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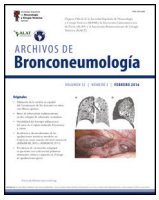

Editorial

Biologic Therapy in COVID-19

Terapia biológica para la COVID-19

Coronavirus (CoV) encompasses a family of viruses responsible for respiratory infections in humans that clinically range from the common cold to a severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and the newly discovered coronavirus disease 2019 (COVID-19). The latter disease is caused by a new coronavirus called SARS-CoV-2.[1]

Most individuals infected by COVID-19 are asymptomatic or have mild symptoms including dry cough, fever, asthenia, widespread pain, nasal congestion, diarrhea, loss of taste or smell. Unfortunately, COVID-19 may yield severe pneumonia with significant lung inflammation, acute respiratory distress syndrome (ARDS), and heart and kidney involvement. It occurs more commonly in people older than 65–70 years, immunosuppressed patients, and those with comorbidities such as obesity, diabetes, hypertension, and heart failure.[2,3] In this regard, some patients develop a cytokine storm with a cytokine release syndrome that resembles as macrophage activation syndrome (MAS). With respect to this, the term MAS-like is used to refer to the syndrome associated with infection by the SARS-CoV-2 virus. Patients with MAS-like experience rapid pulmonary deterioration due to a bilateral pneumonitis about a week after the onset of symptoms. The occurrence of a severe alveolar exudate and the damage caused by an abnormal local inflammatory immune response are likely to lead to hypoxemia and death of the patient. Moreover, a hypercoagulative state, especially in critically ill patients leading to life-threatening thrombotic complications, inflammatory pneumonitis and lung fibrotic changes have also been reported in patients who had previously experienced severe respiratory involvement in the acute phase of the disease.[4]

The immune response plays a key role in the control and resolution of the disease. The innate immunity detects the virus, mainly, through Toll-type receptors, retinoic acid inducible gene I (RIG-I)-like and Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). Some NLRs are activators of a multiprotein complex known as an inflammasome that activates proinflammatory caspase-1, which in turn produces activation of interleukin (IL)-1β and IL-18 (proinflammatory cytokines of the IL-1 family).[5] There is an important relationship between the severity of the disease and the exaggerated production of proinflammatory cytokines, the recruitment of proinflammatory macrophages and granulocytes, also due to the alteration of this immune response.[6] This state of high inflammation is characterized by an excessive elevation of acute phase reactants such as C-reactive protein (CRP) and ferritin, which causes an increase of proinflammatory cytokines such as IL-6 or IL-1.[7] As in a MAS in the context of autoimmune conditions, such as adult Still's disease, systemic juvenile idiopathic arthritis and systemic lupus erythematosus, in patients with severe involvement of the SARS-CoV-2 virus, other laboratory alterations such as thrombopenia, lymphopenia and an increase in D-dimer are often present.[8,9]

Taking all these considerations together and based on often preliminary data or clinical experience, physicians have used immune-modulatory treatments such as interleukin (IL)-6 and IL-1 antagonists, commonly prescribed to individuals with autoimmune and inflammatory rheumatic diseases. The most commonly biologic/small molecules used in patients with severe COVID-19 are shown below.

Anti-IL6. Tocilizumab (TCZ). It was the first recombinant humanized anti-human monoclonal antibody directed against soluble and membrane-IL-6 receptors (IL-6R). TCZ inhibits the binding of IL-6 to its receptors, thus reducing this cytokine's pro-inflammatory activity by competing with both the soluble and membrane-bound forms of the IL-6R.[4] TCZ prevents the interaction of IL-6 with both the IL-6R and the signal transducer glycoprotein 130 complex. It leads to inhibition of both the cis- and trans-signaling cascades involving the Janus kinase (JAK)-signal transducer and the activator of transcription (JAK-STAT) pathway.[10] TCZ initiation after adequate nonselective immunosuppressive therapy, such as pulses of methylprednisolone or a prednisone-based combination of immunosuppressants, has shown efficacy for adult onset Still disease-associated MAS.[7] Rheumatologists have carried out the off-label use of TCZ in interstitial lung disease secondary to rheumatological conditions, in particular in systemic sclerosis.[11] Data from Chinese patients suggest that TCZ improves the clinical outcome immediately in severe and critical COVID-19 patients, being an effective treatment to reduce mortality.[12] Like in other countries such as in Italy, TCZ has been used in different Spanish centers in patients with severe complications, including ARDS.[4] Real-word experience with TCZ, mostly given in an early inflammatory phase, has shown a rapid resolution of fever and improvement of respiratory function and chest imaging changes, as well as the progressive reduction of inflammatory parameters such as CRP and ferritin. Our own experience also supports these observations in patients with bilateral pneumonia and severe respiratory insufficiency.[4] Other anti-IL-6 agents (such as siltuximab and sarilumab) are under investigation in on-going COVID-19 clinical trials in different countries.[4]

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Anti-IL-1 therapy. Anakinra is a recombinant human IL-1 receptor antagonist that has shown benefit in patients with autoimmune diseases-associated MAS.[7] It has also been used in severe COVID-19 patients and in some protocols, it was considered as second-line therapy in these patients.[4] Again, our own experience supports its use in these cases. Unpublished observations by intensive care physicians highlight the rapid and beneficial response related to its use.

Baricitinib. It is a JAK inhibitor useful to block the viral entry into pneumocytes because they target members of the numb-associated kinase (NAK) family, including associated protein kinase-1 (AAK1) and cyclin G-associated kinase (GAK), which are both involved in viral endocytosis. Baricitinib reduces systemic inflammatory responses and cytokine production by inhibiting the JAK-STAT pathway. It may be useful in the treatment and prevention of the cytokine dysregulation associated with COVID-19 since as it could affect the host inflammatory response and viral entry into cells.[13]

Anti-tumor necrosis factor (TNF)-α agents and other therapies. Since TNF-α is an important mediator of acute and chronic systemic inflammatory response, leading to the production of other cytokines and chemokines, anti-TNF- α therapy has been widely used in inflammatory arthritides. Some investigators consider that anti-TNF-α agents could be useful in COVID-19.[14] However, we have no experience in the use of anti-TNFα therapy in this type of patients. It is also the case for other therapies that are used in patients with autoimmune diseases such as intravenous immunoglobulin (IVIg). Since the anti-inflammatory effect of IVIg predominates over its immunosuppressive effect,[15] as occurred with autoimmune diseases where it is difficult to establish a differential diagnosis between autoinflammatory/autoimmune disease and intercurrent infections, IVIg therapy may be considered in COVID-19 patients with bacterial superinfection associated. Recently, four patients with a confirmed diagnosis of SARS-CoV2 infection and severe pneumonia or acute respiratory distress syndrome (ARDS) have been treated with up to 4 infusions of eculizumab, an anti-complement C5a human antibody, showing all of them a marked clinical improvement within the first 48 h after the first administration of eculizumab, including a 82-old woman with several comorbidities.[16]

Finally, there are more than 150 clinical trials on biologic therapy in COVID-19 in progress nowadays (https://www.clinicaltrials.gov/ct2/home).

In summary, based on our experience in the management of autoimmune diseases with biologic therapies and new small molecules, we strongly support the use of these agents in COVID-19 patients with severe disease or in those patients who experience a rapid deterioration due to the development of a MAS-like hyperinflammatory state.

Conflict of Interests

MA Gonzalez-Gay has received grants/research supports from Abbvie, MSD, Jansen and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbvie, Pfizer, Roche, Sanofi, SOBI, Lilly, MSD and Novartis. S Castañeda is assistant professor of cátedra UAM-Roche (EPID-Future), Universidad Autónoma de Madrid (UAM), Madrid. J Ancochea is Director of Cátedra UAM-Roche (EPID-Future), Universidad Autónoma de Madrid (UAM), Madrid, Spain.

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