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# Rationale of a loading dose initiation for hydroxychloroquine treatment in COVID-19 infection in the DisCoVeRy trial—authors' response

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Sir,

We thank Mégarbane and Scherrmann[1] for taking valuable time to comment on our article[2] and the *JAC* Editorial Board for providing us with an opportunity to respond. With hindsight, we are keenly aware of the rapid advances in knowledge concerning hydroxychloroquine treatment for COVID-19 and, thus, of the limitations of the assumptions underlying our dose regimen.

To place all of this in context, our objective in writing Lê *et al.*[2] was, firstly, to justify the use of a loading dose of hydroxychloroquine with respect to its pharmacokinetic characteristics. At the start of the COVID-19 pandemic in France, the doses of hydroxychloroquine sulphate used were mostly derived from those used for the indication of chronic autoimmune disease treatment, with no loading dose and even three administrations per day.[3] For the record, the dose we proposed to evaluate in the C-20-15 DisCoVeRy trial (beginning 22 March 2020) was 400 mg twice daily on day 1 and then 400 mg once daily from days 2 to 10. This choice of dose regimen was based on an acceptable benefit/risk ratio in the context of the pandemic. A number of other trials have also since chosen to evaluate the same hydroxychloroquine dose regimen (www.clinicaltrials.gov).

Most of the arguments put forward in Mégarbane and Scherrmann[1] are based on findings published after the start of the C-20-15 DisCoVeRy trial and, thus, on previously unavailable pharmacokinetic, virological and safety evidence.

We agree with some of the theoretical comments, concerning which optimal $EC_{90}$ anti-SARS-CoV-2 activity marker should be considered, for example, but we preferred to use $EC_{50}$, which is sometimes the only available parameter, is probably easier to obtain in studies *in vitro* and is used in physiologically based pharmacokinetic simulations.

Surprisingly, Mégarbane and Scherrmann[1] passed over the recent evaluation of the antiviral activity of hydroxychloroquine both *in vitro* and in SARS-CoV-2-infected non-human primates.[4] The dose-dependent *in vitro* antiviral activity of hydroxychloroquine against SARS-CoV-2 ($IC_{50}$ values of 2.2 and 4.4 μM at 48 and 72 h post infection, respectively) was demonstrated in cultured Vero E6 cells, but doses of 1–10 μM hydroxychloroquine failed to decrease SARS-CoV-2 apical viral titres at 48 h post infection in the MucilAir™ reconstituted human airway epithelium model. This study also showed hydroxychloroquine treatment with a loading dose (with or without azithromycin) to have no clinical efficacy in cynomolgus macaques, regardless of the timing of treatment initiation with respect to SARS-CoV-2 inoculation, despite high hydroxychloroquine concentrations in blood and lung, with blood exposure similar to that in COVID-19 patients receiving hydroxychloroquine. Moreover, this study reported a lung:plasma ratio of 27:177, suggesting a rapid accumulation of hydroxychloroquine in this compartment.

Interestingly, regarding the lack of a clear relationship between QTc prolongation and hydroxychloroquine blood exposure or daily or cumulative doses, Mégarbane and Scherrmann[1] did not address the difficulty of attributing adverse effects in the midst of a cytokine storm or the issue of synergistic cardiac toxicity with second-generation macrolides. Several studies have highlighted concerns about the safety of combinations of azithromycin and hydroxychloroquine.[5–7] Mégarbane and Scherrmann[1] also seem unsurprised by the very high mortality (25.7%) for the hydroxychloroquine arm in the Recovery trial (primary endpoint at 28 days, not significantly different from the 23.5% for usual care). The possibility of high-dose toxicity (2400 mg on day 1 and 400 mg q12h up to day 10), which could have masked a low antiviral activity of hydroxychloroquine, is not even mentioned. The recent *in silico* study by Garcia-Cremades *et al.*[8] cited by Mégarbane and Scherrmann[1] estimated a plasma concentration of 4.7 μM (1578 μg/L) for 50% viral inhibition. This concentration (close to the *in vitro* $EC_{50}$), which might decrease viral load more rapidly, decrease the proportion of infected patients and shorten the duration of treatment, is also dangerously close to the toxic range of plasma concentrations for hydroxychloroquine.[9] It would be even closer to the limit if the model estimated an *in vivo* $EC_{90}$.

In conclusion, the repurposing of a drug for a different indication seems to be more complex than simply changing the dose. The most relevant of the available models is probable non-human primates, if the animals can tolerate the equivalent human drug. *In vitro* models seem to be very different, with the exception of SARS-CoV-2-infected lung epithelial cell cultures.[10] Although the

maximal effect of the dose may not have been reached, our rationale highlights the major limitation of the narrow therapeutic index of hydroxychloroquine, with important safety concerns, particularly as the objective was to validate the use of a hydroxychloroquine dose regimen in the general population.

Unfortunately, the discontinuation of the C-20-15 DisCoVeRy trial, for reasons of futility, has prevented us from further evaluating our hydroxychloroquine dose regimen and drawing conclusions about the true antiviral efficacy of hydroxychloroquine in humans.

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### *C-20-15 DisCoVeRy (NCT04315948) French Steering Committee*

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## Transparency declarations

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