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SHORT COMMUNICATION

HIGH COLCHICINE DOSES ARE REALLY SILVER BULLETS AGAINST COVID-19

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Abstract. *The numerous attempts to prove a therapeutic effect of low-dose colchicine for the treatment of Coronavirus disease-2019 (COVID-19) have been discouraging. Increase of doses, however, leads to accumulation in leukocytes and inhibition of the cytokine storm thus preventing COVID-19 complications and hospitalizations. Hospital mortality drops up to 7-fold, while outpatients practically do not reach hospitalization.*

Key words: *COVID-19, colchicine, NLRP3 inflammasome, cytokine storm, colchicine toxicity*

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Given the multiple anti-inflammatory and anti-COVID-19 effects of colchicine *in vitro*, several case reports, more than 50 observational studies and randomized clinical trials, small randomized noncontrolled trials and retrospective cohort studies, meta-analyses, were initiated to test its healing effect *in vivo*, leading to conflicting, rather negative results [1]. Colchicine effectiveness in treating COVID-19 continues to be assessed to this day [2]. What all these scientific studies have in common is that they are within the limits of low doses of colchicine. All of these studies concluded that additional investigations are necessary [1-3].

The world's largest randomized controlled trial (RCT) investigating the treatment of COVID-19 is the RECOVERY trial (The RECOVERY Trial is registered at ISRCTN50189673; EU Clinical Trials Register: EudraCT 2020-001113-21; Clinical Trials.gov: NCT04381936). Their analysis of 11,162 randomized patients concluded that "colchicine was not associated with reductions in 28-day mortality…" [4]. Based on this definitive conclusion the World Health Organization (WHO) placed colchicine in the group of anti-COVID-19 drugs with "*strong recommendation against*". It is very important to note that, again, only low doses of colchicine were used. If the RECOVERY team had repeated the clinical trial of Terkeltaub et al. involving low and high doses of colchicine, the results would have been radically different [5]. We believe that, however, as many trials of low-dose colchicine continue, this statement will not disprove Einstein's rule that "Insanity is doing the same thing over and over and expecting different results" [3].

In our opinion, testing different doses of colchicine for the treatment of COVID-19 is imperative for the following reasons [1].

It is well recognized that the cytokine storm (CS) induced by SARS-CoV-2 is a major cause of pneumonia, acute respiratory distress syndrome, multiorgan damage and death. The CS is due to hyperactivation of the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome, which can be activated either directly or indirectly by SARS-CoV-2. Viral replication or infection does not cause tissue injury. Rather, this change is the result of hyperactivation of the NLRP3 inflammasome pathway. Thus, the main molecular target for controlling COVID-19 complications

should be the NLRP3 inflammasome [1, 3]. Colchicine has a number of anti-inflammatory effects, including inhibition of the NLRP3 inflammasome, and it is useful mainly in treating diseases associated with neutrophils and monocytes/macrophages (i.e. the innate immune system) rather than those of the adaptive immune system [6]. Very importantly, leucocytes accumulate colchicine! Thus, the intracellular neutrophil colchicine concentration may be more than 16-fold greater than the peak concentration in plasma [6]. In infected alveolar-resident human macrophages, which drive COVID-19 pathology [7], colchicine inhibits the overactivation of the NLRP3 inflammasome [6]. This finding suggested that an increase in clinically used colchicine doses within acceptable limits may still be sufficient for the suppression of the NLRP3 inflammasome, which is expressed largely in cells of the myeloid lineage [1, 3, 8].

Considering this, beginning in March 2020, we started administrating higher doses of colchicine. We assumed that a safe increase in the colchicine dose required to reach micromolar concentrations in leukocytes would result in NLRP3 inflammasome/CS inhibition. We demonstrated that in 785 inpatients treated with increasing doses of colchicine, mortality decreased sevenfold [8]. Among COVID-19 outpatients, nearly 100% of the colchicine-treated patients escaped hospitalization. In addition, post-COVID-19 symptoms were significantly less common in patients treated with colchicine.

Usually, we use the following formula for loading dose: [(0.5 mg per every 10 kg) -0.5 mg], which is 0.04 mg/kg but does not exceed 5 mg/day. The maintenance dose is half the loading dose [8]. In support of the effectiveness and safety of our treatment regimen, we have described three patients who mistakenly administered very high doses of colchicine. Remarkably, taking a single overdose of 15 mg colchicine over 10 hours, without any additional therapy, resulted in complete recovery from bilateral pneumonia and pericardial effusion. In the other two outpatient cases (12.5 mg colchicine for the first 24 hours), the symptoms resolved within three days [9].

ARE HIGHER DOSES OF COLCHICINE DANGEROUS?

The administration of higher doses of colchicine expectedly increased the incidence of diarrhea, but sometimes the choice is high doses of colchicine and diarrhea but alive or dead without diarrhea [3, 8]. These doses have been used extensively in the past without life-threatening side effects for the treatment of gout or familial Mediterranean fever [1, 3, 5, 10]. Of the thousands of outpatients and inpatients treated with our regimen, we have not had a single case of colchicine intoxication. The deaths described in the distant past with colchicine doses of 7-7.5 mg have been due to drug interactions. When administering colchicine, special attention should be given to patients with liver and kidney damage or incompatible drug interactions [1, 3, 10].

CONCLUSIONS

The CS can be caused by a number of infectious and non-infectious etiologies, including Influenza H5N1 virus, Influenza H1N1 virus, Influenza A and B viruses, Parainfluenza virus, SARS-CoV-1, MERS-CoV, Ebola, etc., through hyperactivation of the NLRP3 inflammasome. It is very likely that higher doses of colchicine will be a successful therapeutic approach in these cases as well [3].

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