CORRESPONDENCE

Hydroxychloroquine in Hospitalized Patients with Covid-19

TO THE EDITOR: We were surprised by the hydroxychloroquine dose chosen in the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial conducted by Horby et al. (Nov. 19 issue).[1] In this trial, patients received a higher dose of hydroxychloroquine (4 g cumulated over the first 3 days) than that administered in the trial conducted by Lagier et al.[2] (600 mg per day), and it was similar to that in the trial conducted by Borba et al.[3]

In vitro studies show that the effect of hydroxychloroquine is mainly mediated by alkalinization of the phagolysosomes,[4] where it can concentrate about 1500 times more than in plasma. This effect can be obtained with low doses of hydroxychloroquine because of its long elimination half-life. High doses may therefore be useless or even deleterious because of the anti-interferon action of hydroxychloroquine,[5] which may result in a more severe form of Covid-19.[6] The dose used in the RECOVERY trial, the second highest after that in the trial conducted by Borba et al., arouses concern because it may have been a disease-aggravating factor negating the therapeutic effect.

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THE AUTHORS REPLY: Hydroxychloroquine was evaluated in the RECOVERY trial primarily as an antiviral drug. Hydroxychloroquine and chloroquine show only modest antiviral activity in cell-culture systems. The dosing schedule of hydroxychloroquine in the RECOVERY trial was therefore designed to provide the highest tissue concentrations that were safe in order to provide the maximum antiviral activity and thus the best chance of therapeutic benefit.[1] These doses were based on pharmacokinetic modeling in malaria and rheumatologic conditions and were informed by safety thresholds determined from toxicokinetic data on intentional overdoses with the closely related chloroquine.[2]

The base equivalent maintenance doses studied in the RECOVERY and World Health Organization (WHO) Solidarity trials[3] are approximately half those evaluated in the study of chloroquine by Borba et al.[4] Whereas the dosing schedule in the trial conducted by Borba et al. was predicted to confer an increased risk of toxicity,[2] the dosing schedule in the RECOVERY and WHO Solidarity trials was not. There was no evidence of cardiovascular toxicity in either trial. We know of no evidence that the anti-interferon activity of hydroxychloroquine would affect disease progression in hospitalized patients.

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Since publication of their article, Drs. Horby and Landray report receiving donated supplies of the REGN-COV2 monoclonal

antibody cocktail for use in the RECOVERY trial from Regeneron Pharmaceuticals. No further potential conflict of interest relevant to this letter was reported.

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