Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients

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Conflict of Interest: In the last two years T.K. received conference attendance sponsorship and was a speaker at a congress sponsored by Pfizer and was a chairman at a meeting organised by Gilead (with no personal payment) unrelated to this work.

Risch makes an impassioned plea that we are “unable to wait for results of randomized controlled trials” for COVID-19 and should “immediately roll out” early outpatient treatment with hydroxychloroquine (HCQ) and azithromycin (AZ).[1] Early treatment that prevents disease progression and hospitalization is desperately needed, and timing of initiation of antiviral therapy may have important effects on the outcomes of therapy for COVID-19.[2] Unfortunately, “based on laboratory and other preliminary evidence to-date”, no treatment is available “effective in preventing hospitalization for the overwhelming majority”, and there are potential hazards associated with HCQ+AZ.

Gautret et al. reported an open-label non-randomized study which showed a significant reduction of patients with detectable virus but included only six patients treated with HCQ+AZ and injudiciously recommended “that COVID-19 patients be treated with HCQ+AZ to cure their infection and to limit the transmission of the virus”.[3] The International Society of Antimicrobial Chemotherapy and the journal publisher have acknowledged that “concerns have been raised regarding the content, the ethical approval of the trial and the process that this paper underwent to be published” and additional independent peer review is ongoing.[4]

Risch contends that criticism regarding the small study size “only applies to studies not finding statistical significance” and that “once a result has exceeded plausible chance finding, greater statistical significance does not contribute to evidence for causation”. However, small trials with very large treatment effects, in particular those with laboratory-defined efficacy, should be considered with caution, and subsequent trials typically show decreased effects and many lose their nominal significance.[5] In a follow up study from

Marseilles of 1061 patients (which excluded 256 patients with "contraindications to HCQ and/or AZ treatment, refusal or other reasons"), 4.4% had persistent viral shedding at day 10, 4.3% had "poor clinical outcome" (death or transfer to ICU or hospitalization for 10 days or more) with a case fatality rate of at least 0.75%.[6]

Risch cites other non-peer reviewed "evidence". A non-randomized trial from São Paulo, Brazil showed a reduced hospitalization rate for 636 outpatients treated with HCQ+AZ (1.9%) compared to a "control" group of 224 patients who "refused treatment" (5.4%).[7.] A New York Family Practitioner proclaimed that of "approximately" 405 patients treated with HCQ+AZ+zinc sulfate, six were hospitalized for pneumonia and only two died.[8] Both of these reports included patients diagnosed "on clinical grounds", without laboratory confirmation.

Risch downplays the risk of potential adverse effects of HCQ+AZ. An international study of 323,122 patients with rheumatoid arthritis demonstrated an increased risk of 30-day cardiovascular mortality when AZ was added to HCQ.[9] QTc prolongation of >500 ms occurred in 11% of hospitalized patients with COVID-19 treated with HCQ+AZ.[10] While cardiac toxicity may be less common in an outpatient cohort, regular QTc monitoring in this setting would be difficult.

Another important adverse effect of azithromycin use is the potential for the development of macrolide and other antibiotic resistance in gastrointestinal and respiratory tract bacteria. Azithromycin is a potent driver of in the selection of resistance due to its very long-elimination half-life, large volume of distribution, high intracellular and prolonged tissue concentration and postantibiotic effect.[11]

Remdesivir, which has demonstrated modest clinical benefit in hospitalized inpatients,[12] is suggested as a possible alternative. However, even if shown to reduce disease progression, remdesivir requires intravenous administration and is not a practical option for outpatient therapy.

Risch declares "it is our obligation not to stand by, just carefully watching". But Zagury-Orly and Schwartzstein remind us to retain healthy scepticism and act "with caution and reason".[13] Anecdotal observations should generate hypotheses for randomized controlled trials for COVID-19. We need to remember the principle of clinical equipoise,[14] particularly when considering potentially harmful interventions.

References

1. Risch H. Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis. Am J Epidemiol [published online ahead of print April 18, 2017]. Am J Epidemiol. (doi:10.1093/aje/kww192).

2. Dolin R, Hirsch M. Remdesivir - An Important First Step. N Eng J Med 2020; [published online ahead of print May 27, 2020]. (doi: 10.1056/NEJMe2018715).

3. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; [published online ahead of print March 20, 2020]. (doi:10.1016/j.ijantimicag.2020.105949).

4. Joint ISAC and Elsevier statement on Gautret et al. paper [PMID 32205204]. https://www.journals.elsevier.com/international-journal-of-antimicrobial-agents/news/joint-isac-and-elsevier-statement-on-gautret-et-al-paper (accessed on 3 June 2020).

5. Pereira TV, Horowitz RI, Ioannidis JPA. Empirical evaluation of very large treatment effects of medical interventions. JAMA 2012;308:1676-84.

6. Million M, Lagier J, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille,

France. Travel Med Infect Dis [published online ahead of print May 5, 2020]. (doi:10.1016/j.tmaid.2020.101738)

7. Barbosa Esper R, Souza da Silva R, Oikawa FTC, et al. Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine. April 15, 2020. https://pgibertie.files.wordpress.com/2020/04/2020.04.15-journal-manuscript-final.pdf. (Accessed June 4, 2020).

8. Zelenko V. To all medical professionals around the world. April 12, 2020. Reproduced in: Tkachenko I. A Detailed Coronavirus Treatment Plan from Dr. Vladimir Zelenko. The Internet Protocol. April 14, 2020 https://internetprotocol.co/hype-news/2020/04/14/a-detailed-coronavirus-treatment-plan-from-dr-zelenko/(Accessed June 6, 2020).

9. Lane J, Weaver J, Kostka K, et al. Safety of hydroxychloro.quine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv 2020 [published online May 31, 2020]. (doi:10.1016/j.tmaid.2020.101738).

10. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nature Med 2020; [published online April 24, 2020]. (doi: 10.1038/s41591-020-0888-2).

11. Mack I, Sharland M, Berkley J, et sl. Klein, N. Antimicrobial Resistance Following

Azithromycin Mass Drug Administration: Potential Surveillance Strategies to Assess Public Health Impact. Clin Infect Dis 2020; 70(7), 1501-1508.

12. Beigel J, Tomashek K, Dodd L, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Eng J Med 2020; [published online ahead of print May 27, 2020]. (doi: 10.1056/NEJMoa2007764).

13. Zagury-Orly I, Schwartzstein RM. Covid-19 - A Reminder to Reason. N Engl J Med. 2020; [published online ahead of print April 28, 2020]. (doi: 10.1056/NEJMp2009405).

14. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317: 141-5.