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Reply to "The myth of hydroxychloroquine in the treatment of SARS-CoV-2 infection"

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Abstract
I respond to a recently-published TMJ Editorial Review,[1] which commented on an article of mine entitled "The Curious Case of Hydroxychloroquine" published in Quadrant magazine (March 2024).[2] I disagree with the reviewer's points of view for the reasons presented here. *Tasman Medical Journal 2024; 6: 17-21*

Introduction

The editorial in the Tasman Medical Journal[1] was a critique of my article in Quadrant entitled "The curious case of hydroxychloroquine".[2] It considered negative data from large clinical trials on hospitalised patients (The Recovery and Solidarity Trials), claimed scanty support from clinical studies in early COVID infection, and expressed concerns regarding the toxicity of hydroxychloroquine. Additional issues raised were the common usage of combined drug therapy in trials, and the potential need for prophylactic therapy if early treatment is beneficial. Issues not raised were the totality of the evidence base presented in the Quadrant article,[2] the modern understanding of "evidence-based medicine", clinical decisions in the context of a pandemic, and the contextual situation of therapy in Covid. Each will be addressed.

What is "Evidenced-based Medicine"?

The central factor in the critique is that the randomised clinical trial (RCT) as the only evidence of serious value in assessing clinical value of a therapy. This is simply incorrect. Numerous sources of evidence contribute to supporting the clinical value of any drug/vaccine.[3] That is recognised by all experienced statisticians. Properly conducted RCT's are accepted as a gold standard form of evidence when done well, but "gold" has become tarnished through the Covid pandemic. The RCT has become the tool of the pharmaceutical industry as expensive, targeted studies geared to selectively support their drug of the day. Covid became a field day for dodgy RCTs – from hidden and blurred data in the initial mRNA vaccine trials, withdrawal of published RCT pertaining to show HCQ did not work on the basis of falsified data, the plethora of documented faults in those studies that remain such as the "Together Trial" labelled as "fraudulent" for data manipulation and over 50 significant defects[3] including "loss" of half the placebo group; and the recent withdrawal of a Cochrane Analysis for ivermectin due to bias and selective handling of data (and following numerous complaints).

The argument that only RCT's can be used to assess clinical validity is not only specious and convenient to criticise repurposed drugs which will never have the financial support of the pharmaceutical industry, but patently incorrect. I shared medical intake at MacMaster University with Dave Sackett for 5 years.[4] Dave, the "father of EBM" would lecture me nearly daily on evidence assessment. His point was always

that evidence-based decisions were based on three platforms: the best published evidence in its entirety; input from experienced clinicians; and patient expectations. The false argument cherry-picking data from selected RCT's without attention to their relevance, so often used in the Covid era, has been exposed by Prof Collen Aldous.[5] Aldous emphasises the importance of the body of support building on many sources. The reviewer has viewed the topic more as a debate than an honest attempt to evaluate the clinical value of HCQ in treating Covid-19.

That the "RCT angle" is no more than that, is evident in the selective way the argument in "The Myth" is used. How would the case for mRNA vaccines or anti-viral drugs in Covid be argued? There are no RCT's supporting value for mRNA Covid vaccine roll-outs and the current RCT's for molnupiravir (Lagevrio™)[6] and nilmatrelvir+ritonavir (Paxlovid™)[7] (the expensive anti-viral drugs used regularly to treat Covid-19), show no benefit.

Late Treatment of Covid with HCQ (or any anti-viral) will not be effective

All clinicians with experience should know that. The reviewer had difficulty separating "early" from "late": This has been clearly shown in a review of all ivermectin studies, where if treatment is delayed by 5 days, efficacy falls to 20%.[3] This is a general principal of treating any viral illness. There were three (not two) large hospital-based HCQ studies through 2020 (Surgisphere,[8] Solidarity,[9] and Recovery[10] Trials). Many patients treated were in intensive care – all were very sick with disease of over 6 days. This was late disease, with mortality rates of 10-26%: no anti-viral drug was ever going to make an impact (note the effort made to run the anti-viral drug trials with patients having disease for only 2-3 days). The difference commented upon by the reviewer for corticosteroid use in the same population, emphasised this conclusion, as anti-viral drugs work on early viral infection, corticosteroids on late-stage inflammation.[11] The reviewer "forgot" to comment on the numerous imperfections of all three studies, including the forced withdrawal of the Surgisphere Trial by the Lancet because of claims of fraud (by Australian doctors).

The reviewer notes how the WHO "acted quickly" to shut down HCQ following these three studies, influencing government decisions throughout the western world in an unprecedented way even to the extent of criminalising the use of HCQ to treat Covid-19. This was a time when the "advice" to anyone with Covid-19 infection, was "there is no treatment; if breathless go to hospital for oxygen and remdesivir". Note that whatever the take on HCQ at that time, it was safe to use in early disease,[12] it was cheap and available, and had far more evidence supporting its use than did remdesivir (used in hospitals costing thousands of dollars, replete with serious adverse events including renal damage AND shown to be of NO value in the very same WHO-sponsored Solidarity Trial noted by the reviewer). These points are made to note the hypocrisy that attends analysis of Covid management: the sheer fervour even passion to discredit repurposed drugs for treating Covid even when there is no alternate, compared to the indifference shown to the limitations of anti-viral drugs and the net benefits of vaccination.

Early Treatment

The only place for the use of HCQ is early treatment – admission to hospital means late treatment (even though the reviewer rightly noted some "early-treatment " trials included patients in hospital. Such inclusion though methodologically improper, would only bias against protection – see above).

A definitive statement on the value of HCQ in early treatment was made by Prof Harvey Risch, an eminent epidemiologist at Yale School of Public Health.[12] This critical paper by one of the world's most respected epidemiologists spells out data-based arguments: 10 studies of high-risk outpatient HCQ use shows risk reduction in meta-analysis of 44% reduction in hospitalisation (p=10 to -5.5) and 75% reduction in mortality (p=10 to -19). Risch makes several additional points:

The importance of studies identifying early disease in high-risk subjects, to enable discrimination;
The value of quality observational studies (including quoting the definitive Cochrane meta-analysis confirming that standard adjusted modern nonrandomised trials show virtually identical results to their RCT counterparts. Risch follows this with review of quality Observational Studies or Case-series studies of high- risk outpatients, emphasising their validity where hard endpoints such as hospitalisation or death are used. The value of "matched" community data is made when 3,300 high risk outpatients were treated with HCQ +/- azithromycin), compared to contemporary community data: 0.09% mortality compared with 12.8% mortality with no significant adverse events; and real life experience using HCQ in regions in India (Vadodara) and Brazil (Para) where community introduction of HCQ made a dramatic

difference to Covid outcome. References to all studies are included in the Risch brief.[12]

The concerns of the reviewer failed to include comment on the Risch contribution which was a key to the argument within the Quadrant article. Rather the arguments regarding early treatment used by the reviewer were as follows:

1. The Marseille Study. The reviewer clouded understanding of the value of this experience by focussing on the flamboyant director, who attracted attention and eventual loss of position for controversial behaviour. There was never suggestions of fraud or improper actions in relation to the Covid studies. It is easy to dismiss the value of this work with comments used by the reviewer "non-randomised; retrospective; non-peer reviewed" to which is added "article withdrawn" for anyone not caught up in the frenetic activities of the first two years of the pandemic. Guided by the principle of analysis of high-risk disease, the Marseille group in a non-withdrawn peer-reviewed observational study of 10,429 subjects; Risch[12] focussed on those over 60 as a "high risk" group of 1,495 with 520 controls, to confirm using an age, sex, and time-period adjusted-regression analysis to show a mortality odds ratio of 0.17 with P = 0.0007 (the "placebo" included some treated for a short period, likely biasing the observed hazard ratio nullward).

2. The reviewer selected two RCT's to make a negative point re "early HCQ treatment":

A. Spivak *et al*.[14] This study of disease treated with HCQ was not completed, and had an "unusual" publication record. It was a "late" not an "early" study. Most patients appeared to be treated 6+ days after onset of symptoms. It was a study of "low risk subjects" making any conclusion with numbers used, problematical. Thus, this study is irrelevant to discussion on early treatment with HCQ.

B. Reis *et al*.[15] Again, a "late" treatment study of 441 subjects, with most subjects starting treatment over 5 days from disease onset. Also, terminated early. Though used by reviewer as an example of "failed early treatment" conflicts and data manipulation may be at play. Pre-publication outcome of relative risks for hospitalisation and death were given as 1.0, though when published results were 66% reduction of mortality and 24% reduction of hospitalisation (neither statistically significant).

The reviewer selectively quotes "all study" RCT's with marginal benefit, identifying small numbers and variability. Considering the broader data base, with all early treatment studies, a 76% reduction in mortality is found (with 53,600 subjects) and in reduced hospitalisation of 41% (50,700 subjects). Of course many studies (both positive and negative) are imperfect – that is the way of largely unfunded studies at a time of great stress (though surprisingly, also found with industry-funded studies). It is the sheer volume of data (533,000 subjects studied in 422 studies) with net highly significant benefit that enables the conclusion that HCQ therapy in Covid is beneficial. Protection data from analysis of all studies on early treatment (showing benefit at 66%) are similar for higher quality and peer-reviewed studies. Only 10% of patients in RCT's were from early treatment, reflecting the association of conflict of interest with negative (and late) studies (not noted by the reviewer, although he expresses concern that the numbers in early RCT's are low. The reviewer comments about confusion re early treatment and prophylaxis, denying that data is available to clarify his question. This is surprising as significant protection of 30% for post-exposure prophylaxis has been demonstrated in 8 studies including over 6,000 exposed subjects.[16]

HCQ toxicity

It is simply nonsensical to suggest that HCQ used in appropriate dose for early Covid treatment over say 5 days (2 to 3G) is dangerous. Minor side effects can occur, but cardiac arrhythmias are unusually rare. I have written over 20,000 prescriptions for HCQ with no acute significant adverse events. This is the published experience of those treating Covid-19 (see also discussion by Risch[12]).

Conclusion

I have not addressed the more personal comments other than to say I stand by my view that the handling of HCQ in Australia (followed by similar handling for ivermectin) has been outside my experience using off-label drugs, over a period of 50 years. It is outside of any reasonable understanding that safe available drugs with quality evidence for efficacy, have been denied to patients early on when no alternate therapy was available. Given the data, it is not unreasonable to suggest, that many Australian patients died that could have survived with early treatment with repurposed drugs. Even if the data was short of ideal (and what drug is not: I point to remdesivir, molnupiravir and Paxlovid costing Australians billions of dollars without evidence they saved one life) how could you not take HCQ or IVM with a broad-spectrum antibiotic if high risk for a severe outcome from Covid infection?

I have responded to each of the arguments against the use of HCQ, pointing to the irrelevance of the arguments using large studies in very sick subjects with late disease, the absence of scientific argument against early treatment (to the contrary, identified strong supportive data), and neutralised any argument based on high toxicity of HCQ in an early Covid circumstance. The gist of the reviewers counter-argument centres around an outdated but much used attachment to the notion of RCTs as the centre of the pharmacological universe, promoted by Big Pharma as a tool to control the drug industry. Not even the Cochrane group believes that anymore, and Dave Sackett never did. Only about 15-20% of registered drugs gained their spot on the back of a RCT. What is disappointing in the narrow arguments used by the reviewer is a lack of understanding of the broad argument base in support of HCQ: exciting mechanism studies; regional use of HCQ in India and South America; the profound impact of bias and conflict of interest in demonising something that could have saved Australian lives when nothing else could; and the profound cynicism by medical professionals (and industry) keen to jump on the bandwagon of destroying effective safe, cheap (without patents) therapy, yet shouting approval of anti-viral drugs that cost thousands of dollars, that are unsafe and simply do not work (even in RCTs).

My comments on the HCQ saga as a metaphor for a wider disruption in medical leadership, with connections to powerful political-pharmaceutical-WHO connections, can await another occasion.

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Editor's note: This paper is a rebuttal of my own editorial review. In the interest of scientific debate it is published here without amendment (other than that required to clarify the origin of the paper) or further reply by me, with the aim of helping to resolve whether or not the central question (whether hydroxychloroquine is efficacious in the early treatment of SARS-CoV-2 infection) is true. Publication of this paper does not indicate the Journal's agreement with Professor Clancy's views. We invite relevant comment from interested medical or pharmaceutical professionals and members of the public (subject to editorial review) who have read *both* papers. Comments meeting normal scientific publication standards (maximum 1000 words) should include the sender's contact details (name and qualifications) and be addressed to The Editor, Tasman Medical Journal and submitted by email to editor@tasmanmedicaljournal.com.

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