RHEUMATOLOGY

Letter to the Editor (Other)

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Why not to use colchicine in COVID-19? An old anti-inflammatory drug for a novel auto-inflammatory disease

Rheumatology key message

- Colchicine: an old anti-inflammatory drug for the SARS-CoV-2 induced auto-inflammatory disease.

Dear Editor, Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) infection disease (COVID-19) is a novel disease identified in a cluster of pneumonia in the Wuhan province (China), which has taken on pandemic proportions. Italy has been the most affected country in Europe with 119 827 cases up to 4 April 2020. Despite aggressive containment efforts, the number of cases is rapidly increasing. A wide range of clinical manifestations are seen in patients with SARS-CoV-2 from mild, moderate, to severe and progressive disease (acute respiratory distress syndrome and multi-organ failure). Leukopenia, lymphopenia with an hyperactivation of T cells, and thrombocytopenia were found in more than 40% of the COVID19 patients followed up in nine studies [1]. These data suggested that a cytokine storm syndrome takes place during the course of the disease to favour viral clearance, with subsequent effects on circulating blood cells. It was also reported that patients requiring admission in intensive care units displayed high circulating levels of pro-inflammatory cytokines, suggesting that the cytokine storm was associated with disease severity. A recent retrospective analysis of predictors of mortality highlighted the role of ferritin and IL-6 as potential biomarkers, strengthening the hypothesis that hyperinflammation could lead to a worse prognosis [1].

Currently, there is no specific treatment for the disease.

We read with great interest the editorial by Lucchino B. and colleagues [2], suggesting that COVID-19 represents the first example of an infectious disease that can be successfully treated with anti-rheumatic drugs. Anti-rheumatic drugs, such as chloroquine/hydroxychloroquine (immunomodulatory agents), tocilizumab (anti-IL-6 receptor monoclonal antibody), adalimumab (anti-tumor necrosis factor alpha monoclonal antibody) and ruxolitinib (Janus kinases 1 and 2 inhibitor) are in use or investigated for the treatment of COVID-19 [2]. IL-1 blockade is used in rheumatologic diseases that display a systemic inflammation together with an excessive secretion of pro-inflammatory cytokines (such as IL-1, IL-6 and IL-18) which is at the basis of disease complications such as haemophagocitic lymphohistiocytosis syndrome (HLH). Considering the hypothesis that COVID-19 in its worst manifestations resembles a secondary, viral-driven HLH, a rationale for the use of IL-1 blockade with anakinra (IL-1 receptor antagonist) was postulated and trials are underway. The key mediator of IL-1 family cytokine is NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome, which is an innate immune signalling complex responsible for the response against infections and is assembled in response to upstream intracellular sensors of pathogens. Furthermore, IL-1 was demonstrated to be involved in neutrophil recruitment during inflammatory responses in the lung. Colchicine, a tricyclic alkaloid extracted from plants of the genus Colchicum, is another drug that was demonstrated to display an inhibitory effect on this complex. Colchicine is used in a wide range of auto-inflammatory conditions such as gout, familial Mediterranean fever, Behçet's disease, recurrent idiopathic pericarditis, but also other inflammatory and fibrotic conditions such as coronary artery disease [3]. Other interesting mechanisms of action of colchicine are the capacity to bind to tubulins, blocking the assembly and polymerization of microtubules, the inhibition of neutrophil chemotaxis, and the decrease in superoxide production [3]. Recent *in vitro* studies demonstrated the relevance of the functionality of microtubules in the process of the first steps of human coronavirus infection into susceptible cells [4]. Furthermore, there are *in vivo* examples of the use of colchicine for the inhibition of virus replication and reduction of airway inflammation in rats [5]. From a clinical point of view, several experiences demonstrated that colchicine was efficacious in viruses-related manifestations. It was successful in the long-term outcome of Epstein Barr/Citomegalovirus myocarditis [6] and of the Influenza B-related pericarditis [7]; it was effective also for the treatment of interstitial autoimmune-related pneumonia [8].

In our opinion, colchicine could have a place in the treatment of COVID-19 as evidence for the role of auto-inflammation in the disease course is accumulating. In the light of the failure of anti-viral drugs in severe COVID-19 [8], there is a need to search for drugs with a wide availability, low cost, and a well-known safety profile, derived from decades of use in clinical practice. To the best of our knowledge, no reports have been published about the use of colchicine in patients with COVID-19 yet.

In conclusion, immunomodulatory properties and anti-viral effects were demonstrated for colchicine . There is, therefore, a rationale to consider colchicine as a therapeutic option in those patients who have contraindications to other drugs or in the context of shortage/unavailability of anti-viral drugs (such as in

underdeveloped countries). Selection of patients and timing of colchicine administration would be crucial factors in designing studies about its use in COVID-19. A more precise clustering of patients based on markers of autoinflammation is needed. The use of colchicine could be promising in the early phase of COVID-19, prior to the development of a full-blown hyperinflammatory status that might require the use of targeted treatments. This potential application of colchicine should be verified in properly designed clinical trials.

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