



## Letter to the Editor

# Biological therapy as an alternative treatment for cytokine release syndrome in patients with COVID-19<sup>☆</sup>

## Terapia biológica como tratamiento alternativo al síndrome de liberación de citocinas en pacientes con COVID-19

Mr. Editor,

At the end of the year 2019, the world heard about the emergence of a viral disease in China that in a few days had spread throughout the rest of the Asian continent until it was considered by the World Health Organization (WHO) a pandemic that has affected the 5 continents and impacted negatively all aspects of the life of the people, both from a biological point of view as well as in the personal, social and economic aspects.<sup>1</sup> The disease, called COVID-19, has become the health event of 2020 and has affected more than 5 million people, of whom more than 340,000 have died.<sup>2</sup>

According to data from the WHO, 13.8% of the patients had severe respiratory failure, while 6.1% experienced a critical situation.<sup>3</sup> The first reports of the disease announced a respiratory-type infectious process as the main cause of respiratory distress and failure, for which a leading role was assigned to the use of hydroxychloroquine and azithromycin. Subsequently, it was identified that the respiratory involvement was generated due to the increased production of inflammatory cytokines combined with local coagulation disorders.<sup>4</sup>

The increased production of proinflammatory cytokines was called cytokine release syndrome (CRS), among these, interleukin 1 $\beta$  (IL-1 $\beta$ ), IL-6, induced protein-10 and monocyte chemoattractant protein, known as MCP-1 stand out. These cytokines, in addition to being found in positive patients, show an extremely high concentration in patients with severe disease in comparison with less severe cases of the disease. Based on these discoveries, the therapeutic schemes turned

towards the control of the inflammatory process. Three biological drugs capable to inhibit IL-6 and IL-1 $\beta$ : tocilizumab, anakinra and ruxolitinib stand out in this context.<sup>3</sup>

It is important to note that there are other components involved in CRS, including inflammasomes and tumor necrosis factor-alpha, which play a fundamental role in the activation of the trans and JAK-STAT3 pathways and in the perpetuation of the cytokine storm. In this sense, a series of drugs, such as colchicine, anakinra, tofacitinib, anti-TNF biologic drugs and baricitinib, among others, are being experimented. However, there are no reports of their use in patients with severe disease due to COVID-19.<sup>3</sup>

Tocilizumab is a biological drug approved by the Food and Drug Administration and whose main prescription is for the treatment of patients with rheumatoid arthritis and juvenile idiopathic arthritis.<sup>5</sup> Its mechanism of action includes the blockade of soluble and insoluble IL-6 receptors. In studies conducted in animal models, it has also been identified that it inhibits the nuclear factor kappa-B and the perpetuation of IL-6, thus reducing the circulating volume of IL-6 and therefore the generation of T lymphocytes and the union of the latter with the dendritic cells.<sup>3</sup> However, its use in patients with severe COVID-19 disease is based on the results of clinical trials related to CRS inhibitor drugs. Currently there is no consensus in this regard, so the author considers it appropriate to wait for the ongoing studies to evaluate the effectiveness of tocilizumab in COVID-19.

In the case of anakinra and ruxolitinib, their main indications are focused on the control of the markers of the macrophage activation syndrome/hemophagocytic lympho-

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histiocytosis (MAS/HLH). It has been reported that these processes and their laboratory markers are elevated in patients with severe COVID-19 disease.<sup>3</sup> Anakinra is a version of the human IL-1 receptor antagonist that competitively inhibits the binding of IL-1 with its receptor. Its use in patients with severe COVID-19 disease has shown significant improvement in the survival of patients with superimposed sepsis and activation of MAS/HLH.<sup>6</sup>

The indication of ruxolitinib is considered a necessary action to inhibit small molecules of kinases; its action not only includes the blockade of IL-6 activation signals, but it is also capable to block interferon activation signals, thus opening a range of possibilities for the treatment of the MAS/HLH as a serious complication in patients with COVID-19.<sup>7,8</sup>

Other biological drugs, such as interferon  $\gamma$  inhibitors have been started to be used recently in order to control the CRS and its relentless consequences in the patients with COVID-19 who are seriously or critically ill.<sup>3</sup> However, a reasonable period of time must still elapse to allow the accumulation of data and results that faithfully reflect the real role of biological therapy and its benefits in patients with severe disease. The study of the mechanisms of action of these drugs and the experimental outcomes, as well as the little reference that exists on their use, show a favorable path, but the last word has yet to be said. However, the current results have prompted the Chinese specialists and scientists of the Health Commission to suggest the incorporation of these drugs in the protocols of action against serious complications of the disease.<sup>3,9</sup>

The management of biological therapy is common in the daily work of specialists in rheumatology; this situation makes it easier for the rheumatologist to approach the CRS that causes complications in patients with severe COVID-19 disease. For this reason, it is considered that, due to their experience in the use of this type of drugs, their knowledge in the management of sustained inflammatory processes and the comprehensive management of the patients, the specialists in rheumatology constitute one of the groups of health professionals with greater preparation and capacity to care for patients with severe illness due to COVID-19.

The disease continues to be an enigma for health professionals, there is still much to investigate and learn about its pathophysiological, clinical and therapeutic characteristics, but giant steps had been taken with the identification of pharmacological groups that theoretically and practically improve the state of health of patients and allow the recovery from serious disease states, thus reducing mortality from COVID-19.

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