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INVITED EDITORIAL

The strange case of hydroxychloroquine and COVID-19

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This editorial refers to 'QTc-interval prolongation and increased risk of sudden cardiac death associated with hydroxychloroquine', by F. Ahmadizar *et al.* doi:10.1093/eurjpc/zwaa118

> 'Good and evil are so close as to be chained together in the soul'
> *Robert Louis Stevenson, The Strange Case of Dr. Jekyll and Mr. Hyde*

The use of (hydroxy)chloroquine (HCQ), often in association with azithromycin, was extremely widespread during the first phase of COVID-19 pandemic. This practice, essentially empirical,[1] recognized as a unique clinical and scientific basis a small observational study with an open-label non-randomized design enrolling 36 patients diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Furthermore, the solidity of this study to sustain the clinical practice raised perplexity and scepticism.

The need for further research to establish the efficacy and to explore the side effects and long-term outcomes of HCQ was emphasized since the very early phase of COVID-19 pandemic. Indeed, already in March 2020 over 20 *in vivo* clinical trials have been registered to test the use of HCQ for the treatment of COVID-19.

Subsequently things got out of hand. On one side, politics, civil society, and mass media took over the concept that HCQ was an effective and safe treatment, sometimes opposed by the scientific and productive world. On the other, observational studies reporting an unfavourable risk/benefit ratio of HCQ found unfortunate publication on leading journals, since they were flawed by serious defects in data collecting and management. These studies were then retracted with severe damage for the image of the scientific community. No example is better than that of HCQ to represent the phenomenon named 'infodemics', as defined by the World Health Organization (WHO).[3]

Sadly, COVID-19 pandemics has still being devastating around the world, but the quality of the scientific information is starting to provide scenarios of evidence-based medicine. Firstly, arge observational studies found a neutral role of HCQ on clinical outcomes such as death or intubation.[4] Recently, reliable randomized clinical trials have been published about HCQ administration in different phases of COVID-19.[5,6] More in detail, HCQ did not improve clinical status at 14 days[6] nor lowered the incidence of death at 28 days.[5]

In this issue of *EJPC*, the study by Ahmadizar *et al.* 'QTc-interval prolongation and increased risk of sudden cardiac death associated with hydroxychloroquine' provides an useful component to our knowledge, reporting the results of a longitudinal follow-up analysis of individuals within the prospective population-based Rotterdam Study about the use of HCQ as a time-varying exposure. The study focuses on the safety of the treatment and found a dose-dependent QTC interval prolongation and a 3.7-fold times risk of sudden cardiac death among HCQ users.[7] Yet the enrolled cohort is different from that affected by COVID-19, but probably more suitable to assess the intrinsic effects of HCQ exposure. We can hypothesize that these effects: (i) can be much more present in patients affected by COVID-19 given the possibility of electrolytes imbalance, hepatic and renal impairment, cardiac disease, and/or myocardial injury; (ii) can be enhanced due to the possible concomitant use of other QT-prolonging drugs for COVID-19 itself (e.g. azithromycin) or to treat comorbidities which are frequent in these patients (e.g. antiarrhythmic, anti-epileptic drugs); and (iii) were unknown considering that efficacy study about HCQ were probably underpowered or inadequate to detect some safety issues.

For all these reasons, we do think that the paper by Ahmadizar *et al.*[7] usefully contributes to the clinical possibility to share a decision making thanks to an evidence-based risk/benefit ratio. Science has different rules than socio-politics, and does not share anything with panic and hurry. Its rules take time but save lives and must be respected overall.

Conflict of interest: none declared.

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