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LETTER TO THE EDITOR

Comment on: "Pharmaco-Immunomodulatory Therapy in COVID-19"

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Dear Editor

We read with great interest the review by Rizk et al. [1] on pharmaco-immunomodulatory therapy in coronavirus disease 2019 (COVID-19) in which they extensively discuss the pathophysiological rationale and the available data (as of 8th of July 2020) on these treatments. The novel severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) pandemic has literally urged bench and clinical researchers to not only think "out of the box" but also to utilise treatments, especially in early 2020, based only on pathophysiological assumptions rather than data on randomised control trials (RCTs) or at least observational studies. Therefore, during the first semester of 2020, a vigorous everlasting scientific exchange of information was held often leading to a total reversal of "current best-practice".

As early clinical and laboratory data accumulated, the role of over-inflammatory response to SARS-CoV-2 infection has been speculated to be implicated in adverse complications and patient outcomes [2]. Expectedly, based on its pathophysiological properties, among other potential treatments, colchicine has been hypothesised to be of benefit [3, 4]. Indeed, a series of RCTs evaluating colchicine have been announced in late March 2020 in clinicaltrials.gov for both in-patients and out-patients suffering from COVID-19 [3].

Therefore, waiting for the results of RCTs, a wide discussion on colchicine clinical aspects was conducted. Although one could not pathophysiologically support a protective role of colchicine for SARS-CoV-2 infection, upon the announcement of colchicine as a potential treatment for established COVID-19 and given the available subsets of patients in the community already on chronic colchicine treatment, a large retrospective study provided real-life data proving that COVID-19 rates were comparable among patients on- or off- such medication [1, 5].

On the other hand, Cure et al. [6] supported that colchicine was not only ineffective in COVID-19 patients, but could also exert a negative effect. However, one-by-one the arguments posed by Cure et al. have been seriously challenged by Parra-Medina et al. [7], Kobak [8] and Piantoni et al. [9]. Unfortunately, this is not clearly presented in the review by Rizk et al. [1] therefore providing a misleading picture. In particular, acute respiratory distress syndrome has been reported only after toxic doses of colchicine (i.e. 80 mg of colchicine or 1.6 mg/kg; 15–20 mg or 0.25–0.3 mg/kg) while common therapeutic doses in gout and utilised in COVID-19 protocols are in the range of a total dose of 1–1.5 mg per day (not per kg; i.e. 20- to 80-times lower doses) [4, 7]. Further, to the best of our knowledge, there is no evidence that colchicine at therapeutic doses may reduce the release of surfactants by affecting alveolar type II pneumonocytes. In support of our argument, no references are cited by Cure al [6] or by Rizk et al. [1], who include this statement. Conversely, in a pre-print by Dupuis et al. (17 July 2020; https://doi.org/10.21203/rs.3.rs-43204/v1), colchicine was administered in an experimental study and authors reported a reduced acute lung injury and improved blood oxygenation by reducing lung neutrophil recruitment in rats pre-treated with colchicine.

Further, GRECCO-19 was a prospective, open-label RCT, which evaluated the effects of colchicine (on top of standard medical treatment; at that time mainly hydroxy-chloroquine plus azithromycin) on 105 hospitalised patients with COVID-19 [10]. Study results became available on the 24th of June 2020, i.e. after the authors declared last day of literature search. GRECCO-19 was the first published RCT on the effects of colchicine in COVID-19 and showed a beneficial effect. In particular, patients under colchicine treatment had

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statistically significantly improved time to clinical deterioration, mainly driven by less need for invasive mechanical respiratory support. Moreover, a potential antithrombogenic effect was observed as colchicine attenuated maximum D-dimer levels [10]. Indeed, adverse events, with the exception of the expected gastrointestinal side effects of colchicine (none of which were serious), were comparable between the two groups [10]. On top of these findings, more recently, the COLCORONA study (NCT04322682) has officially been reported to have passed futility test in interim analyses. Therefore, we shall await with great interest results from COLCORONA study.

As a conclusion, first RCT data on colchicine in COVID-19 are rather encouraging, while the Hippocratic rule "first do no harm" is undeniably supported by available data.

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Declarations

Conflict of interest Authors declare that they have no conflict of interest.

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