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Colchicine as a potent anti-inflammatory treatment in COVID-19: can we teach an old dog new tricks?

The recent pandemic has called for urgent treatment solutions for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-infected patients. Undeniably, the pathophysiological process of coronavirus disease-19 (COVID-19) is yet to be revealed. Although the clinical life-threatening hallmark is acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), systemic COVID-19 complications may also develop. Myocardial injury appears to be a major adverse development even in the absence of pre-existing cardiovascular disease.[1] While the most apparent mechanism of myocardial injury would be an imbalance of oxygen supply and demand due to ARDS/ALI, histologically diagnosed myocarditis by SARS-CoV-2 has been described,[2] while a cytokine storm, vascular inflammation/endothelial dysfunction, increased sympathetic activity/stress cardiomyopathy, or even true type I acute coronary events as a result of plaque disruption by the aforementioned factors could also play a role. While awaiting data regarding the exact mechanism of action of SARS-CoV-2, data for SARS-CoV are implicating NLRP3 inflammasome activation initiated by viroporin E, a SARS-CoV-2 component.[3]

Exploration of drugs already introduced into clinical practice inevitably leads to consideration of the potential of colchicine. This is an inexpensive, lipid-soluble alkaloid which within 24–72 h of oral administration accumulates in granulocytes and monocytes (in multiple concentrations in comparison with plasma levels) with ensuing anti-inflammatory effects. Recently, colchicine has been recognized as an inhibitor of NLRP3 inflammasomes and mitigating interleukin activation.[4] During the previous decade, several studies have shed light in the potential cardioprotective effects of colchicine in various clinical settings such as pericarditis, prevention of atrial fibrillation (post-cardiac surgery and post-ablation procedures), and even in the acute phase of myocardial infarction.[5–8]

Therefore, it was reasonable that, among others, colchicine would be tested in the context of COVID-19. Indeed, at the present time, four randomized studies regarding colchicine in COVID-19 patients have been announced: (i) COLCORONA (ClinicalTrials.gov Identifier: NCT04322682) will recruit 6000 high-risk outpatients half of whom will be administered colchicine for a month and will assess the composite endpoint of need for hospitalization or mortality; (ii) GRECCO-19 [9] (Clinical Trials.gov Identifier: NCT04326790) will recruit 180 COVID-19 diagnosed patients who will be administered colchicine for up to a maximum of 21 days and will evaluate its effect on prevention of complications (C-reactive protein, troponin, clinical course); (iii) 'Colchicine Efficacy in COVID-19 Pneumonia' (ClinicalTrials.gov Identifier: NCT04322565) will assess whether colchicine will result in clinical improvement in a randomized fashion (n = 100); and, finally (iv) the 'The ECLA PHRI COLCOVID' Trial (ClinicalTrials.gov Identifier: NCT04328480) aims to recruit 2500 COVID-19 hospitalized patients who will receive colchicine co-administered (or not) with lopinavir/ritonavir.

Should colchicine be successful in altering the adverse clinical course or even ameliorate COVID-19 complication is to be proved, keeping the words of William Shakespeare in mind 'New friends may be poems but old friends are alphabets. Don't forget the alphabets because you will need them to read the poems'.

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References

1. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.1017.
2. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F, Paolucci S, Pelenghi S, Iotti GA, Mojoli F, Arbustini E. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020;doi: 10.1002/ejhf.1828.
3. Castaño-Rodriguez C, Honrubia JM, Gutiérrez-Álvarez J, DeDiego ML, Nieto-Torres JL, Jimenez-Guardeño JM, Regla-Nava JA, Fernandez-Delgado R, Verdia-Báguena C, Queralt-Martín M, Kochan G, Perlman S, Aguilella VM, Sola I, Enjuanes L. Role of severe acute respiratory syndrome coronavirus viroporins E, 3a, and 8a in replication and pathogenesis. *MBio* 2018;**9**:e02325-17.
4. Misawa T, Takahama M, Kozaki T, Lee H, Zou J, Saitoh T, Akira S. Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome. *Nat Immunol* 2013;**14**:454–460.
5. Vrachatis DA, Giannopoulos G, Deftereos SG. Colchicine: conventional and contemporary indications. *Curr Pharm Des* 2018;**24**:647–647.
6. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;**381**:2497–2505.
7. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, Sianos G, Goudevenos J, Alexopoulos D, Pyrgakis V, Cleman MW, Manolis AS, Tousoulis D, Lekakis J. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation* 2015;**132**:1395–1403.
8. Deftereos S, Giannopoulos G, Papoutsidakis N, Panagopoulou V, Kossyvakis C, Raisakis K, Cleman MW, Stefanadis C. Colchicine and the heart: pushing the envelope. *J Am Coll Cardiol* 2013;**62**:1817–1825.
9. Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, Gargalianos P, Giamarellou H, Gogos C, Daikos G, Lazanas M, Lagiou P, Saroglou G, Sipsas N, Tsiodras S, Chatzigeorgiou D, Moussas N, Kotanidou A, Koulouris N, Oikonomou E, Kaoukis A, Kossyvakis C, Raisakis K, Fountoulaki K, Comis M, Tsiachris D, Sarri E, Theodorakis A, Martinez-Dolz L, Jorge S-S, Reimers B, Stefanini GG, Cleman M, Filippou D, Olympios CD, Pyrgakis VN, Goudevenos J, Hahalis G, Kolettis TM, Iliodromitis E, Tousoulis D, Stefanadis C. The GReek study in the Effects of Colchicine in COvid-19 complications prevention (GRECCO-19 study): rationale and study design. *Hellenic J Cardiol* 2020;doi: 10.1016/j.hjc.2020.03.002.

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