Correspondence on 'Anti-inflammatory therapy for COVID-19 infection: the case for colchicine'

It is well recognised that hyperinflammation induced by SARS-CoV-2 is a major cause of disease severity and mortality in infected patients and many of the proposed treatments include agents currently used in rheumatologic clinical practice.[1] One critical question, however, is which anti-inflammatory drugs are most appropriate. Among the most traditional non-biological anti-inflammatory therapies, corticosteroids appear to provide some benefit in advanced stages of the disease,[2] but concerns may arise from immunosuppression induced during viral replicative phase. On the contrary, no data are available on possible effects of non-steroidal anti-inflammatory drugs (NSAIDs).

In their interesting paper,[3] Reyes *et al* highlighted the potential anti-inflammatory role of colchicine in COVID-19. The primary mechanism of action of colchicine is tubulin disruption leading to down-regulation of multiple inflammatory pathways.[4] Among these, colchicine is able to impair platelet aggregation and leucocyte migration through an action on adhesion molecules,[5] effect shared with NSAIDs, including salicylates.[6 7] However, another important anti-inflammatory effect of colchicine, not described for NSAIDs, derives from its ability to inhibit the NLR family pyrin domain containing 3

(NLRP3) inflammasome with consequent reduction of proinflammatory cytokines.[4] It is for this reason that colchicine is currently used to treat and prevent classical inflammasome activation disorders, including gout.[8 9]

We agree that colchicine may represent an inexpensive drug, without significant immunosuppressive effect, potentially able to prevent severe COVID-19. However, Reyes questioned about three critical points: timing for treatment, optimal dosing and duration of colchicine therapy. Although we cannot have certainty, we believe that possible answers should be found by the combination of rheumatologic clinical experience and pathogenic knowledge on COVID-19.

It is conceivable that colchicine may be less effective in advanced phases of the disease, but difficulty in identifying a clear cut-off between early and advanced disease suggests that a benefit may be observed not only in outpatients to prevent hospitalisation, but also in inpatients to reduce intensive care admission. On the basis of this idea, the Italian Society of Rheumatology promoted two different ongoing randomised trials, approved by Italian Medicines Agency, investigating the effects of colchicine in reducing the rate of either entering critical stage in hospitalised patients with moderate disease (COLVID-19, EudraCT number: 2020-001475-33) or hospitalisation in outpatients (CHOICE-19, EudraCT number: 2020-001806-42).

Identification of optimal colchicine dose deserves some considerations. The narrow therapeutic index of colchicine makes critical the balance between efficacy and adverse events.[10] Dosing importance is supported by experimental data showing that colchicine, at low concentrations, inhibits expression of E-selectin on endothelial cells and prevents neutrophil adhesion.[4] At high concentrations, however, it promotes shedding of L-selectin from neutrophils and prevents further recruitment, thereby potentially reinforcing the anti-inflammatory activity of the drug.[4] Interestingly, administration of 1.8 mg colchicine to healthy subjects decreases platelet activity markers and inhibits leucocyte-platelet aggregation, but not homotypic platelet aggregation.[11] This suggests that colchicine in clinically relevant concentrations may have beneficial cardiovascular effect by targeting platelet-inflammatory axis, with possible reduction of COVID-19 thrombotic complications by interfering with inflammation without increasing the bleeding risk observed with traditional platelet-directed therapies.

The strong inflammation degree induced by SARS-CoV-2 appears to be comparable to that observed in gout flares that are treated with 1.8 mg colchicine according to the American College of Rheumatology (ACR) guidelines and 1.5 mg colchicine according to the European League Against Rheumatism (EULAR) recommendations.[8 9] It is also important to remind that the low-dose colchicine after myocardial infarction trial, using a daily dose of 0.5 mg in patients after myocardial infarction, resulted in reduction of coronary revascularisation and stroke, but not significant c-reactive protein decrease.[12]

Thus, our protocols have been designed adopting a dosage of 0.5 mg three times a day that appears to be the best agreement to ensure good therapeutic efficacy and minimal gastrointestinal toxicity. In fact, the proportion of patients who experienced diarrhoea or other adverse effects with this therapeutic schedule is rather low.[10]

Regarding treatment duration, colchicine has a satisfactory safety profile when used for less than 5 weeks for the management of gout flares and familial Mediterranean fever, and there is a wealth of safety data with continuous decade-long use in these conditions.[13] For gout flare prevention, the US Food and Drug Administration (FDA)-approved dose is 0.6–1.2 mg/day.[4] On the basis of these suggestion, we chose the daily dosage of 1.5 mg for the entire study in the COLVID-19 protocol and only for the first week in the CHOICE-19 study, followed by a preventive treatment with 1 mg/day for other 3 weeks, dose usually adopted for the prevention of gout flare.[9]

In conclusion, we agree that an old anti-rheumatic drug, such as colchicine, may be useful to treat COVID-19, but we have to wait for conclusive results from ongoing trials. However, we also think that the large experience gained by rheumatologists over years in using this and other anti-rheumatic drugs should be taken into account in approaching new COVID-19 treatments.

Carlo Perricone ,[1] **Elena Bartoloni** ,[1] **Giacomo Cafaro** ,[1] **Roberto Caporali**,[2] **Roberto Gerli** [1]

[1]Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[2]Department of Clinical Sciences and Community Health, ASS G Pini, University of Milan, Milano, Italy

Correspondence to Professor Roberto Gerli, Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy; roberto.gerli@unipg.it

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ORCID iDs
Carlo Perricone http://orcid.org/0000-0003-4771-6981
Elena Bartoloni http://orcid.org/0000-0003-4776-2136
Giacomo Cafaro http://orcid.org/0000-0003-1774-1916
Roberto Gerli http://orcid.org/0000-0002-4684-575X

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