


## Colchicine treatment in community healthcare setting to prevent severe COVID-19

We read with interest the article from Scarsi and colleagues about the efficacy of colchicine in hospitalised patients with severe COVID-19.<sup>1</sup> Colchicine is an 'old drug' originally approved for the treatment of gout and subsequently repositioned in numerous disease settings characterised by systemic inflammation and uncontrolled activation of the innate immune response.<sup>2,3</sup> During the recent outbreak of SARS-CoV-2 infection, uncontrolled release of major proinflammatory cytokines such as interleukin (IL)-1 and IL-6 soon emerged as a major pathological feature of COVID-19 as well as a predictor of patients' morbidity and mortality.<sup>4,5</sup>

Based on this evidence, hospitalised patients with severe COVID-19 are currently being treated with anti-cytokine biological drugs including the IL-1 receptor antagonist anakinra, the anti-granulocyte-macrophage colony-stimulating factor mavrilimumab and the IL-6 receptor blockers tocilizumab and sarilumab.<sup>6-9</sup> Yet, although these targeted approaches have provided encouraging results in preliminary retrospective cohorts, they do not seem to induce a prompt recovery as optimistically expected, likely because administered at a later stage of the disease when irreversible organ damage is already established.<sup>6-10</sup> Hence, if there is any rationale to use anti-inflammatory therapies in COVID-19, timely treatment before the establishment of full-blown systemic inflammation becomes imperative in order to prevent respiratory failure, to relieve pressure on healthcare infrastructures and ultimately to impact disease mortality.

Scarsi *et al* report a 20% improvement in the survival rate at 21 days in patients treated with colchicine compared with the local standard of care.<sup>1</sup> Despite potential caveats related to a more frequent use of glucocorticoids in patients treated with colchicine and to an unusually high overall mortality rate (37%) compared with other international cohorts, the authors provide important evidence on the ability of colchicine to interfere with established COVID-19-related inflammation.<sup>11-14</sup> In this sense, in order to gain clues about the optimal window for therapeutic success, it would have been informative to report the time from symptoms onset to colchicine administration and to correlate it with patient outcome. In a recent experience on domiciliary patients, for instance, we successfully administered colchicine after a median of 8 days of influenza-like symptoms and after 3 to 5 days of spiking fever despite acetaminophen or antibiotic treatment.<sup>15</sup> In our study, colchicine was used in patients with a hyper-inflammatory phenotype clinically characterised by persistent high fever in order to intercept 'cytokine storm' early in its rampant phase, to prevent establishment of lung damage, and to avoid hospitalisation due to COVID-19 progression.<sup>15</sup> Identifying the right therapeutic window where anti-inflammatory treatment might perform better is, indeed, not a trivial concern since early colchicine administration could impair physiological immune response to SARS-CoV-2 while late administration might not be as effective on established acute respiratory distress syndrome. Patients included in the active arm by Scarsi and colleagues, in fact, showed advanced respiratory impairment (mean PaO<sub>2</sub>/FIO<sub>2</sub> ratio of 176.6 mm Hg/%) and their mortality rate was still considerable when compared with other cohorts even if treated with colchicine (16%).<sup>11-14</sup> Hence, based on their prime experience, we would be grateful if the authors could share more details about the timing of colchicine administration in their study and insights into the best hypothetical window of opportunity for this promising therapeutic approach.

While Italy is slowly getting out of the pandemic's grip, given its safety profile, widespread use and affordable costs, colchicine may provide an additional therapeutic option in areas where SARS-CoV-2 infection is rapidly spreading and healthcare systems are overwhelmed such as in South America, Africa and India. In the absence of effective antivirals and vaccines for SARS-CoV-2, results of large randomised controlled trials in both inpatient and outpatient settings are eagerly awaited to confirm the use of colchicine in the current and future COVID-19 outbreaks.

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