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Editorial

Hydroxychloroquine for Covid-19 - When the pandemic runs faster than research

Maria Frigerio *

2nd Section of Cardiology, Heart Failure & Transplantation, DeGasperis CardioCenter, Niguarda Hospital, Milan, Italy

In this number of the International Journal of CardIology, a brief report by A. Cipriani et al. shows that treatment of patients with Covid-19 pneumonia with hydroxychloroquine plus azythromycin is associated with prolongation of QT interval, but it does not seem to correlate with an increased probability of relevant cardiac events, including arrhythmias, at least in subjects without prior cardiac disease (except hypertension). Moreover, the analysis of standard EKG plus 24-h Holter monitoring does not show significant circadian variations of QT interval in these patients. The Authors suggest that continuous EKG monitoring isn't necessary when using hydroxychloroquine plus azythromycin in Covid-19 patients without heart disease [1].

This is a single-center study with strict inclusion and exclusion criteria, and a very detailed analysis of EKG tracings, resulting into a small study cohort (22 patients). Nevertheless, it may have some implications for patient management. Among various empirical therapies that are currently used for Covid-19 pneumonia, chloroquine or hydroxychloroquine, and azythromycin, are widely available, are employed for other medical indications in an outpatient setting since a long time, may be taken orally, and cost less than drug regimens that include anti-virals or biological agents targeted to the so-called cytokine storm that may be associated with this disease. Thus, they are possible candidates for home-based, early treatment of less severe cases, or for post-exposure prophylaxis, but there are concerns about their safety, mainly due to prolongation of QT interval that could facilitate cardiac arrhythmias [2,3].

A recent study on telemonitoring of 117 Covid-19 patients treated with hydroxychloroquine, of whom a about 5% had an history of coronary artery disease and/or heart failure, and 43% received also azythromycin, shows a significant prolongation of QT interval and a very low incidence of ventricular arrhythmias over around 300 patient days [4]. Thus hydroxychloroquine appears to be reasonably safe in patients with Covid-19 pneumonia – but is it effective?

In an observational study on about 1400 patients admitted with moderate to severe Covid-19 pneumonia, of whom >800 were treated as per medical choice with hydroxychloroquine, in most cases associated with various other agents, after adjustment for baseline patient characteristics no significant differences were found between treated and untreated patients regarding the endpoint of intubation or death within the study period (potential follow-up 17–49 days) [5]. Some readers may infer that hydroxychloroquine is simply not effective in Covid-19 pneumonia, while others may reply that adjustment could not completely correct for the more severe baseline conditions of treated patients, or that the variety of accompanying therapies made it impossible to evaluate the impact of a single drug. Moreover, criteria for intubation were not defined, and at the end of the study a relevant proportion of patients were still hospitalized – which somehow limits the clinical relevance of actuarial survival analysis. Thus, the main implication of this paper is that a randomized study is needed [6].

At present, protocols that define first, second, or third line therapies for Covid-19 pneumonia are more a matter of opinions and local practices than of science. In particular, the debate about the use of chloroquine and hydroxychloroquine for SARS-CoV2 infection has gone beyond the the boundaries of the medical community, and here and there has taken sociological if not political nuances [7–9]. Similarly, in Italy there is a debate on the media and in the social networks regarding the use of convalescent plasma, which is presented by its promoters as a low-cost, easily available, solidarity-driven therapy ("from the people, for the people") - as opposed to profit-oriented, "Big Pharma" products such as drugs and vaccines.

The interplay between medical and social issues is not surprising, taking into account the profound impact of this coronavirus pandemic not only on life expectancy of the affected patients, but also on healthcare organization and delivery, and, additionally, on lifestyle, education and economics worldwide.

However, it is clear that we, as physicians, need evidences, to improve our understanding of the disease and our capabilities of treating patients successfully [6,10]. Unfortunately, with almost 5 millions confirmed cases worldwide, and despite the adoption of expedite procedures for authorizing clinical studies, evidence-based recommendations on Covid-19 therapy are still lacking. As of today, >500 observational studies and over 600 randomized trials for Covid-19 have been registered (clinicaltrials.gov, accessed May 14th, 2020), of

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* Corresponding author at: Cardiologia 2-Insufficienza Cardiaca & Trapianto, DeGasperis CardioCenter, Ospedale Niguarda, Piazza Ospedale Maggiore 3, 20162 Milano, Italy.

E-mail address: maria.frigerio@ospedaleniguarda.it.

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whom around 50% only are actively recruiting patients, and <50 have been completed.

A huge number of subjects presenting within a limited timeframe could be supposed to facilitate a faster than usual building of evidences. Unfortunately, during this pandemic the burden of patients simultaneously asking for care not rarely exceeded the standard capacity of the healthcare systems- and this cannot help uniform, standardized patient management and reporting. Moreover, the excess of patients with a highly transmissible disease that required hospitalization -and, frequently, intensive care- may have implied the need for sparing personal protection equipments, the urgency of quick education of non-specialized personnel in caring for critical patients, the reduction of the available time for assistance and care of each patient, and the limitation of the use of diagnostic procedures and monitoring facilities to what strictly needed for immediate patient management.

Basically, research needs time and resources, while emergency may require rationing.

Now in many countries the diffusion of SARS-CoV2 is slowing down. May be that it will disappear, either spontaneously or as an effect of quarantine, social distancing, and other preventive measures. If this will not be the case, we should count on therapy and vaccines to prevent other serious outbreaks and their consequences. In theory, the occurrence of some new cases in the next weeks or months at a lower, sustainable pace, could allow to carry on and complete at least some of the planned observational studies and randomized trials.[1] By then, hopefully, also one or more of the studies testing chloroquine or hydroxychloroquine will ultimately define if they have a role for treating Covid-19 patients [10].

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[1] After the acceptance of this article, a large observational study on >95000 Covid-19 patients hospitalized worldwide, has been published on Lancet by M Mehra et al (https://doi.org/10.1016/S0140-6736(20)31180-6). The study showed a higher rate of deaths and of ventricular arrhythmias in patients who received chloroquine or hydroxychloroquine (with or without macrolides) with respect to those who did not. The WHO and several national regulatory bodies (e.g. in Italy and France) halted further studies with these drugs - but this did not put an end to the debate. Thus, it is probably true that science is not neutral. Meanwhile, we should do our best to be unbiased and objective.