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LETTER TO THE EDITOR

Authors' Reply to Vrachatis et al. "Pharmaco-Immunomodulatory Therapy in COVID-19"

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Dear Editor,

We would like to thank Vrachatis et al. [1] for their interest in our paper entitled "Pharmaco-Immunomodulatory Therapy in COVID-19" [2] and for expressing their concerns.

In their letter to the editor [1], Vrachatis et al. noted that the use of colchicine at therapeutic doses is generally safe and effective for the management of severe acute respiratory syndrome coronavirus 2-associated coronavirus disease 2019 (COVID-19), and is unlikely to result in toxicities in this patient population. These findings are supported by the GREECO-19 study (NCT04326790), a Greek open-label, randomized trial [3]. In this study, 55 patients received colchicine plus standard treatment (hydroxychloroquine or chloroquine and azithromycin) and 50 received standard treatment alone. Colchicine was given as a loading dose of 1.5 mg followed by 0.5 mg after 1 h (reduced to a single 1 mg dose in those receiving azithromycin) and followed by a maintenance dose of 0.5 mg twice daily (reduced to 0.5 mg once daily in those weighing < 60 kg) until hospital discharge or for a maximum of 21 days. The GREECO-19 study was published in JAMA Network Open on the 24 June 2020, 2 days after we submitted our paper to the journal *Drugs* for peer review. We stated that the cutoff date of literature review was 8 July 2020, because some studies were added to the manuscript during the short period of revision and resubmission based upon the reviewers' comments and suggestions [2]. We agree that this important study is relevant and thank Vrachatis et al.

Although we agree that colchicine is a potentially effective treatment for COVID-19, there are certain situations where the use of colchicine should be carefully handled. Of note, colchicine has a narrow therapeutic index between efficacy and toxicity [4]. Although rare, toxic effects of colchicine occur in settings that impair colchicine excretion, such as hepatic impairment, renal failure, and interacting co-medications [5]. Colchicine toxicity initially presents as gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea), which may clinically progress into respiratory failure, acute respiratory distress syndrome (ARDS), bone marrow suppression and pancytopenia, rhabdomyolysis, renal failure, metabolic acidosis, and cardiac dysrhythmias [6].

Besides pneumonia and ARDS, COVID-19 may cause damage to many other organs, including the liver and kidneys [7]. In healthy subjects, colchicine is known to be excreted in urine [5]. The presence of impaired renal

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function is known to be associated with colchicine toxicity. In patients with end-stage renal disease undergoing dialysis, total body clearance of colchicine is reported to be reduced by 75%. Similarly, liver dysfunction may result in significantly reduced clearance and prolonged plasma half-life [5]. Thus, dose adjustment is necessary for these patients. In the setting of acute gout, a maximum dose of 3 mg, instead of a traditional dose of 6 mg, should be used in those who weigh less than 50 kg and those with co-existing renal or hepatic disease [8, 9]. Additionally, published cases of death have been reported at doses as low as 7 mg [10, 11].

Colchicine is a substrate of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) [12]. The US Food and Drug Administration (FDA) label for colchicine mentions that the use of colchicine in patients with renal or hepatic impairment receiving P-gp inhibitors or potent CYP3A4 inhibitors is contraindicated due to potential toxicities and fatalities [5]. A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function who are receiving interacting drugs. Co-administration of colchicine and lopinavir/ritonavir is expected to increase colchicine concentrations. In fact, ritonavir (100 mg twice daily) has been shown to significantly increase colchicine maximum concentration (C_{max}) (2.7-fold) and area under the concentration–time curve (AUC) (3.5-fold) when given with a single dose of colchicine (0.6 mg) [13]. In addition, colchicine C_{max} and AUC are also expected to increase when co-administered with a macrolide (e.g., clarithromycin or azithromycin), cyclosporine, some azole antifungals (e.g., fluconazole), and calcium channel blockers (e.g., diltiazem, verapamil) [4], and cases of fatal colchicine toxicities in patients with renal insufficiency have been reported [14].

It seems reasonable in our practice to consider the dosing regimen presented in the GREECO-19 study as a quite benign therapy for COVID-19 patients with no renal or hepatic impairment with potentially some benefits. We anxiously await the results of COLCORONA (NCT04322682), a phase 3, randomized, double-blind, placebo-controlled study that is expected to enroll 6,000 patients. With the potential benefits of colchicine for pericardial disease, acute myocardial infarction [15], and now for COVID-19, colchicine appears to be much more than just an agent for acute gouty arthritis and potentially has profound cardiovascular benefits.

Declarations

Conflict of interest JGR, CJL, YR, DNF report no conflicts of interest to disclose relative to this research. KKZ has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, Ardelyx, ASN (American Society of Nephrology), Astra-Zeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, IFKF (International Federation of Kidney Foundations), ISH (International Society of Hemodialysis), International Society of Renal Nutrition and Metabolism (ISRNM), JSDT (Japanese Society of Dialysis Therapy), Hospira, Kabi, Keryx, Kissei, Novartis, OPKO, NIH (National Institutes of Health), NKF (National Kidney Foundations), Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, VA (Veterans' Affairs), Vifor, UpToDate, ZS-Pharma. MRM reports consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticus, Roivant, Baim Institute for Clinical Research and Intrexon (Triple Gene).

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