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Point of view about biologic therapy in covid-19.

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Abstract

COVID-19 (Corona virus Disease firstly reported in December 2019) is a complex and heterogeneous disease whose clinical spectrum ranges from asymptomatic cases or with mild symptoms to severe acute respiratory distress syndrome, with/without heart and kidney involvement, especially in people with comorbidities. Treatment we use today is quite empirical, depending on the severity of the disease, associated risk factors and access to medication. In severe cases, a combination of potent anti-cytokine monoclonal antibodies associated to low-dose dexamethasone and remdesivir and/or favipiravir is recommended. Here, we review the clinical evidence and indications of main biologic therapy in the treatment of COVID-19 patients.

Keywords: Coronavirus, COVID-19, Acute respiratory distress syndrome, Interleukin-6, Interleukin-1, tocilizumab, Anakinra, Canakinumab, Baricitinib.

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Point of View about Biologic Therapy in Covid-19

Coronaviridae (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 firstly reported in Wuhan (China) in December 2019 (COVID-19). This latter disease is caused by a new coronavirus called SARS-CoV-2 [1]. Since the first cases were described, the pandemic has spread worldwide, affecting more than 20 million people, and causing around a million deaths to date.

Although most individuals infected by COVID-19 are asymptomatic or have mild symptoms, COVID-19 may frequently yield severe pneumonitis, acute respiratory distress syndrome (ARDS), and heart and kidney involvement, especially in aged people, immunosuppressed patients, and those with comorbidities such as obesity, diabetes, hypertension and heart failure [2,3]. Additionally, a hypercoagulability state, particularly in critically ill patients leading to life-threatening thrombotic complications have also been reported [4,5].

Currently, there is no completely effective therapy, and until first vaccines are available, there is an unrestrained race in search of an effective and safe treatment applicable to the general population. Certainly, the treatment we use today is quite empirical, depending on the severity of the disease, the associated risk factors and access to medication, all of which has generated enormous confusion in the general population, even among physicians. Overall, clinical guidelines and daily practice recommend using chloroquine/hydroxychloroquine and lopinavir/ritonavir in mild cases; remdesivir and dexamethasone/hydrocortisone (5-10 days maximum) in moderate cases; and remdesivir, dexamethasone and biologics in severe cases. Here, we will briefly discuss the biologic therapy used in COVID-19 patients.

Indeed, the immune response plays a key role in the control and resolution of the disease. The innate immunity detects the virus through Toll-type receptors, retinoic acid inducible gene I (RIG-I)-like and Nucleotide binding oligomerization domain (NOD) like receptors (NLRs). Some NLRs activate inflammasome triggering the production of proinflammatory caspase-1, which in turn stimulates the production of interleukin (IL)-1β and IL-18 [6]. In severe cases, a state of acute hyperinflammation occurs with the release into the medium of a large amount of pro-inflammatory cytokines, situation named as cytokine storm syndrome (CSS), and giving rise to an exaggerated pathological hyperimmune response which can often cause pneumonitis, fibrotic lung changes in the long run, and even the death of the patient who suffers it. These cytokines/mediators include interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8(CXCL8), IL-10, IL-17, IL-25, IL-33, IL-37, IL-38, GCSF, GM-CSF, MCP-1, IFN-γ, IFN-α, TRAIL, MCSF and TNF-α among others [7]. Of all of them, the best targets in COVID patients are IL-1 and IL-6.

IL-6 inhibition

The greatest accumulated experience in COVID therapy is with tocilizimab (TCZ). Tocilizumab is a recombinant humanized monoclonal antibody directed against both soluble and membrane-

IL-6 receptors (IL-6R). TCZ reduces the pro-inflammatory activity of IL-6, which is particularly increased in patients with COVID-19 and has been related to severity of the disease and pulmonary involvement [8]. 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 [9]. As well, real-word experience with TCZ, mostly given in early inflammatory stages, has shown a rapid resolution of fever and improvement of respiratory function and chest imaging changes, and the progressive reduction of inflammatory parameters such as C-reactive protein and ferritin. A recent meta-analysis confirms these data demonstrating the efficacy of TCZ in severely ill COVID-19 patients [10]. Thus, TCZ is currently considered the election biologic for patients with ARDS and severe systemic or lung involvement. Other IL-6 blocking agents (such as sarilumab and siltuximab) have demonstrated similar efficacy in this kind of patients [4,5].

IL-1 inhibition

Anakinra (ANK) is a recombinant human IL-1 receptor antagonist that has shown benefit in patients with severe inflammatory manifestations of autoimmune diseases [11]. Iglesias-Julián et al. recommend using high dose subcutaneous ANK to treat ARDS secondary to CSS among severely ill COVID-19 patients [12]. In a recent study comparing 9 COVID-19 ARDS-CSS patients with a cohort of 18 patients treated with TCZ and selected by propensity score matching, favorable outcome in median PaO2/FiO2 ratio was achieved in 55.6% and 88.9% of the ANK and TCZ cohorts, respectively [12]. Noteworthy, aminotransferase levels significantly increased in the TCZ group. Thus, ANK may be a potential alternative to TCZ for patients with elevated aminotransferases, and in non-responders to TCZ, especially in severely ill COVID-19 patients [12]. A recent study (the three C study) has shown that canakinumab, another IL-1 antagonist, may also improve to patients with myocardial injury and increased lung inflammation associated to SARS-CoV 2 [13]. In another study in ten hospitalized adult patients with COVID-19 and bilateral pneumonia, hyperinflammation and respiratory failure, canakinumab was safe, well tolerated, and associated with a rapid reduction in the systemic inflammatory response and an improvement in oxygenation [14]. In addition, all patients had also received hydroxychloroquine (200 mg twice daily) and the antivirals lopinavir-ritonavir [14].

Other biologics and advanced therapies

Some investigators consider that anti-tumor necrosis factor (TNF)-α agents could be useful in COVID-19. However, we have no experience with 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, IVIG therapy may be considered in COVID-19 patients with bacterial superinfection associated. A recent review found low-certainty evidence of the therapeutic effectiveness and safety of convalescent plasma or hyperimmune immunoglobulin for people with COVID-19 [15].

Baricitinib is a JAK inhibitor that 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 also viral entry into cells [16]. However, results with baricitinib in COVID-19 patients are still contradictory.

Another hopeful approach in COVID therapy is the complement pathway inhibition. In fact, there are different studies testing the efficacy of several antagonists of this pathway such as omalizumab that binds to the CH3 domain [7], eculizumab, an anti-complement C5a (complement 5) human antibody [17], and ravulizumab, an anti-C5 humanized antibody used to treat paroxysmal nocturnal hemoglobinuria in adults, with promising results [18].

In summary, the therapeutic strategy in patients with COVID-19 is challenging and not well established yet. In light of the knowledge accumulated throughout this year, we propose the triple combination of a monoclonal antibody associated to low-dose dexamethasone and remdesivir and/or favipiravir in severe COVID-19 cases such as those with septic shock, ARDS, multi-organic failure or in those patients who experience a rapid deterioration due to the development of a hyper inflammatory state.

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