reported by physicians, and it shows that 24% of those 777 patients (188 of them) were taking antimalarials such as HCQ when they tested positive for the virus, so if that percentage holds up, then there are indeed about 21 Italian rheumatology patients taking HCQ that have have tested positive and been reported on in detail by their physicians. But as for those 65,000 Italians who are taking HCQ, I can find no evidence of that at all, and I have no idea how many of the Italian HCQ patients are being so monitored. The 65,000 number may well be coming from Italian researcher Annabella Chiusolo, interviewed **here** at the Jerusalem Post, but the *worldwide* patient survey numbers at the Rheumatology Alliance are only 11,762. The most recent breakdown of those numbers look at 9,541 patient responses, with about 28% of them were taking antimalarials, and a total of 465 coronavirus cases.

That's not the only new hydroxychloroquine-related preprint out there, although it's certainly the one that people have been sending me. **Here's another** from the Cleveland Clinic-Abu Dhabi (didn't realize that they were over there) with another retrospective study looking at viral clearance in HCQ-treated coronavirus patients. It's a small study, but out of 34 positive patients, the 21 treated with HCQ had significantly delayed viral clearance compared to those received other standard of care. If the early hydroxychloroquine studies had shown numbers like these we probably wouldn't have heard much more about it, to be honest, although with such small patient groups one result is probably as nearly likely as the other. **And here** is a joint preprint from NYU and the University of Milan on the hydroxychloroquine/azithromycin combination specifically, a retrospective study of 251 patients on that regimen who were monitored by ECG. QT prolongation is of course the worry here, and it was certainly picked up in an exposure-responsive manner, with 16% of the patients showing clearly dangerous levels. Overall, the cohort did not completely return to normal after HCQ/AZ dosing ceased, either, and the paper concludes that the efficacy of the drug combination remains unproven but that the risks seem much more clear. Similarly, this team from Cedars-Sinai in Los Angeles **reports** analysis of a series of 490 positive cases, who received no HCQ, HCQ alone, and HCQ-azithromycin, mostly that last combination. QT prolongation was again noted, with 12% showing dangerous levels and with a trend towards being most prolonged on the combination (especially when compared with azithromycin without HCQ). Interestingly the cardiac effects were noted only in men – I haven't seen anyone else mentioning that. This group also concludes that the benefits of this treatment are unclear but the risks are much easier to quantify, and urge caution.

So overall we have one positive report (very positive indeed, and an outlier in that respect) and two safety warnings. Make of this what you will. We have more controlled trial data coming, and the arguing can re-commence when it hits. . .