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Approach to management of SARS-CoV-2 infection

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Management of hyperinflammation in COVID-19 patients

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ABSTRACT

In response to SARS-CoV-2 infection, the immune system physiologically upregulates to try to clear the virus from the body; failure to compensate for this inflammatory response with an anti-inflammatory response leads to dysregulation of the immune system that ultimately leads to a situation of uncontrolled hyperinflammation called cytokine storm. This cytokine storm can cause ARDS or multi-organ failure leading to patient death. This review exposes the different mechanisms of the inflammatory response in COVID-19 infection and the therapeutic options to treat this process.

Keywords: COVID19, corticosteroids, tocilizumab, immunomodulators.

MECHANISMS OF HYPERINFLAMMATION IN COVID-19 INFECTION

Theoretically, it has been proposed that COVID-19 infection can be divided into three phases: early infection phase involving viral replication and mild symptoms; pulmonary phase involving adaptive immunity stimulation and predominance of respiratory symptoms; and hyperinflammation phase involving hyperinflammatory conditions such as ARDS or multiorgan failure (MOF) [1].

Infection is initiated when the spike glycoprotein of SARS-CoV-2 binds to the human angiotensin-converting enzyme-2 (ACE-2) receptor on the cell surface in the epithelial cells of the nasal cavity, respiratory tract and lungs. The virus is also recognized by pattern-recognition receptors on immune cells, which are responsible for the initiation of the host defence

mechanisms. The subsequent production of immune mediators is essential to fight the infection. However, these can be deleterious when produced in excess [2].

Briefly, low levels of the antiviral IFNs and high levels of proinflammatory cytokines (IL-1β, IL-2R, IL-6, IL-7, IL-8, IL-17 and TNF-α) and chemokines (CCL-2, CCL-3, CCL-5, CCL-7, CXCL-10) are produced by various immunological cells. These secretions from pro-inflammatory cells lead to an uncontrolled inflammatory response that plays a key role in the pathogenesis of COVID-19 and worsens the infection (Figure 1) [3].

IMMUNOMODULATORY DRUGS FOR THE TREATMENT OF HYPERINFLAMMATION IN COVID-19 INFECTION

Proinflammatory phase-specific therapeutics include general inflammatory drugs, cytokine inhibitors, JAK-STAT signalling inhibitors, complement pathway inhibitors, immunomodulatory drugs, cell-based therapy, and convalescent plasma therapy [4]. Below we will refer to those treatments that have shown better results to date (Table 1 and Figure 2).

Steroids. Glucocorticoids strongly inhibit the immune system. Glucocorticoids function as glucocorticoid receptor agonists. Binding of the glucocorticoids to the GR activates the receptor to exert anti-inflammatory effects, such as suppressing the production of pro-inflammatory cytokines [5]

The indication for the use of steroids in patients with COVID-19 infection is based on the RECOVERY study, which showed a reduction in 28-day mortality in patients with COVID-19 with mechanical ventilation or oxygen therapy but not in patients without respiratory support [6].

Based on these results, the World Health Organization (WHO) [7] has established two recommendations regarding the use of corticosteroids in COVID-19 patients:

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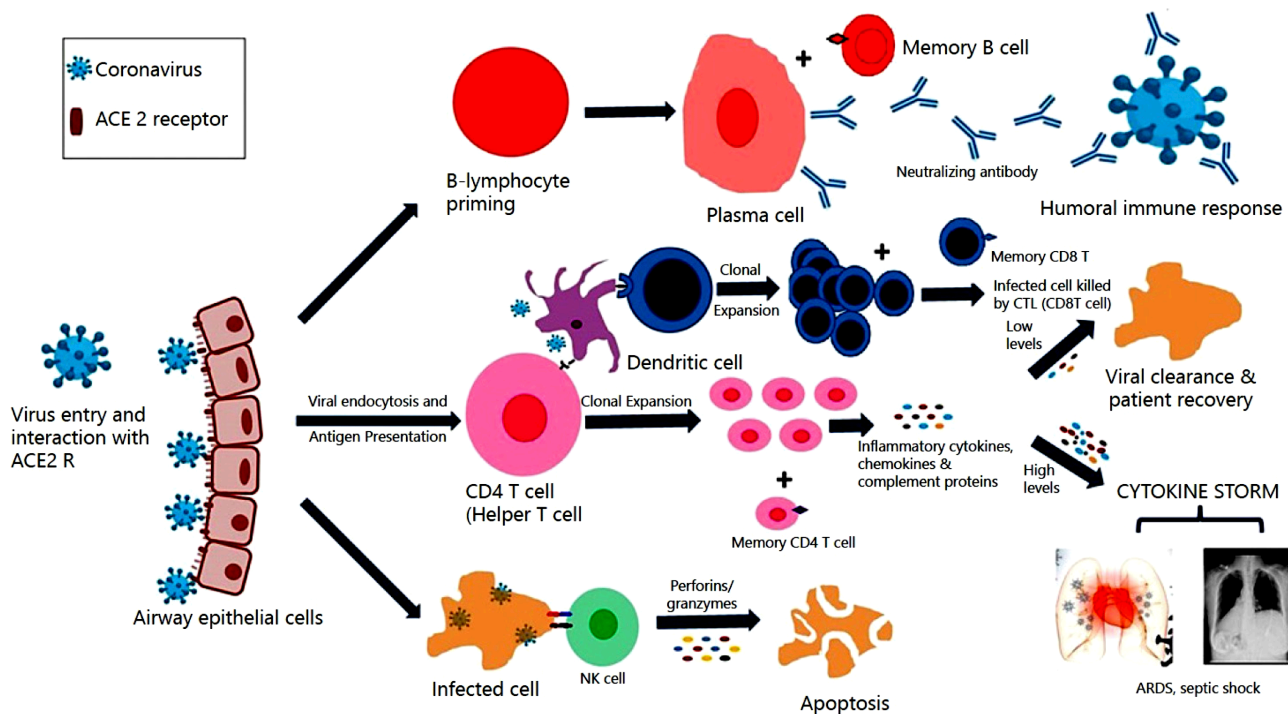E-mail: borjasuberviola1977@gmail.com

Figure 1 | Immune response generation in COVID-19 infection [3] . Reproduced from Mishra KP. Hyperinflammation and Immune Response Generation in COVID-19. © 2020 Karger AG, Basel (https://www.karger.com/Article/FullText/513198)

Table 1 | Immunomodulatory drugs investigated in the treatment of COVID-19 (Adapted and modified from García-Lledó A et al [4])

| Class	Drugs	Currently recommended drugs in Spain*
Corticosteroids	Dexamethasone Methylprednisolone Hydrocortisone Prednisone	Dexamethasone Methylprednisolone, hydrocortisone and prednisone only if dexamethasone is not available
IL-6 inhibitors	Tocilizumab Sarilumab	Tocilizumab Sarilumab only if tocilizumab is not available
IL-1 antagonists	Anakinra Canakinumab	Anakinra
Bruton`s Tirosin Kinase (BTK) inhibitors	Acalabrutinib	
Janus Kinase (JAK) inhibitors	Baricitinib Tofacitinib Ruxolitinib	Baricitinib
TNF inhibitors	Adalimumab Certolizumab Infliximab Etanercept Golimumab	
Anti CD6 monoclonal antibodies	Itolizumab	
C5 complement inhibitors	Ravulizumab	
GM-CSF inhibitors	Lemilumab	

* At the time this document was written.
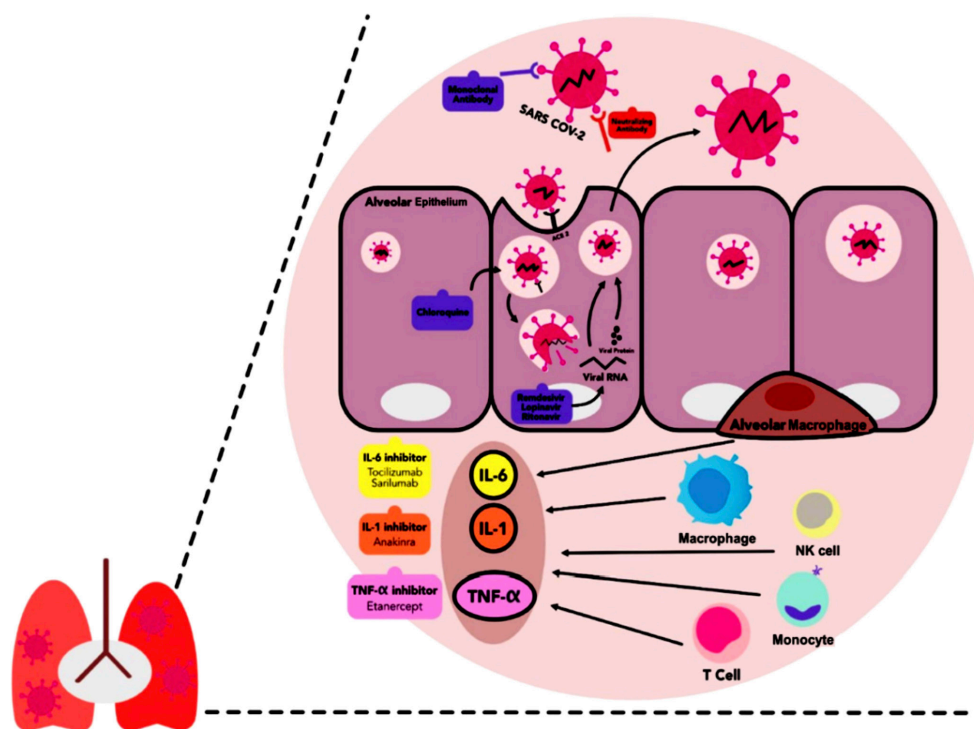
Figure 2 | Mechanisms of action of the main immunomodulatory drugs [14]. Reproduced from Hertanto DM. Immunomodulation as a Potent COVID-19 Pharmacotherapy: Past, Present and Future. 2021 (https://www.dovepress.com/getfile.php?fileID=71836) http://creativecommons.org/licenses/by-nc/3.0/

1. Administration of systemic corticosteroids in preference to no administration for the treatment of severe and critically ill patients (strong recommendation, based on moderate certainty evidence).

2. Refraining from the use of corticosteroids in the treatment of non-critically ill COVID-19 patients (conditional recommendation, based on low certainty evidence).

Regarding the type of corticosteroid to be used, dexamethasone at a daily dose of 6 mg daily for 10 days or until hospital discharge is the drug of choice. Comparison of higher doses of the drug has shown no difference in the results regarding efficacy and safety [8]. If dexamethasone is not available, other glucocorticoids at equivalent doses (total daily doses of hydrocortisone 160 mg, methylprednisolone 32 mg or prednisone 40 mg) may be considered, although the data supporting the use are limited.

IL-6 inhibitors. Tocilizumab, a recombinant humanized monoclonal antibody for IL-6 receptor (IL-6R), exerts therapeutic effects by blocking the binding of IL-6 to IL-6R. Tocilizumab was previously found be effective against the cytokine release syndrome resulting from chimeric antigen-receptor T-cell therapy.

The possible benefit in terms of survival of the use of tocilizumab in patients with COVID-19 infection has been evaluated in different clinical trials and observational studies. However, the indication of its use is based on two of them, the studies RECOVERY and REMAP-CAP. In the RECOVERY study, patients with oxygen saturation <92% or who required oxygen therapy and who had inflammatory parameters defined as C-reactive protein ≥75 mg/L were randomized to tocilizumab versus standard of care. The mortality of both groups was 29% versus 33% p=0.007, (CI 0.77-0.96). In particular, the greatest benefit in mortality was in those patients who concomitantly received corticosteroids. Among patients not receiving invasive mechanical ventilation at baseline, patients assigned to tocilizumab less frequently met the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%, (95% CI: 0.78-0, 93), p=0.0005) [9]. The REMAP-CAP study was focused on patients in the first 24 hours after starting ventilatory support in the ICU. 93% of the patients had received or received corticosteroids within 48h after tocilizumab. Mortality in the selective IL-6 inhibition group was 27% and in the control group 36% [10].

Sarilumab is another IL-6 inhibitor that has been evaluated in clinical trials. The number of patients treated does not

allow conclusions to be drawn and, at this time, it is recommended for use only in patients who for whatever reason cannot receive tocilizumab [11].

Based on the clinical evidence available at the time of writing, the use of tocilizumab concomitantly with dexamethasone is recommended in patients with SatO2 <92% (basal or with low-flow O_2) and CRP >7.5 mg/dL or if the patient requires high-flow O_2, NIMV or MV. Its use is also recommended in patients with worsening despite treatment with dexamethasone [7].

JAK inhibitors. JAK inhibitors suppress the kinase activity of JAKs by competitively binding to the ATP-binding site of JAKs, thereby inhibiting signal transduction of a wide variety of cytokines.In this group of drugs, baricitinib and tofacitinib have obtained positive results in clinical trials. Both drugs have shown a decrease in progression to mechanical ventilation and mortality, independent of concomitant steroid use [12].

IL-1 inhibitors. An IL-1 inhibitor, anakinra, has also shown beneficial effects on clinical progression and mortality in patients with severe pneumonia [4]. In a double-blind clinical trial, the drug demonstrated benefit especially in patients who had elevated suPAR levels (>6 ng/mL), a marker of severity in patients with COVID-19 [13].

CONFLICT OF INTEREST

Authors declare no conflict of interest

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