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Letter to the Editor

Should we still consider colchicine in treating patients with COVID-19?

Dear Editor,

The COVID-19 pandemic is still a serious health problem until now. Patients with severe coronavirus disease (COVID-19) commonly experienced a cytokine storm, characterized by elevated level of inflammatory biomarkers[1]. A wide range of clinical manifestations, uncertain pathogenesis, and the absence of effective drugs for treating COVID-19 encourage the use of different off-label drugs. Given the lack of a specific treatment for COVID-19, several drugs including antiviral, anti-inflammatory, and immunomodulatory agents, are used to combat the novel coronavirus. One of the drugs that has been proposed to treat COVID-19 is colchicine. It has been used to reduce inflammation in gout arthritis for many years, and now it is being evaluated as an alternative treatment for COVID-19[2]. It prevents neutrophil chemotaxis, attachment and motility, and limits superoxide production. Moreover, it inhibits the nucleotide binding domain (NOD)-like pyrin domain 3 (NLRP-3) inflammasome and releases IL-1β. At relatively low concentrations (3 μg/ml), it promotes dendritic cell maturation, cytokine formation, and the presence of antigens against allogeneic $CD4^+$ lymphocytes[3,4].

The study related to the benefit of colchicine to be used against COVID-19 in Indonesia is rare. However, a study related to the role of colchicine in reducing the degree of inflammation in COVID-19 patients in Indonesia was reported by Prabowo and Apriningsih[5]. The study stated that administration of colchicine for seven days at a dose of 0.5 mg twice daily significantly reduce the levels of neutrophil lymphocyte ratio (NLR) and High sensitivity c-reactive protein (HsCRP) (p-value <0.05). However, the study did not report the concomitant therapy of COVID-19 and the absence of comorbidities that affected the severity of COVID-19. Furthermore, the study did not report the mortality rate during the observation period.

A meta-analysis and meta-regression study by Nawangsih et al[6] reported that colchicine could reduce mortality in COVID-19 patients, although this benefit decreased with age. However, this study was conducted in three RCTs and five observational studies with varying doses and duration of colchicine, and therefore this study should be interpreted with caution. The RECOVERY trial, a large RCT study conducted in three countries, including Indonesia, reported that colchicine was not associated with lower 28-day mortality, length of hospital stay, risk of mechanical ventilation or death in hospitalized patients with COVID-19. Colchicine with a dose of 1 mg was given immediately after randomization, followed by 500 mcg 12 hours later and then 500 mcg twice daily for a total of 10 days or until discharge[7]. This is an alarm for us not to use colchicine as a routine therapy for the treatment of COVID-19 patients. Interestingly, it was supported in a meta-analysis study by De-Miguel-Balsa et al[8] published in the European Review for Medical and Pharmacological Sciences, stated that colchicine did not reduce mortality in COVID-19 patients. The study consisted of six observational and five RCT studies and the effect of colchicine on reducing mortality was only found in observational studies but not in RCTs. It may explain in observational studies that several factors cannot be controlled by the researcher such as dose and duration of colchicine, concomitant therapy of COVID-19, comorbidity, severity of COVID-19, etc., and thus lead possible bias.

Unlike glucocorticoids, colchicine does not have an intrinsic immunosuppressive effect that can increase the risk of secondary infection in COVID-19 patients. While colchicine is effective in various chronic inflammatory diseases, its lack of benefit in COVID-19 has been attributed to its effect on intracellular pH. Its effect on intracellular pH is dynamic, and as a result, it fails to raise intracellular

Corresponding Author: Oki Nugraha Putra, MD; e-mail: oki.nugraha@hangtuah.ac.id

pH to a level that inhibits virus binding to ACE2[9]. To conclude, due to limited information about the effectiveness of colchicine in treating patients with COVID-19 especially in Indonesia, the use of colchicine must be carried out considering the risks and benefits. If there is a side effect of diarrhea, the dose of colchicine should be adjusted to 0.5 mg/day. In addition, caution is required when using colchicine in patients with renal impairment[10]. Since the liver and intestine metabolize colchicine by the cytochrome P450 3A4/5 and P-glycoprotein p (P-gp), respectively, concomitant use of drugs that inhibit these protein increases the risk of colchicine toxicity[11]. Until now, it has not been included as standard therapy for treating COVID-19 patients in Indonesia. A randomized, double blind, placebo-controlled trial is needed to prove its effectiveness and safety against COVID-19 in the Indonesian population.

Conflict of Interest

The authors declare no conflicts of interest.

References

1) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan Gm Xu J, Gu X, Vheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
2) Reyes AZ, Hu KA, Teperman J, Muskardin TLW, Tardif JC, Shah B, Pilinger MF. Anti-inflammatory therapy for COVID-19 infection: the case for colchicine. Ann Rheum Dis 2021; 80: 550-557.
3) Rodrigues TS, de Sa KSG, Ishimoto A, Becerra A, Oliviera S, Almeida L, Goncalves AV, Perucello DB, Andrade WA, Castro R, Veras FP, Toller-Kawahisa JE, Nascimento DC, de Ilma MHF, Silva CMS, Caetite DB, Martins RB, Castro IA, Pontelli MC, de Barros FC, do Amaral NB, Giannini MC, Bonjorno LP, Lopes MIF, Santana RC, Vilar FC, Martins MA, Assad RL, de Almeida SCL, de Oliviera FR, Batah SS, Siyuan L, Benatti MN, Cunha TM, Alves-Filho JC, Cunha FQ, Cunha LD, Frantz FG, Kohlsdorf T, Fabro AT, Arruda E, de Oliveira RDR, Junior PL, Zamboni DS. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med 2021; 218: 20201707.
4) Martinez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis 2018; 269: 262-271.
5) Prabowo NA, Apriningsih H. Colchicine reduces the degree of inflammation on COVID-19 patients. IOP Conf Ser: Earth Environ Sci 2021; 824: 012087.
6) Nawangsih EK, Kusmala YY, Rakhmat II, Handayani DR, Juliastuti H, Wibowo A, Lim MA, Pranata R. Colchicine and mortality in patients with coronavirus disease 2019 (COVID-19) pneumonia: A systematic review, meta-analysis, and meta regression. Int Immunopharmacol 2021; 96: 10772.
7) Horby PW, Campbell M, Spata E, Emberson JR, Staplin N, Pessoa-Amorim G, Peto L, Wiselka M, Wiffen L, Tiberi S, Caplin B, Wroe C, Green C, Hine P, Prudon B, George T, Wight A, Baillie JK, Basnyat B, Buch MH, Chappell LC, Day JN, Faust SN, Hamers RL, Jaki T, Juszczak E, Jeffery K, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Mafham M, Haynes R, Landray MJ. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. Lancet Respir Med 2021; 9: 1419-1426.
8) De-Miguel-Balsa E, Estevan-Ortega R, Sempere-Selva MT, Latour-Perez J, Baeza-Roman A, Moya-Martinez A, Ramos-Rincon JM. Can we still consider treatment effective in SARS-COV-2 infection? Systematic review, meta-analysis, and trial sequential analysis. Eur Rev Med Pharmacol Sci 2021; 25: 7151-7161.
9) Cure MC, Kucuk A, Cure E. Colchicine may not be effective in COVID-19 infection; it may even be harmful? Clin Rheumatol 2020; 39: 2101-2102.
10) Scarsi M, Piantoni S, Colombo E, Airó P, Richini D, Miclini M, Bertasi V, Bianchi M, Bottone D, Civelli P, Cotelli MS, Damiolini E, Galbassini G, Gatta D, Ghirardelli ML, Magri R, Malamani P, Mendeni M, Molinari S, Morotti A, Salada L, Turla M, Vender A, Tincani A, Brucato A, Franceschini F, Furloni F, Andreoli L. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis 2020; 79: 1286-1289.
11) Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. Circ Res 2019; 124: 1568-1583.

O.N. Putra, S. Sofia, A. Widad, C.R. Oktaviani

Department of Clinical Pharmacy, Study Program of Pharmacy, Hang Tuah University, Surabaya, East Java, Indonesia