Response to: "Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients" and "Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis"

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Abbreviations: AZ, azithromycin; Dox, doxycycline; HCQ, hydroxychloroquine; SOC, standard-of-care

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Running Head: Outpatient Treatment of High-Risk Covid-19

Conflicts of Interest: Dr. Risch acknowledges past advisory consulting work with two of the more than 50 manufacturers of hydroxychloroquine, azithromycin and doxycycline. This past work was not related to any of these three medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any other potential conflicts-of-interest to disclose.

Dr. Korman's thesis is that no available treatments are effective in preventing hospitalization for the overwhelming majority of COVID-19 patients, and that potential hazards are associated with use of hydroxychloroquine (HCQ) + azithromycin (AZ) (1). The studies that I reviewed (2) contradict this. Dr. Korman superficially describes the same studies that I discussed at length, except with negative adjectives and numerous terms in "quotation" marks to imply, without evidence, their lack of validity. He calls all these studies "anecdotal," to distinguish from the "magic" of randomized controlled trials (3), when government medical and scientific regulatory agencies of western countries around the world routinely use epidemiologic evidence to establish facts of causation, benefit and harm (4). This disingenuous argument has been discussed at length elsewhere (5). Dr. Korman's only novel point is that macrolide antibiotics such as AZ can lead to development of antibiotic resistance. Such instances can occur but are uncommon, and this issue has seemingly not been of substantial concern in the hundreds of millions of uses of AZ world-over during the past 30 years.

Drs. Peiffer-Smadja and Costagliola (6) discuss the data in some of the studies that I reviewed. They first question the small non-randomized trial by Gautret et al. (7). I also have concerns about subject baseline differences between the treated and untreated subjects in that study and thus limit my conclusions to the 26 treated patients. Gautret et al. (7) provided individual-subject data on all 26 which enabled me to carry out my own Cox-regression analyses. The data are that 14 patients received HCQ only, 6 received HCQ+AZ, and under intention-to-treat

principles, 6 were lost to follow-up and had received 3 days or fewer of HCQ but were unspecified as to receipt of AZ. I conducted my analyses starting with the 20 subjects with completed medication usage, and then included bracketing of the unknown-exposure subjects, first assuming all had taken HCQ+AZ and then only HCQ, and in each case, whether the 6 subjects presented with upper vs lower respiratory infections. In the 20 main subjects, for HCQ+AZ vs HCQ alone, the hazard ratio for viral clearance = 7.4 (95%CI 1.12-48.4). Across the four bracketed-combination analyses, the hazard ratios ranged from 3.5 to 8.0 and *P*-values from .078 to .021. Drs. Peiffer-Smadja and Costagliola need to use the outcome event times in Cox regression in order to obtain proper *P*-values. They also say that the trial was not conducted in outpatients and therefore cannot be applied to outpatients. However, the Marseille hospital was used as both an outpatient clinic and a small inpatient facility for a city-wide COVID-19 population screening and treatment program and patients were seen as daily "inpatients" as well as stayed overnight in it. Many of the patients in the Gautret et al. study were asymptomatic or very mildly symptomatic and would be treated as outpatients in most circumstances.

Second, Drs. Peiffer-Smadja and Costagliola refer to the larger Marseille screening program (8). I have discussed those data at length in my response (9) to Dr. Fleury (10). Third, they label a carefully performed, sequential-patient non-randomized controlled clinical trial an "unpublished, poorly designed studies whose quality is even lower than the papers discussed above." I disagree with this characterization as it is unsupported by the evidence. Fourth, Drs. Peiffer-Smadja and Costagliola assert that the Boulware prevention trial (11) demonstrates lack of treatment efficacy. That prevention trial is not relevant to treatment of high-risk outpatients, because virtually all its subjects were low-risk; it would be difficult for any active treatment to do much better than the one hospitalization observed among the 58 test-positive placebo patients. In fact, a preventive medication that allows subjects to develop antibodies while protecting them from

severe disease and hospitalization is a better goal than blocking infection altogether. Fifth, Drs. Peiffer-Smadja and Costagliola take issue with the use of case series of treated patients. In the mass-mortality circumstances we face, a cohort of 400 treated high-risk outpatients with one or two deaths can only be considered informative about the fact of treatment efficacy.

Finally, in pandemic times when months and years of delay cannot be tolerated before large randomized controlled trials are completed, it is possible to quibble with apparent imperfections in almost any study. That misses the forest for the trees. Since my paper (2) discussing five studies was published, data from seven other studies of high-risk outpatients have become available, all showing the same substantial and significant benefit of use of HCQ along with AZ or other companion medications (Table 1). Two additional large studies of hospital patients given HCQ within 48 hours of admission show significant benefit adjusted for age and comorbidities (12, 13), and a meta-analysis of studies to-date completely demonstrates this benefit (14). Perhaps even more important, the exponential COVID-19 mortality explosion in the northern state of Pará, Brazil (15), reversed direction, downward dramatically about 5 weeks after a shipment of 75,000 doses of AZ and 90,000 doses of HCQ began to be distributed to infected individuals (Figure 1). No such decline has been observed in the rest of Brazil. This is a compelling, large-scale experiment demonstrating efficacy of HCQ+AZ in saving lives of high-risk people infected with SARS-CoV-2.

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Table 1. Studies Examining High-Risk Outpatient COVID-19 Disease Treated Early with HCQ

Principal Investigator	Location	Subject Status	Number Treated with HCQ	Number of Comparison Subjects	Other Medications with HCQ	Comparison-Subject Medications	Outcome	Direction of Benefit	RR (95% CI), Statistical Significance or Number of Deaths	Reference
P. Gautret	Marseille, France	Mixed older adults	6	14	AZ	HCQ alone	Nasopharyngeal viral clearance	Reduced risk	7.4 (1.12-48.4)	(6)
V. Zelenko	Kiryas Joel, NY	High-risk	405 (series 1)		AZ, zinc sulfate		Mortality	Reduced risk	2 deaths/405	(16)
V. Zelenko	Kiryas Joel, NY	High-risk	400 (series 2)		AZ, zinc sulfate		Mortality	Reduced risk	0 deaths/400	PC[a]
R. Barbosa Esper	São Paulo, Brazil	Mixed older adults	412	224	AZ	SOC	Hospitalization	Reduced risk	0.35 (0.14-0.87)	(17)
I. Ahmad	Long Island, NY Nursing Home	High-risk	200		Dox		Mortality	Reduced risk	9 deaths/200	(18), PC[b]
J.-C. Lagier	Marseille, France	High-risk	199	199	AZ	Propensity-score matched; HCQ or AZ alone or neither	Mortality	Reduced risk	0.41 (0.17-0.99)	(19)
M. Leriger	Indiana Nursing	High-risk	105	113	None, AZ, Dox	SOC, +AZ or Dox	Mortality	Reduced risk	*P*<.05	PC[c]

	Homes									
L. Kacmar	Aurora, IL	High-risk	68		AZ		Mortality	Reduced risk	0 deaths/68	PC[d]
S. Fonseca	Brazil HMO	High-risk	159	558	Prednisone	Neither HCQ nor Prednisone	Hospitalization	Reduced risk	*P*<.05	PC[e]
B. Procter	McKinney, TX	High-risk	50		AZ, zinc sulfate, losartan, aspirin		Mortality	Reduced risk	0 deaths/50	PC[f]
S. Crawford	Festus, MO Nursing Home	High-risk	52		Rehydration		Mortality	Reduced risk	0 deaths/52	(20)
B. Tyson	El Centro, CA	High-risk	219		AZ (2 with Dox)		Mortality	Reduced risk	0 deaths/219	PC[g]

Abbreviations: AZ, azithromycin; Dox, doxycycline; HCQ, hydroxychloroquine; PC, personal communication as described in the following footnotes; SOC, standard-of-care.

[a] Vladimir Zelenko MD, PC, Family Practice, Monroe, NY, personal communication, 2020.

[b] Imtiaz Ahmad, 21st Century Oncology, Inc., Fort Myers, FL, personal communication, 2020.

[c] Monica Leriger, American Senior Communities, Indianapolis, IN, personal communication, 2020.

[d] Lawrence Kacmar, The Center for Primary Care and Sports Medicine, Aurora IL, personal communication, 2020.

[e] Silvia Fonseca, Hospital São Francisco, Ribeirão Preto, Brazil, personal communication, 2020.

[f] Brian Procter, McKinney Family Medicine, McKinney TX, personal communication, 2020.

[g] Brian Tyson, All Valley Urgent Care, El Centro, CA, personal communication, 2020.

Figure 1. Pará and Brazil-Minus-Pará Daily COVID-19 Deaths, April 1, 2020 through July 9, 2020. Points plotted are 7-day symmetrical moving averages of the raw data, which are available from CORONAVÍRUS BRASIL as posted daily (15). Solid line, daily COVID-19 deaths in Pará; dashed line, daily COVID-19 deaths in the rest of Brazil. The daily numbers of newly identified COVID-19 cases in Pará were increasing through May 28 and then have stayed roughly flat at about 2,100 per day, whereas the daily numbers of new cases in the rest of Brazil have risen throughout the period (data not shown). On April 6, the public hospital network of Pará purchased 75,000 doses of azithromycin (AZ) and 90,000 doses of hydroxychloroquine (HCQ) and started distributing them to infected individuals over the next few weeks; the Hapvida HMO hospitals in the state also acquired the medications and started using them in the same period (Alexandre Wolkoff, Hapvida Saúde HMO, Fortaleza, Brazil, personal communication, 2020). The gray arrow denotes when the medications were initially purchased. Approximately five weeks after the medications began distribution, the mortality numbers in Pará turned down dramatically. In Pará, the July 2 mortality (n=40) as a fraction of June 2 incidence (n=2,068) = 1.9%, whereas the same for the rest of Brazil was 1,026/23,733 = 4.3%. Brazil outside of Pará was not systematically using HCQ and AZ over the time period shown in the figure.