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# Blogger Extraordinaire Derek Lowe on the Hydroxychloroquine Clinical Mess

*By Special to ACSH — April 16, 2020*

*Dr. Derek Lowe, arguably the finest and most influential chemistry blogger in the universe, has put together an excellent summary of the complex and confusing clinical data of hydroxychloroquine, which he published recently in his blog in Science and Translational Medicine. We thank Derek and AAAS for allowing us to reprint this important article.*

Dr. Derek Lowe, cool dude and great writer.

*# From The Latest Hydroxychloroquine Data, As of April 11 [1]. Derek Lowe, Ph.D., Science and Translational Medicine, April 11, 2020. Republished with permission from AAAS.*

We have new data on hydroxychloroquine therapy to discuss. The numbers will not clear anything up.

First off is an abstract [2] from the Marseilles IHU group of Dr. Didier Raoult. It presents 1061 patients treated for at least 3 days with their hydroxychloroquine/azithromycin combination, with followup of at least 9 days. It includes the statement “98% of patients cured so far” and says also “No cardiac toxicity was observed”, and also says that mortality figures were improved in these patients as compared with others receiving standard-of-care without such treatment. The other

release is a data table [3] on these patients (there is no full manuscript as of yet). It does not include any sort of control group, nor (as far as I can see) does it even have a comparison in it to those other patients mentioned in the abstract. Let's hold on to these thoughts as we discuss the next data.

Here is a preprint [4] from a large multinational collaboration presenting data obtained from health care systems (claims data or electronic medical records) in Germany, Japan, Netherlands, Spain, UK, and the USA. It (1) compares the safety of hydroxychloroquine in rheumatoid arthritis patients (956, versus thost patients (310,350 of them) taking another common RA drug, sulfasalazine [5], (2) compares the safety of the combination of hydroxychloroquine and azithromycin taken together (in 323,122 patients) versus the combination of hydroxychloroquine and another common antibiotic, amoxicillin (in 351,956 patients). Nothing like digging through the big health databases, is there?

The good news is that the HCQ/sulfasalazine comparison does not show any real differences in adverse events over one-month courses of treatment. I should note that sulfasalazine is not the most side-effect-free medication in the whole pharmacopeia, but it has not been associated with (for example) QT prolongation, which is one of the things you worry about with hydroxychloroquine. The paper concludes that short-term HCQ monotherapy does appear to be safe, but notes that long-term HCQ dosing is indeed tied to increased cardiovascular mortality.

The trouble comes in with the azithromycin combination. Like many antibiotics (although not amoxicillin), AZM is in fact tied to QT prolongation in some patients, so what happens when it's given along with HCQ, which has the same problem?

> *Worryingly, significant risks are identified for combination users of HCQ+AZM even in the short-term as proposed for COVID19 management, with a 15-20% increased risk of angina/chest pain and heart failure, and a two-fold risk of cardiovascular mortality in the first month of treatment.*

That isn't good. I am very glad to hear that the Raoult group has observed no cardiac events in their studies so far, but I wonder how they have managed to be so fortunate, given these numbers. The authors again:

> *As the world awaits the results of clinical trials for the anti-viral efficacy of HCQ in the treatment of SARS-Cov2 infection, this large scale, international real-world data network study enables us to consider the safety of the most popular drugs under consideration. HCQ appears to be largely safe in both direct and comparative analysis for short term use, but when used in combination with AZM this therapy carries double the risk of cardiovascular death in patients with RA. Whereas we used the collective experience of a million patients to build our confidence in the evidence around the safety profile, the current evidence around efficacy of HCQ+AZI in the treatment of covid-19 is quite limited and controversial.*

Indeed it is. And this morning, there is a picture of what appears to be the summary page of a manuscript under review at the *NEJM*. This is quite irregular, of course; this stuff is not supposed to be floating around on Twitter. It is apparently a study from Detroit of 63 consecutive patients admitted with coronavirus infection, with 32 assigned to receive hydroxychloroquine therapy and the others to standard-of-care. So this is again not a large study, and is rather similar in size to the Wuhan study discussed here [6] that showed some benefit.

That's not the case in this work. If we are seeing is an accurate summary of the work, then HCQ treatment was actually associated with *worse* outcomes. I won't go into more detail until this becomes more official and we can verify that we're looking at a real manuscript – a quick check shows that the authors' affiliation appear to be correct, but that many of them are ophthamologists, and I'm not sure what to make of that. I am of two minds about whether to mention it at all, but these are unusual circumstances. More to come as the situation gets clearer.

*Update:* here is another new preprint [7] from a multinational team lead out of Brazil. It enrolled 81 patients in a trial of high-dose chloroquine *(note: not hydroxychloroquine as this post initially stated)* (600 mg b.i.d. over ten days, total dose 12g) or low-dose (450mg b.i.d. on the first day, qd thereafter for the next four, total dose 2.7g). All patients also received azithromycin and ceftriaxone [8] (a cephalosporin antibiotic). The high-dose patients showed more severe QT prolongation and there a trend toward higher lethality compared to the low dose. The overall fatality rate across both arms of the study was 13.5% (so far), which they say overlaps with the historical fatality rate of patients not receiving chloroquine. The authors actually had to stop recruiting patients for the high-dose arm of the study due to the cardiovascular events, but they're continuing to enroll people in the low-dose group to look at overall mortality. The paper mentions that chloroquine and HCQ have been mandated as the standard therapy in Brazil, so there is no way to run a control group, though.

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**Links**

[1] https://blogs.sciencemag.org/pipeline/archives/2020/04/11/the-latest-hydroxychloroquine-data-as-of-april-11
[2] https://www.mediterranee-infection.com/wp-content/uploads/2020/04/Abstract_Raoult_EarlyTrtCovid19_09042020_vD1v.pdf
[3] https://www.mediterranee-infection.com/wp-content/uploads/2020/04/Table_final_website_IHU_09_04_2020.pdf
[4] https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v1.full.pdf
[5] https://en.wikipedia.org/wiki/Sulfasalazine
[6] https://blogs.sciencemag.org/pipeline/archives/2020/03/31/comparing-chloroquine-trials
[7] https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v1.full.pdf
[8] https://en.wikipedia.org/wiki/Ceftriaxone