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Immunomodulation for the management of severe SARS-CoV2 infections. State of the art and review of the literature

Erica Bacca [a, *], Margherita Digaetano [b], Marianna Meschiari [b], Erica Franceschini [b], Marianna Menozzi [b], Gianluca Cuomo [b], Cristina Mussini [a]

[a] Department of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy
[b] Infectious Diseases Clinic, Azienda Ospedaliero-Universitaria Policlinico and University of Modena and Reggio Emilia, Modena, Italy

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ABSTRACT

This Mini Review of the literature aimed to assess the role of tocilizumab for the treatment of severe coronavirus disease 2019 (COVID-19).

Based on the available scientific evidence, it is not clear to date what is the best therapeutic strategy for the treatment of COVID-19. Since SARS-CoV-2 infection stimulates a vigorous proinflammatory response and may cause the so-called "cytokine storm", immunomodulator drugs have been investigated as potential treatment for severe COVID-19 pneumonia. Among immunomodulators, tocilizumab, a recombinant humanized monoclonal antibody directed against IL-6 receptor, seems to be promising. An increasing number of clinical trials are exploring the role of tocilizumab in COVID-19, focusing on outcomes like mortality, risk of intensive care unit admission and the need for mechanical ventilation.

At the moment, there is no conclusive evidence that tocilizumab would be proper outright in all patients with COVID-19 pneumonia, but some studies suggest that its use may be beneficial in selected categories of patients.

1. Introduction

First identified at the end of 2019 in the midst of an outbreak of severe pneumonia in Wuhan City, Hubei Province, China, the new severe acute respiratory coronavirus syndrome 2 (SARS-CoV2) is the causative agent of coronavirus disease 2019 (COVID-19) [1,2]. On January 30, 2020 the WHO declared the COVID-19 epidemic a global health emergency, on March 11, 2020 it was declared a global pandemic (second case after H1N1 influenza in 2009).

The clinical presentation of COVID-19 varies greatly from complete asymptomaticity to severe pneumonia with respiratory failure requiring invasive mechanical ventilation and possibly leading to unfavorable outcome [3]. Although it is difficult to compare mortality rates between different countries due to variable capacity to perform tests and different policies regarding the calculation of deaths, official data seem to show a higher mortality rate in Europe compared to China in the first half of 2020 [4–9].

2. SARS-CoV2 infection and role of the immune system

The pathogenesis of the disease is characterized by a first phase of viral replication that can affect both the high and low airways, and a second phase guided by the inflammatory response.

Viral infections induce a proinflammatory response by promoting the production and release of cytokines and chemokines. Both viral surface proteins, viral RNA and intracellular viral proteins have the ability to induce cytokines expression through the activation of signal transduction cascades involving mediators like the IRF family transcription factors (Interferon regulatory factors), NF-κB (nuclear factor kB) and NF-AT (nuclear factor of activated T cells) [10].

SARS-CoV-2 infection stimulates a vigorous proinflammatory response and may cause an uncontrolled systemic inflammatory response associated with acute respiratory distress syndrome and a state of hypercoagulability whose pathogenesis is not yet fully understood [11,12]. In the most severe cases, the so-called "cytokine storm" develops, characterized by increased production of cytokines that produce long-term damage and fibrosis of lung tissues [13]. The spectrum of proinflammatory cytokines and chemokines induced by SARS-CoV2 include TNF-α, IL-1, IL-2, IL-6, IL-8, IL-17,

* Corresponding author. Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Modena, 41124, Italy.
E-mail address: 53416@studenti.unimore.it (E. Bacca).

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CXCL10 and CCL2 [14,15] [Fig. 1].

3. Therapeutic strategies

Based on the available scientific evidence, it is not clear to date what is the best therapeutic strategy for the treatment of COVID-19 pneumonia, current clinical approaches consider the combination of antivirals and immunomodulatory drugs [16,17].

Among treatments for SARS-CoV2, either approved or investigational, we have chloroquine and hydroxychloroquine (used for the treatment of malaria and autoimmune diseases, these drugs have proven ability to inhibit SARS-CoV2 in vitro, but data from experimental studies showed no clinical benefit); azithromycin alone or in combination with hydroxychloroquine (no demonstrated efficacy of the combination, ongoing azithromycin monotherapy trial); lopinavir/ritonavir and other HIV protease inhibitors (inhibiting viral proteases reduce viral replication, but clinical studies have not demonstrated efficacy in SARS-CoV2); remdesivir (an antiviral drug initially developed for the treatment of Ebola hemorrhagic fever, it has also demonstrated in vitro activity against SARS-CoV2, as well as significant clinical benefits in patients with severe pneumonia); corticosteroids (the use of dexamethasone in patients with severe forms of COVID-19 has proven beneficial); COVID-19 convalescent plasma and neutralizing monoclonal antibodies (several ongoing clinical trials); targeted immunomodulatory treatments (interleukin inhibitors, kinase inhibitors).

Recently published interim results from the Solidarity Therapeutics Trial, supported by the World Health Organization, suggest that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens have little or no effect on overall mortality, initiation of ventilation and duration of hospital stay among COVID-19 hospitalized patients [18].

4. The role of immunomodulation

Systemic inflammation and hypoxic respiratory failure in COVID-19 are associated with increased release of pro-inflammatory molecules, including *C*-reactive protein (CRP), D-dimer, ferritin and cytokines [19]. Viral replication induces the synthesis of several pro-inflammatory cytokines; in particular, the increased production of interleukin 6 (IL-6) by lymphocytes, monocytes, fibroblasts and bronchial epithelial cells has been observed. IL-6 levels can be considered a major marker of severe systemic inflammatory status in patients with SARS-CoV2 infection.

A model for understanding the pathogenesis of SARS-CoV2-mediated harm has been hypothesized to be hemophagocytic syndrome. Hemophagocytic syndrome is a rare life-threatening disease characterized by immune hyperactivation that causes fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, hyperferritinemia and hemophagocytosis in the bone marrow, liver, spleen and lymph nodes. It can be either primary or secondary to malignant tumors, autoimmune diseases (SLE, Still's disease) or infections. Viruses that have been associated with the development of a hemophagocytic syndrome include herpetic viruses (particularly EBV, CMV), the human immunodeficiency virus, but also SARS-CoV and MERS-CoV [20,21].

In view of the similar hyperinflammatory profile, the use of immunomodulatory therapies has been hypothesized for COVID-19, as well as for hemophagocytic syndrome. Drugs involved in the cytokine cascade, specifically, may reduce the impact of the hyperinflammatory state on lung tissue.

To date, anakinra, an IL-1 receptor antagonist, is approved for rheumatoid arthritis and for the treatment of neonatal-onset multisystem inflammatory disease (NOMID), its possible use in COVID-19 is currently under investigation.

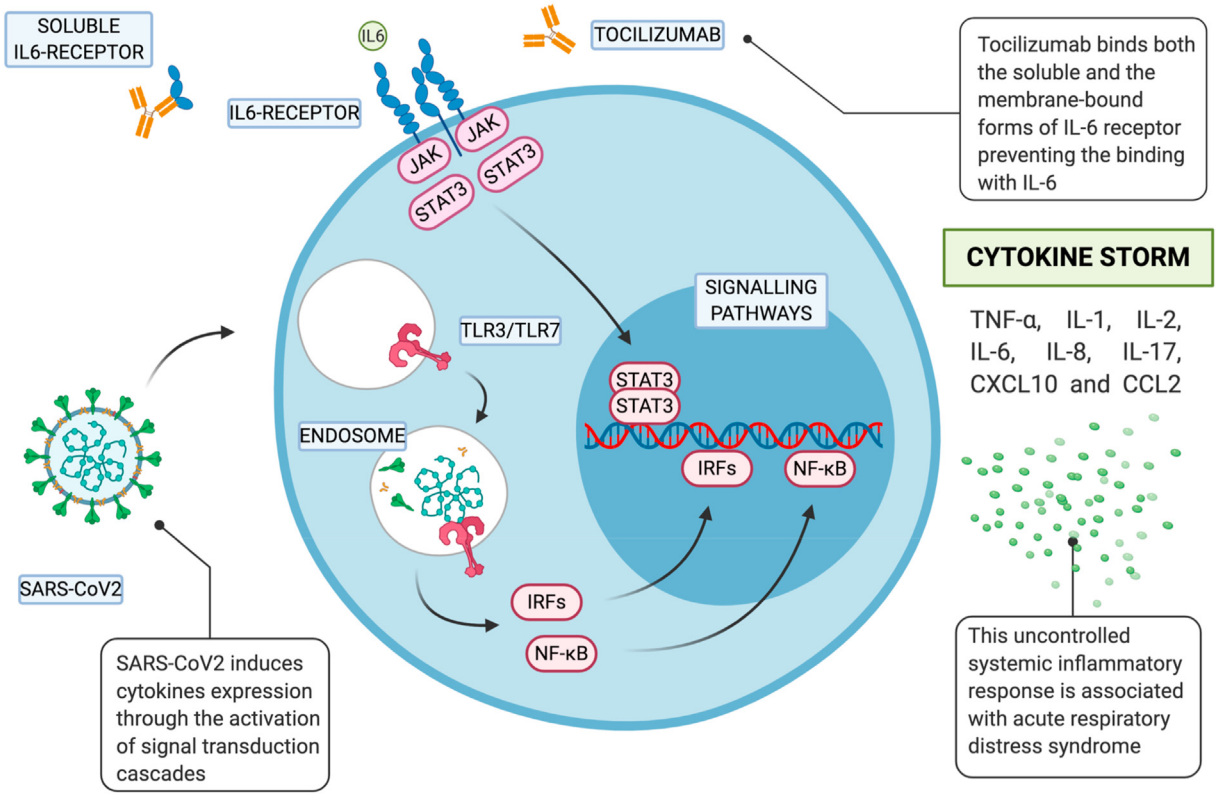

Fig. 1. Intracellular signaling pathways following SARS-CoV2 infection with focus on IL-6 mediated signal transduction and the role of tocilizumab.

Starting with a first Chinese study [22], several drugs active on the IL-6 pathway have been evaluated in clinical trials for the treatment of COVID-19. Among the pathway inhibitors are tocilizumab and sarilumab, the latter being a humanized recombinant monoclonal antibody directed against IL-6 receptor currently approved for use only in patients with rheumatoid arthritis. Tocilizumab is a recombinant humanized monoclonal antibody of the IgG1 class directed against both the soluble and the membrane-bound forms of IL-6 receptor. Tocilizumab is approved for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis and cytokine release syndrome induced by CAR T gene therapies [23] [–] [25].

Based on the pathogenesis of COVID-19 disease and due to the urgency of this pandemic, the hypothesis was suggested to use tocilizumab off-label for the treatment of patients with severe COVID-19 pneumonia, so that in many centers around the world tocilizumab has become one of the current therapeutic options. Although the regimen for these purposes is not definitively established, in order to obtain appropriate plasma levels based on pharmacokinetic data, tocilizumab is preferably administered intravenously at a dose of 8 mg/kg up to a maximum of 800 mg in two administrations 12 h apart. If the intravenous formulation of the drug is unavailable, tocilizumab may also be administered subcutaneously at a dose of 162 mg in two simultaneous administrations, for a total of 324 mg [26,27].

5. Methods

A review of online databases, namely PubMed and Cochrane Library, was conducted until October 22, 2020 using the following search terms: 'SARS-CoV2', 'COVID-19', '2019 nCoV' 'coronavirus', 'pneumonia', 'cytokines', 'cytokine storm', 'tocilizumab', 'roactemra', 'sarilumab'.

All studies comparing the clinical efficacy of tocilizumab and its comparators for the treatment of COVID-19 pneumonia were included. Due to the limited scope of the Mini Review, systematic reviews and meta-analyses were not included.

6. Results and discussion

Tocilizumab has been the subject of an increasing number of observational studies, nevertheless, since data from randomized clinical trials are conflicting and most of them unpublished, current international guidelines from regulatory agencies [28,29] recommend against the use of tocilizumab except in the context of a clinical trial.

Randomized, double-blind, phase III placebo-controlled trials (REMDACTA, COVACTA, EMPACTA) have been launched to assess the safety and efficacy of tocilizumab in combination with the standard of care in hospitalized patients with severe COVID-19 pneumonia compared to the standard of care plus placebo. ROCHE press release on the subject of the COVACTA study stated that although it showed a reduction in hospitalization time in patients treated with tocilizumab, it did not reach its primary endpoint of clinical improvement, nor its secondary endpoint of mortality reduction [30]. The EMPACTA study conducted in ethnic minorities showed preliminary results meeting the primary endpoint of reduction of mechanical ventilation by day 28, although no difference in mortality was observed at day 28 and other key secondary endpoints were not met as well [31]. The REMDACTA study, which began on May 28 and is also close to completing enrolment, aims to evaluate the safety and efficacy of the combination of tocilizumab and remdesivir in patients hospitalized with severe COVID-19 pneumonia [32].

Several clinical studies show the efficacy of tocilizumab in reducing inflammation markers and the need for oxygen supplementation, suggesting that its use in patients with severe forms of COVID-19 pneumonia may reduce mortality rates [26,33] [–] [37]. Among these, a multicenter observational retrospective study conducted in the Hospitals of Modena, Reggio Emilia and Bologna on 544 patients with severe pneumonia has provided evidence that the use of tocilizumab in patients with severe COVID-19 pneumonia reduces the risk of invasive mechanical ventilation and death significantly [26]. In a recent French randomized clinical trial enrolling COVID-19 non-ICU hospitalized patients requiring oxygen support without high-flow oxygen, noninvasive ventilation or mechanical ventilation, the use of tocilizumab was also associated with reduced risk of both invasive and non-invasive mechanical ventilation or death by day 14 [38]. Not least, the STOP-COVID tocilizumab study, a large observational study conducted on more than 4000 ICU patients across the United States, reports the efficacy of early use of tocilizumab (within 2 days of ICU admission) in reducing 30-day mortality in critically ill patients [39].

Still, the picture is apparently different in patients with a less severe disease in the attempt to prevent cytokine storm. An Italian randomized multicenter trial aimed at evaluating the efficacy of tocilizumab administered early (within 8 h of randomization) in patients with moderate COVID-19 pneumonia requiring hospital care, but not invasive or semi-invasive mechanical ventilation procedures, has just ended prematurely. The study was discontinued for futility after an interim evaluation that showed the absence of benefits in treated patients in terms of reduced clinical aggravation or survival, even though mortality was only 3% in the standard care arm probably due to the strict criteria for inclusion in the study [40]. Likewise, a US-based randomized, double-blind, placebo-controlled trial involving moderately ill hospitalized patients with Covid-19 reported no significant effect on the risk of intubation or death, nor on any of the secondary outcomes examined [41].

Finally, concerning the possible side-effects of immunomodulatory drugs, while the use of tocilizumab in CAR-T cell therapy apparently do not increase the infection risk [42], its use in patients with severe COVID-19 pneumonia has been associated with increased infection rate and hepatotoxicity, especially when used in combination with steroids [26,35,43,44]. Other adverse effects include neutropenia and thrombocytopenia. This topic is worthy of further investigation.

Notoriously, several randomized clinical trials are currently under way, among these the much-awaited Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial would possibly clarify some of the still outstanding issues [45]. This randomized clinical trial aimed at enrolling 15,000 in the United Kingdom investigates whether treatment with either Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, Convalescent plasma, Synthetic neutralizing antibodies or Tocilizumab prevents death in patients with COVID-19.

7. Conclusions

On the basis of all these evidences, even if no clear evidence is available at present, immune-modulatory agents may be promising therapeutic options for the treatment of severe COVID-19. Given the complexity of a scenario so delineated, the timing of tocilizumab administration therefore appears crucial: although the use of tocilizumab has not been shown to be beneficial outright in all patients with COVID-19 pneumonia, it is likely to maximize its positive effects in selected categories of patients with severe clinical manifestation (characterized by parameters such as peripheral oxygen saturation below 93%, a PaO2/FiO2 ratio below 300 and/or a worsening of more than 30% in 24 h) sustained by a

hyperinflammatory profile (demonstrated by high values of CRP, LDH, ferritin, IL6). More precise identification of predictive factors for disease progression may help to identify the best time for treatment with tocilizumab.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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