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Letter to the Editor

The unfinished story of hydroxychloroquine in COVID-19: The right anti-inflammatory dose at the right moment?

Dear Editor,

Uncontrolled inflammation, partly related to activated macrophages, is widely recognised as an independent cause of clinical deterioration and mortality in hospitalised coronavirus disease (COVID-19) patients (Webb et al., 2020; Del Valle et al., 2020). Following the results of the RECOVERY trial and of an additional meta-analysis, corticosteroids are now recommended as a standard of care for hospitalised patients with severe and critical COVID-19 (WHO, 2020). Importantly, the benefit of this anti-inflammatory intervention has been observed with a low dose of dexamethasone, while observational studies using higher dosage of corticosteroids have not reported any favourable effect on mortality (Hasan et al., 2020).

The observation by Lammers et al. (2020) that early hydroxychloroquine (HCQ) treatment after admission at low dosage (2400mg in total) is associated with a lower risk of admission to an intensive care unit coincides with large observational studies showing a lower mortality rate in patients exposed to HCQ therapy compared to no or other treatment. Of note, in all these studies and in contrast to the RECOVERY trial, low doses of HCQ (<2.5 g in total) were used, often soon after admission (Arshad et al., 2020; Ayerbe et al., 2020; Catteau et al., 2020; COVID-19 RISK and Treatments (CORIST) Collaboration, 2020). Another recent large cohort study of patients on low-dose HCQ for inflammatory disorders reported an association between chronic HCQ use and reduced mortality following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Gentry et al., 2020).

As highlighted by the findings of Lammers et al. (2020), the timing of HCQ therapy (administration within 1 day of admission) could explain discrepancies between different studies. In the RECOVERY trial, the median time between symptoms onset and randomisation was 9 days and a substantial proportion of patients (16.7%) was already on mechanical ventilation at randomisation (The RECOVERY Collaborative Group, 2020).

HCQ has been used as an anti-inflammatory drug for decades as a therapy for inflammatory disorders and its impact on inflammatory responses is well documented. HCQ inhibits the production of the pro-inflammatory cytokines interleukin (IL)-6, tumour necrosis factor-alpha (TNF-α), and IL-1-β by activated macrophages (Sperber et al., 1993; Jang et al., 2006), which are notoriously associated with COVID-19 severity (Del Valle et al., 2020; Webb et al., 2020) and also the production of chemotactic cytokines involved in the recruitment of pro-inflammatory cells in the lungs (Grassin-Delyle et al., 2020). Consistent with this, an Italian study suggests that the benefit of HCQ is restricted to patients with elevated C-reactive protein levels (COVID-19 RISK and Treatments (CORIST) Collaboration, 2020).

Thrombotic events are another well-recognised complication of severe COVID-19 (Llitjos et al., 2020) and the presence of lupus anticoagulant has been reported in hospitalised COVID-19 patients (Bowles et al., 2020). HCQ therapy has been associated with a decrease of lupus anticoagulant levels as well as of platelet activation and thrombotic events in lupus patients (Broder and Putterman, 2013). Interestingly, B cell abnormalities similar to those reported in autoimmune disease such as active lupus were reported in patients with severe COVID-19 (Woodruff et al., 2020).

HCQ has no antiviral activity *in vivo* against SARS-CoV-2 as shown in pre-clinical models such as in Syrian hamsters, non-human primates and in human lung cells, and should therefore not be used as an antiviral therapy in COVID-19 (Maisonnasse et al., 2020). However, to further understand the positive effects observed in large observational studies that used HCQ off-label in the early months of the pandemic, the hypothesis of an anti-inflammatory action should not be discarded. We suggest that ongoing trials evaluating HCQ specifically look at its effect on inflammatory parameters with add-on studies if necessary. In the same vein, ongoing trials are investigating colchicine to prevent hospitalisation in SARS-CoV-2-infected subjects, and the rationale is based on anti-inflammatory properties that are partly shared by HCQ, i.e. inhibition of pro-inflammatory cytokines and chemotaxis of pro-inflammatory cells (Ben-Zvi et al., 2012; Parra-Medina et al., 2020).

Conflict of interest

N.D. and E.B. are members of the Belgian Task Force for the Writing of Therapeutics Guidance for COVID-19 in Belgium. No other COI to declare.

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