BioSpectrum the business of Bio & Health Sciences

HCQ in COVID-19 under trial: With RCTs in witness box

28 July 2020 | Views | By Dr Dhananjay Bakhle

The Case of 3MA (Minnesota-McGill-Manitoba-Alberta) Studies

One of the most important aspects of a clinical trial publication is the way it is presented. In today's deceptive times, we have to scrutinize every research publication carefully when we see leading authorities fumbling with their decisions regarding COVID-19.

Before this pandemic, we could close our eyes and believe the words printed in top medical journals like The Lancet, NEJM, Annals of Internal Medicine, but not now. The same applies to the study on Hydroxychloroquine (HCQ) in prevention or treatment of COVID-19.

HCQ study was highly in news due to the political angle with the US president endorsing it prior, and was also entangled in the monetary maze of huge COVID market. When we dissect out some of the "quick" studies in the name of Randomized Controlled Trials (RCT), shocking anomalies tumble out of the pandora's box.

For the benefit of non-clinical researchers, I will simplify this story to elucidate how data has been massaged and incongruence in findings polished sophisticatedly to provide a masterly shape.

I will provide links to the relevant documents at the end, and quote these references like it is done in a research paper. Such research papers have become the toast of the mainstream media to make you believe that HCQ is dead and that we (the people) "should move on" (actual quote) to other methods and medicines.

Let us start with the recently published study on 16th July in Annals of Internal Medicine by Dr. David Boulware from Minneapolis who has published his 2nd negative study on HCQ in recent months (1,2) funded by a "private donor" as stated in the paper.

He was the first author of an earlier study published in NEJM (1) and filled an ICJME form disclosing no conflict of interest (3), conveniently forgetting about the 2019 annual meeting of ASTMH where he declared his financial relationship with commercial interest with Gilead- Makers of Remdesivir (4).

Interestingly, he has split both studies from a single protocol listed on clinical trials.gov (5). The objectives of both studies are

not just different, but the objective of 2nd study starts where the first ends. One is about trying to prevent COVID-19 in patients exposed to infection through a close primary contact and second is to treat when COVID-19 has developed. Do you need confirmation with RT-PCR in such a study?

According to this author who is an infectious disease specialist, not necessary for both studies since symptoms should suffice. Thus, in the first study on post-exposure prophylaxis, only 18 per cent people were confirmed to have developed Covid positive status as tested by RT-PCR and in the second study, only 34 per cent patients had RT-PCR confirmed diagnosis. Was this a limitation for them? Apparently not, as was articulated that 4 infectious disease Physicians “carefully” evaluated the symptoms developed to “generate a consensus” that it was COVID-19, if RT-PCR was not available.

Sadly, that was the case with 82 per cent of patients in the 1st study and 66 per cent of the 2nd study. How does it matter if a patient had muscle pain (myalgia) or little bit of loose motions to have classified as COVID-19?

Clinical science is paramount and can supersede laboratory science according to these authors. What was the proposed sample size as per original protocol? 3,000 for both studies as per statistical sample size calculation based on the primary endpoints in each study. What if the numbers enrolled would not be adequate? No issue, provide for interim analysis at multiple steps and re-estimate sample size that can reduce from one analysis to other and if required stop the study. How is it possible? Why not, we have stopping rules to our rescue. Thus, when the 1st interim analysis was done in the first study, sample size was reduced from 1500 to 956 and in the 2nd interim analysis, trial was stopped because the endpoint was reached, since RT-PCR was not required to confirm development of COVID-19.

So how does it matter if a patient of sore throat, diarrhoea or muscle pain was confirmed as Covid-19? We found HCQ doesn’t prevent COVID-19 even if such patients are 66 per cent of our population. For drawing actionable conclusions, it is necessary to read the fine print if RT-PCR was done for all or not. This is fact and not fiction or satire, as seen when one of the frontline warrior doctor from a leading Mumbai hospital, himself suffering from COVID-19 in his own ICU, came on TV to state that his hospital switched from HCQ to Remdesivir.

To continue our story, this winning team of Minnesota having accomplished the first goal of hitting post-exposure prophylaxis, moved on to demolish the claim that HCQ can work if given early.

This was necessary because most of the earlier studies were in hospitalized patients and the primary care users around the world were striving to use it early to prevent hospitalizations.

Dr. Zelenko in upstate New York was making it a crusade and was much vilified by the political opposition since he gave this idea to his President. In Brazil, there was war raging between right and left wing with many people opposing their President’s attempts at spreading the use of HCQ. He has sacked two of his health ministers in succession allegedly on account of their stiff resistance to use HCQ.

In France, the PM was sacked by the President again allegedly due to his banning of HCQ despite studies from Prof Didier in Marseille having shown great results. Whole world was split on its use but the end of this war could come closer, if the early use is struck down with a powerful RCT weapon.

Both recovery and solidarity stoppage of HCQ arm was not enough to wipe out HCQ because social media spread the word that the dosage used in these two studies were toxic that was not highlighted by any mainstream media.

When the Chief investigator of Recovery study (Martin Landray) made a mistake in his interview given to France Soir by citing the high dose coming from “Amoebic Dysentery” as he had possibly mistaken Hydroxychloroquine with hydroxyquinolones that were used for amoebiasis once upon a time (even there the dose of diiodohydroxyquinoline should not exceed 2000 mg/day, Recovery gave 2400 mg of HCQ on day 1). When he denied what he said in his telephonic interview, France Soir published his audio tape of the interview on their website embarrassing him further.

While this was all happening in the background the Minnesota team could not wait any further to finish recruitment in the 2nd split study. What followed with rapid speed was manoeuvring the data collected from their internet surveyed, remotely monitored & no “human contact” ethical & scientific mail-box RCT. I am only trying to recreate the chain of events that are likely to have happened, while the facts presented below can be easily verified from the sources quoted.

Architects of the 2nd trial had realized that the sample size was far below the required 1500. They decided to move 100 subjects from the first study of post-exposure prophylaxis to be added to the second study that dealt with treatment. The same dose given in both studies came very handy to do this feat, though completely non-compliant to global guidelines.

However, the issue was the difference between patient population based on symptoms. First being prophylaxis study,

patients had to be asymptomatic but 2nd being early treatment study had to be symptomatic.

But what if some of these patients developed any of the symptoms hours before they took their first dose of HCQ distributed for their enrolment in the first study? *Voila*, that solved the problem, these 100 patients were moved from 1st to 2nd study claiming to have developed at least one symptom hours before consuming their first dose. Will that be acceptable? Why not, if you insert a line in the paper saying that it was prespecified in the protocol? Which protocol - study 1 or 2?

Don't you worry, both studies are under the same protocol and same unique no. (ClinicalTrials.gov Identifier: NCT04308668) (5). But, what if the protocol doesn't specifically mention possibility of such a transfer? Most clinicians do not bother to search the protocol and read it once the paper is published in a top journal.

Still there is a big issue, the numbers do not stack up to the sample size requirement of 1500 for the early treatment study. The bigger problem is that hospitalizations are very few, maybe because patients with sore throat and a bout of diarrhea or muscle pain don't need hospital admissions as RT-PCR is not mandatory in this trial too.

Then a brilliant solution could have been suggested. Can we change the primary endpoint? Why not, if NIH could do that for Remdesivir and the product was approved even without meeting the original endpoint, why not in this study? In any case, no regulatory authority could bother about this study, in fact they would be happy with such results, having banned HCQ use in many countries. But what could be the justification for such a major change in the middle of the study? Can we say that hospitalizations were less and sample size would be much more than what we planned (1500)? Wonderful, if you have a friendly DSMB, such justifications will fly. A strict DSMB (data safety monitoring board) will not allow change of endpoint in the middle of study because some parameter like less hospitalization will increase sample size. But not in this case.

Thus, the goalpost of this study was shifted dramatically from "Ordinal Scale of COVID-19 Disease maximum severity at day 14" which included the following measurements: 1. No illness 2. Illness with outpatient observation 3. Hospitalization (or post-hospital discharge) 4. Hospitalization with ICU stay or Death to the following new endpoint.

Change in symptom severity score (visual analog scale 0-10) over 14 days. Was it there before as a secondary endpoint? Ok, it was there but we simply removed 5 day and kept it at 14 days which should be enough. Original secondary endpoint: Severity of symptoms at Day 5 and 14, whereas secondary outcome measure as per section 3.2.2 in original protocol was only at day 5 with VAS.

Since secondary endpoints are not statistically powered, there was a need for new statistical estimation of sample size because it became a primary endpoint. While elevating secondary endpoint to primary, they also shaved it off by removing intermediate time point keeping only at 14 days. Why you may ask? There is no explanation provided except that there is a small co-incidence of day 10 symptom severity score showing statistical significance (p=0.05) between HCQ and placebo (table 4, page 11 of supplemental material) (6). Can you imagine that the only significant finding in the whole study being buried in supplemental material and doesn't find any mention in the main paper which declares that HCQ doesn't work.

This burial was possible by changing the primary endpoint in the middle of the study. Were the regulatory authorities in US and Canada kept informed of this plastic surgery on the protocol mid-stream? There is no way to know since it has not been reported.

What about individual symptom measurement? After changing an objective endpoint to a highly subjective endpoint by measuring with visual analog scale (by providing a slider from 1 to 10 cm scale), at least all symptom grading should have been provided. Venn diagram in the paper identifies 174 patients who had at least 2 symptoms out of 3 important ones (fever, cough, dyspnea), how do they rate their improvement for each? Anyway there is no human contact with the patients, they are the ones who agreed to participate. So if a patient's fever comes down with HCQ but cough doesn't, he would still not be considered as improved.

Now we come to the last 3 alleged manipulations that were without even any attempt at justification or explanation in the paper or protocol. Before we reach there, it is important to know some more details. Since the DSMB on 24th April had agreed to change the endpoint, statistical estimation was required again for this new shaved secondary endpoint that just became primary.

The statisticians from the DSMB suggested that at least 400 patients will be required for the new endpoint. However, there were only 237 patients meeting the inclusion criteria even after moving 100 patients into this study that were removed from the 1st study. So, they decided to add 35 patients who hadn't consumed a single dose of either HCQ or placebo, who would normally not form part of the analysis population. Then there were additional 69 patients who were tested negative for SARS-CoV-2 by RT-PCR (supplemental Table 1) who should not have been enrolled in the study. If their reports came in after

enrolment, they should still be excluded from analysis as they violate the inclusion criteria as spelt out below from the protocol-

If a symptomatic person tests negative for SARS-CoV-2, they are not eligible for enrolment. (page 11 of protocol v1.0) (7). This statement continues to exist in the revised protocol v2.3 on page 14 and hence still valid.

Despite adding all these patients in violation of the protocol, only 341 patients could stack up, which was less than 25 per cent of the sample size of 1500 and also short of the 400 mark suggested by DSMB. Now nothing else from their grey doctrine outside of rule book could help. Then they had to rely on their instinct, which suggested to take advantage of those clauses of the protocol readers can easily miss or overlook. If readers miss the difference between an AND and an OR, it would be possible to add 82 more patients who were symptomatic but not having any primary contact PCR positive but the following inclusion criteria was prohibiting their addition-

Exposure to known PCR+ SARS-CoV-2 case within 14 days **AND** compatible symptoms of fever, cough, or shortness of breath (and no available testing for the individual).

Mark the word AND, if this is treated as OR then 82 cases which had one of the symptoms but no known PCR+ contacts could be added to take the number above 400 (precisely 423).

Thus, If you apply all inclusion criteria strictly framed in the protocol available, the total number reduces to 237 which reduces the statistical power of this study to only 37 per cent which nobody will consider acceptable since the minimum required power is 80 per cent for any good RCT.

There are so many questions that need an answer from the architects of these 2 studies as narrated above. Instead of waiting for the full trial to be completed as per pre-determined sample sizes, what was the tearing hurry to wrap it up with warp speed? What about the 4 reputed universities involved in this study, viz Minnesota, McGill, Manitoba and Alberta? What about the regulatory agencies? Will they inspect data from all these studies to review their decisions to ban a product being sold for 65 years for daily use of many years in other indications? The treatment course for Covid-19 is only 6 days that is being prevented while its daily use in rheumatoid arthritis & SLE continues for chronic use?

Just like the advanced regulatory agencies inspect clinical trial data before approving a new drug, should they not be inspecting data from such studies based on which they ban safe drug in the midst of a pandemic where people are dying. Does it all make sense?

References

1) https://www.nejm.org/doi/full/10.1056/NEJMoa2016638

2) https://www.acpjournals.org/doi/10.7326/M20-4207#f5-M204207

3)https://www.nejm.org/doi/suppl/10.1056/NEJMoa2016638/suppl_file/nejmoa2016638_disclosures.pdf

4)https://www.astmh.org/ASTMH/media/2019-Annual-Meeting/ASTMH-2019-Speaker-Disclosure-Statement.pdf

5) https://clinicaltrials.gov/ct2/show/NCT04308668

6)https://www.acpjournals.org/doi/suppl/10.7326/M20-4207/suppl_file/M20-4207_Supplement.pdf

7) https://www.nejm.org/doi/suppl/10.1056/NEJMoa2016638/suppl_file/nejmoa2016638_protocol.pdf

Dr Dhananjay Bakhle, Executive Vice President – Medical Research, Lupin.

(He is profiled in a book "Thought Leaders" among 22 personalities from different fields published by Tata McGrawHill in 2000)

The views expressed here are his own and do not represent the views of the organization that he works for.

Statement on conflict of interest: Hydroxychloroquine is exported to US by the company he works for but not marketed in

India.