Pseudoscience at the expense of rheumatic disease patients during the Coronavirus disease 2019 pandemic

Sirs,

COVID-19 is a potentially lethal disease, for which an effective therapy is urgently needed. Chloroquine and hydroxychloroquine have been tested to this purpose in trials in China and France, respectively. Based on some good efficacy data obtained from over 100 patients, chloroquine has been included in the Chinese guidelines for the treatment of COVID-19 pneumonia. These data have not been disclosed to the scientific community yet. Hydroxychloroquine alone or in combination with azithromycin was also reported to be effective in an uncontrolled small French study. High publicity of these dubious, but hopefully invoking data led to the shortage of these drugs, causing dire consequences for the rheumatology patients who rely on them.

Chloroquine (CLQ), in use since 1944 to treat malaria and, subsequently, its safer derivative hydroxychloroquine (HCQ), have been used to treat patients with rheumatic diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Discontinuation of HCQ therapy in SLE patients may lead to disease flare-ups and worsens long-term survival (1-4). In RA, HCQ, not only improves arthritic symptoms, but also shows favourable effects on metabolic and cardiovascular outcomes (5). Nowadays, patients with rheumatic diseases in many countries, including in the USA, are having trouble in accessing these medicines due to the shortage of these drugs (6). The problem was triggered by recent claims around the efficacy of the CLQ and HCQ in the treatment of COVID-19. Despite their questionable reliability, these claims attracted immense publicity in the media, boosted with contributions from high public figures, including Donald Trump and Elon Musk (Fig. 1). In the midst of fears of a growing potentially fatal pandemic with no proven effective therapy, intense media coverage led to panic causing unnecessary stockpiling of these drugs, which put our patients at a tough spot, and added on the new challenges posed by COVID-19 on the patients and rheumatologists (7). Therefore, as a rheumatologist, it makes sense to critically review the available evidence, to ease this panic.

In mid-February, a Chinese state official announced at a press conference that a group of Chinese experts suggested CLQ be included in the next version of the COVID-19 treatment guidelines on the basis of its superiority over controls in abating fever, improving lung CT images, achieving viral clearance and shorter recovery time (8). The subsequently published article by the Expert Consensus Group (9) did not add much on these findings, and simply stated that their recommendation was based on the previously demonstrated *in vitro* antiviral effects of CLQ, including against coronaviruses (10, 11) and on the recent favourable clinical experience in China with this drug in the treatment of novel coronavirus pneumonia, without communicating any scientific data.

A narrative letter which was published on the 18th of March, on the very day it was submitted, endorsed the efficacy of CLQ in the treatment of COVID-19 pneumonia and characterised this development as a "breakthrough" in its title (12). Notably, the first author of this publication was a senior editor of the journal, where it was published. This highly cited article based its claim solely on the statements made at the News Briefing but did not present any clinical data. However, the authors of a recent systematic review found no evidence whatsoever for the effectiveness of CLQ in the Chinese trial registries when they reviewed (13).

The first clinical data regarding the efficacy of antimalarials came from a small French study aimed to test the effectiveness of HCQ (600 mg/d x10 days) in clearing the virus from nasopharyngeal swabs of the patients with COVID-19 (14). The study was described as a single-arm study, but the authors nevertheless compared their results to 16 control patients who did not receive HCQ, most of them being from other centres, and also to a group of 6 patients, who in addition to HCQ received azithromycin (AZT), 500mg on day 1 followed by 250 mg per day for the next four days. No sub-study was described in their original protocol (Table I). The rate of viral clearance on day 6 was 12.5% (2/16) in

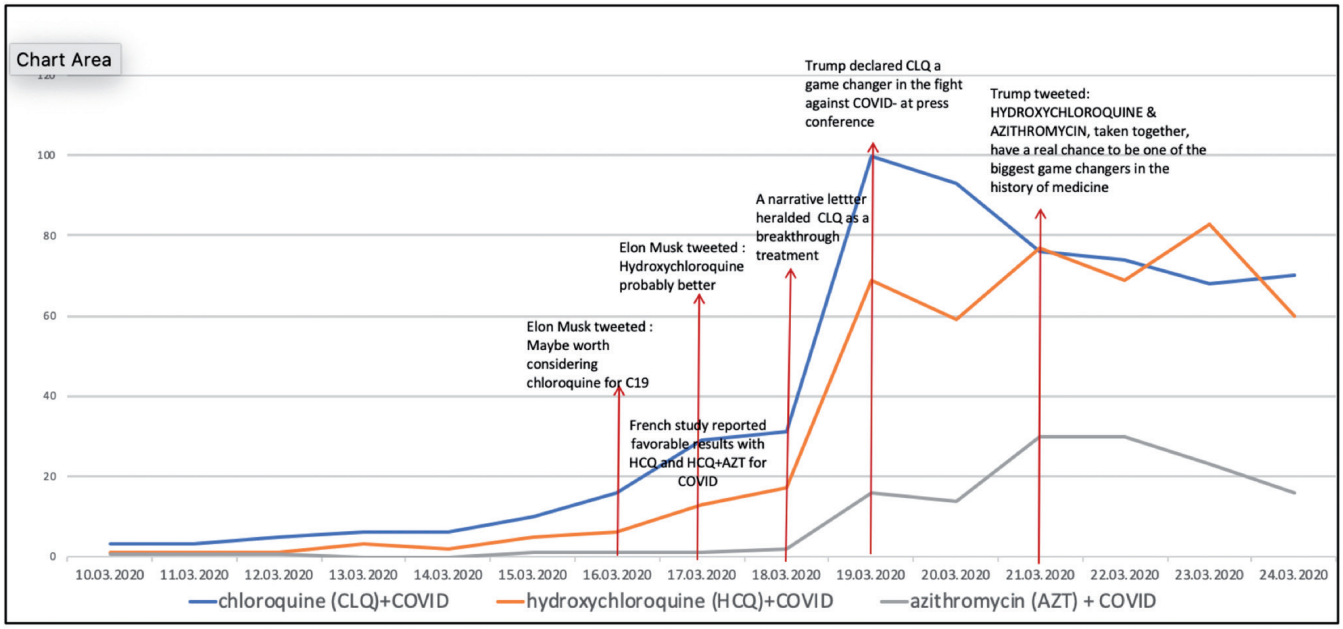

Fig. 1. The impact of high public figures on google trend results as an indicator of publicity for "chloroquin + COVID", "hydroxychloroquine + COVID" and "azithromycin + COVID".

Table I. Discrepancies between the information provided in the protocol (2020-000890-25) submitted to the EudraCT and those reported in the published manuscript. Comments were added where appropriate.

	What was planned	What was done
Full title of the trial	Treatment of Coronavirus SARS-Cov2 Respiratory Infections with Hydroxychloroquine	HCQ and AZT as a treatment of COVID-19: results of an open label non-randomized clinical trial
Trade name (for IMP)	Plaquenil 200 mg, comprimé pelliculé	
Trial contains a sub-study	No	
It is clear that the study had been initially planned as a single-arm study.		
Included in the principal inclusion criteria	Women and men with documented respiratory infection with Coronavirus SARS CoV 2	PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission whatever their clinical status
	Teenager girls and boys aged more than 12 years old	age >12 years
Six patients who were asymptomatic apparently did not have respiratory infection. *Case 1, 2 and 4 in the control group were 10, 12, 10 years old, respectively.*		
Primary end point(s)	Results of SARS-COV2 virus detection	Presence and absence of virus
Timepoint(s) of evaluation of this end point	Day 1, Day 4, Day 7 and Day 14	The primary endpoint was viral clearance on day-6 post-inclusion
Secondary end point(s)	Apyrexia, normalisation of respiratory rate, and average length of hospital stay and mortality.	Body temperature, respiratory rate, long of stay at hospital and mortality, viral clearance overtime, occurrence of side effects
"Virological clearance overtime" was not included as a secondary end-point in the original protocol, neither the occurrence of side effects		
Timepoint(s) of evaluation of this end point	Day 1, Day 4, Day 7, Day 14 and Days of hospital discharge Day 6	During the study period (No specific time point was given).
Controlled	No	
The trial involves single site in the Member State concerned	Yes	Centres in Marseille, Nice, Avignon and Briançon were involved
Initial estimate of the duration of the trial (years)	1	from early March to March 16th
Planned number of subjects to be included	25	24 patients and 24 controls (16 controls, 14 patients HCQ, 6 patients AZT + HCQ)
Plans for treatment or care after the subject has ended the participation in the trial (if it is different from the expected normal treatment of that condition)	None	Depending on clinical presentation, AZT was added to the treatment

AZT: azithromycin; EudraCT: European Union Drug Regulating Authorities Clinical Trials Database; HCQ: hydroxychloroquine; SARS-CoV2: severe acute respiratory syndrome coronavirus 2.

controls, 57.1% (8/14) in patients solely on HCQ, and 100% (6/6) in patients receiving HCQ + AZT.

Many of the bias of this study have been discussed in a recent article (15), and in the web, including at pubpeer, an online journal club. It was mostly criticised for its non-randomised design, use of controls from other centres, small sample size, exclusion of 6 patients (4 of whom had clinical worsening) in the treatment group, low cycle threshold to define viral clearance, ethical problems and its rapid acceptance, the very next day of its submission, by the journal, that includes three of the authors in its editorial board, one being the Chief Editor.

But, the flaws of this study are not limited to the previously raised issues. There are striking differences between the registered study protocol and the protocol in the article, which are summarised in Table I, with some comments where necessary. Some of these discrepancies merit further elaboration to fully fathom the extent of the flaws in the study.

The authors excluded 6 patients from their analysis due to the lack of 6 days follow-up data, despite that such criterion did not exist in their registered protocol. Astoundingly, 5 out of the 16 control patients did not have PCR results on day 6 either, with two of them not even being tested on day 1 and day 2 (Supplementary Table S1 in the authors' original manuscript).

The 6-day follow-up criterion for inclusion creates further heterogeneity between the control and active treatment arms. Considering that the study had been planned at a hospital setting, with daily quantitative PCR testing, one can infer from the Supplementary Table S1 in the authors' original manuscript that cases 1 to 5 were from the study centre, of whom two (40%) were PCR negative on day 6. On the other hand, the viral clearance rate among the other 10 controls (apparently from other centres) was 0%. This difference may be due to the discharge of control patients who had become PCR negative before Day 6, leaving only PCR positive controls to be included in the analysis. This may also explain no drop-out being observed among control patients.

Another major defect in this study, is the "parachuted" HCQ + AZT group that came out of nowhere. No clear explanation is given neither for the indication nor for the timing of adding AZT on top of HCQ. The authors state that azithromycin was added to hydroxychloroquine, but seemingly at different times as can be deducted from the information given for the two patients in the AZT and HCQ group, who can be identified as Case 31 and Case 33 as the best fitting cases in the Supplementary Table S1 in the authors' original manuscript. Then it is clear that the data for day 6 in the AZA + HCQ group, do not correspond to the day-6 post-inclusion

data in the control and HCQ only groups, and are therefore not comparable.

The description of the sample size calculation also reflects the original single arm design of the study, since assumptions for the control and combined treatment groups were completely disregarded, indicating that the inclusion of these group was decided somewhere along the study.

Despite all its many serious flaws, the "hope invoking" results reported in the French study attracted immense public attention, as opposed to a subsequently published small Chinese study (16), that found no difference between the patients receiving HCQ (400 mg/d x 5, n=14) and standard treatment (n=15), regarding the viral clearance rates at nasopharyngeal swabs on day 7, 86.3% and 93.3%, respectively.

We hope and pray that the several ongoing randomised controlled trials will demonstrate efficacy and safety of CLQ and HCQ in the treatment of COVID-19, as well as in its prophylactic treatment. However, the credit should not go to the hastily published flawed studies. At the moment, all the necessary action should be taken to ease access to these medications for the patients who are using them for approved indications and protect them from being victimised by hyped science.

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