International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	THE ROLE OF TOCILIZUMAB IN TREATMENT OF COVID-19
ARTICLE INFO	Aleksandra Gradek, Marcin Sawczuk, Dominika Nowak, Adam Zarzycki, Julia Tarnowska, Filip Szydzik, Bartosz Żegleń, Katarzyna Kozon, Monika Grudzień, Patryk Macuk. (2025) The Role of Tocilizumab in Treatment of Covid-19. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3484
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3484
RECEIVED	09 June 2025
ACCEPTED	18 July 2025
PUBLISHED	21 July 2025
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THE ROLE OF TOCILIZUMAB IN TREATMENT OF COVID-19

Aleksandra Gradek *(Corresponding Author, Email: aleksandragradek99@gmail.com)*
University Clinical Center in Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0000-5112-3439

Marcin Sawczuk
University Clinical Center in Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0003-1204-0624

Dominika Nowak
University Clinical Hospital No. 4 in Lublin, ul. Doktora Kazimierza Jaczewskiego 8, 20-090 Lublin, Poland
ORCID ID: 0000-0002-0195-1102

Adam Zarzycki
University Clinical Hospital No. 4 in Lublin, ul. Doktora Kazimierza Jaczewskiego 8, 20-090 Lublin, Poland
ORCID ID: 0009-0004-9589-1842

Julia Tarnowska
University Clinical Center in Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0000-3231-669X

Filip Szydzik
University Clinical Center in Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0003-3291-4923

Bartosz Żegleń
University Clinical Center in Gdansk, ul. Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0008-6150-6191

Katarzyna Kozon
Masovian Brodnowski Hospital, ul. Ludwika Kondratowicza 8, 03-242 Warszawa, Poland
ORCID ID: 0009-0009-6536-946X

Monika Grudzień
University Clinical Hospital No. 4 in Lublin, ul. Doktora Kazimierza Jaczewskiego 8, 20-090 Lublin, Poland
ORCID ID: 0000-0002-4855-8308

Patryk Macuk
Medical University of Gdansk, Dębinki 7, 80-952 Gdańsk, Poland
ORCID ID: 0009-0005-1615-5036

ABSTRACT

Introduction and Aim: COVID-19, especially severe in the elderly, causes symptoms ranging from mild to critical organ failure and death. Treatments have included chloroquine, hydroxychloroquine, and corticosteroids. Tocilizumab, a monoclonal antibody blocking the IL-6 receptor, offers a promising biological therapy by reducing inflammation and possibly lowering thrombosis risk in COVID-19 patients. The aim of this review is to summarize current evidence on tocilizumab's mechanism and its role in treating SARS-CoV-2 infection.
Material and Methods: A PubMed literature search was conducted using terms: "tocilizumab in COVID-19", "interleukin-6 in COVID-19", "interleukin-6 blockade with tocilizumab", and "COVID-19 and inflammation". Filters included Free Full Text, Clinical Trial, Randomized Clinical Trial, within the last 10 years.
Results: Studies show that tocilizumab reduces inflammation, shortens hospitalization, and accelerates recovery in COVID-19 patients, especially those with respiratory failure not yet on mechanical ventilation. Additionally, tocilizumab exhibits anticoagulant effects, potentially reducing thrombosis risk.
Conclusion: Originally used for rheumatologic diseases, tocilizumab shows therapeutic potential in COVID-19 by lowering inflammation and reducing mechanical ventilation needs, improving clinical outcomes. However, inconsistent study results highlight the need for further large, well-designed clinical trials to confirm its efficacy and safety.

KEYWORDS

Tocilizumab, COVID-19, Interleukin-6, Inflammation

CITATION

Aleksandra Gradek, Marcin Sawczuk, Dominika Nowak, Adam Zarzycki, Julia Tarnowska, Filip Szydzik, Bartosz Żegleń, Katarzyna Kozon, Monika Grudzień, Patryk Macuk. (2025) The Role of Tocilizumab in Treatment of Covid-19. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3484

Introduction.

COVID-19 is a disease caused by the SARS-CoV-2 virus, a member of the Coronaviridae family that contains single-stranded RNA as its genetic material. This virus induces respiratory tract infections in humans, ranging from mild illness to severe acute respiratory syndrome. The disease originated in Wuhan, China, in December 2019, from where it rapidly spread worldwide, prompting the World Health Organization (WHO) to declare it a pandemic. Transmission occurs via direct contact, fomites, and airborne routes. The most common clinical symptoms include fever, cough, myalgia, headache, chills, nausea, vomiting, diarrhea, and anosmia or ageusia. Clinically, COVID-19 can be classified as mild, moderate, or severe with symptoms such as dyspnea and hypoxemia and critical, characterized by respiratory failure, multiorgan dysfunction, and septic shock. Many patients experience persistent symptoms months after recovery, necessitating intensive respiratory rehabilitation. A notable complication is "brain fog," characterized by cognitive impairment and chronic fatigue. In April 2020, reports emerged of pediatric inflammatory multisystem syndrome (PIMS), a severe complication affecting the heart, brain, and gastrointestinal tract, often requiring prolonged hospitalization. The diagnosis of COVID-19 is primarily confirmed by RT-PCR testing, typically using nasopharyngeal swabs. Additional diagnostic tools include chest radiography and computed tomography (CT), alongside monitoring of inflammatory biomarkers. Elevated levels of interleukins, tumor necrosis factor alpha (TNF-α), and granulocyte colony-stimulating factor (G-CSF) have been observed in patients. Initially, antimalarial drugs such as hydroxychloroquine and chloroquine were employed due to promising in vitro results; however, clinical trials failed to demonstrate clear therapeutic benefits. Following vaccine deployment, incidence and mortality rates have significantly declined, though infections persist and remain a major clinical challenge. Furthermore, the pandemic has engendered substantial adverse health, social, and economic impacts. Consequently, the pursuit of effective prevention and treatment strategies for COVID-19 remains critically important. [1,2,3,4,5]

Tocilizumab is a humanized recombinant monoclonal antibody targeting interleukin-6 (IL-6), widely used in the treatment of rheumatologic disorders. Emerging evidence supports its efficacy in managing viral

hemorrhagic fevers by mitigating cytokine storm syndromes. Although the pathogenesis of COVID-19 is not yet fully elucidated, an excessive inflammatory response and immune dysregulation, characterized by elevated levels of cytokines such as IL-6, IL-10, TNF-α, and interferon-gamma (IFN-γ), are considered key contributors. IL-6 is a pro-inflammatory cytokine integral to granulopoiesis and the proliferation and differentiation of T and B lymphocytes. Elevated serum IL-6 levels serve as markers of infection severity, as observed in pneumococcal pneumonia, and are strongly associated with severe disease progression and mortality in COVID-19. Therefore, tocilizumab represents a promising therapeutic option by suppressing the cytokine storm and potentially improving clinical outcomes. [6,7,8,9]

In this paper, we analyze and present the results of studies investigating the effects of tocilizumab therapy in COVID-19 patients. We summarize its impact on symptom alleviation, reduction of inflammatory markers, and improvement in lung imaging findings.

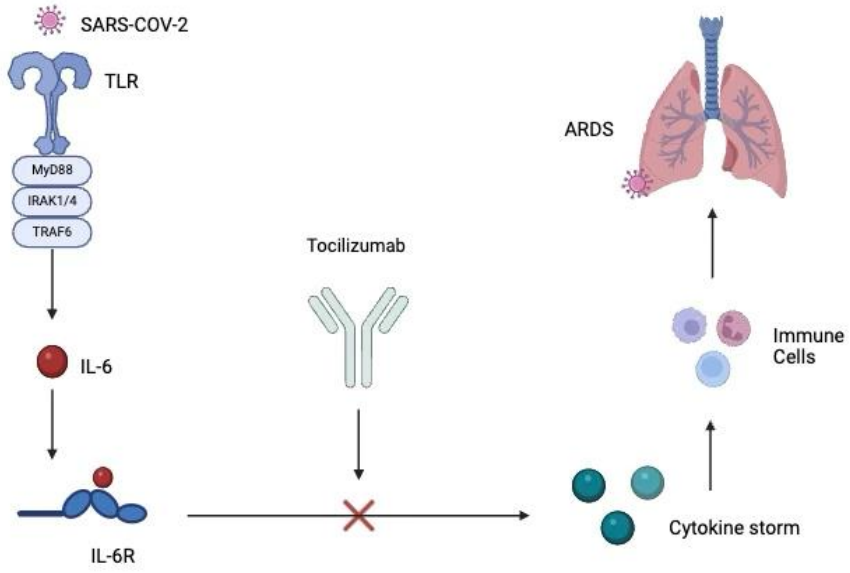

Fig. 1. *Simplified diagram of tocilizumab action in the context of blocking cytokine storm development mediated by IL-6 in COVID-19. Figure created using BioRender.com.*

1. Results

1.1. Tocilizumab in Patients with Severe Pneumonia Due to COVID-19.

In their study, O'Rosas et al. administered tocilizumab at a dose of 8 mg/kg body weight or a placebo to 479 patients hospitalized with severe COVID-19 pneumonia. After 28 days, they assessed the patients' clinical status using a 7-point ordinal scale, where 1 indicated hospital discharge and 7 indicated death. No significant difference was found in clinical status or mortality between the tocilizumab group and the placebo group. However, the frequency of infections was lower in the tocilizumab group, and the data suggested a possible benefit of tocilizumab in reducing the time to hospital discharge and Intensive Care Unit (ICU) stay, which requires further investigation. [10,11]

1.2. Tocilizumab in Treatment of Patients Hospitalized with COVID-19 Pneumonia.

Salma et al. enrolled patients hospitalized with COVID-19 pneumonia who were not receiving mechanical ventilation and randomly assigned them to two groups. One group received one or two intravenous doses of tocilizumab (8 mg/kg body weight), while the other received a placebo. The primary efficacy endpoint was the initiation of mechanical ventilation or death by day 28 following treatment initiation. The study demonstrated that tocilizumab, combined with standard medical care, was more effective than placebo plus standard care in reducing the risk of progression to mechanical ventilation or death. Furthermore, the findings suggest that patients with moderate to severe disease who have not yet required mechanical ventilation are the most likely to benefit from tocilizumab therapy. Tocilizumab may also potentiate the therapeutic effects of glucocorticosteroids and antiviral agents in the management of COVID-19. [12,13,14]

1.3. Interleukin-6 Receptor Antagonists in Treatment of Patients in Critical Condition with COVID-19.

Gordon et al. investigated the effects of tocilizumab (8 mg/kg body weight) and sarilumab (400 mg) in COVID-19 patients who had required organ support for multiorgan failure within the previous 24 hours in ICU setting. The primary outcome measured was the number of days free from respiratory and cardiovascular organ support. In critically ill COVID-19 patients receiving organ support, treatment with IL-6 receptor antagonists significantly improved clinical outcomes and survival compared to glucocorticosteroid therapy alone. [15,16]

1.4. Tocilizumab in Patients with Moderate or Severe COVID-19.

Wang et al. conducted a study to evaluate the efficacy and safety of tocilizumab therapy in COVID-19 patients, motivated by reports suggesting that tocilizumab may mitigate the cytokine storm. Patients were assigned to two groups: one receiving standard medical care and the other receiving standard care plus tocilizumab. The researchers monitored recovery rates, changes in oxygen saturation, and inflammatory biomarkers. Among patients treated with tocilizumab, improvements were observed, including fever reduction, increased oxygen saturation, and a significant decrease in inflammatory markers. [17,18]

1.5. Promising Effects of Tocilizumab in the Treatment of COVID-19.

Dastan et al. monitored interleukin-6 (IL-6) levels as well as lung imaging findings from computed tomography (CT) and chest X-rays before and 14 days after administration of a single 400 mg dose of tocilizumab. The median IL-6 level was 28.55 pg/ml at baseline, decreasing to 21.25 pg/ml by day 4 and further to 8.5 pg/ml by day 9 following initiation of tocilizumab therapy. Significant improvement in chest CT and X-ray findings was observed in 28 of 76 patients. Based on these results, tocilizumab may represent a promising therapeutic option for patients with severe SARS-CoV-2 infection when administered early. However, the lack of a randomized controlled trial and the relatively small sample size should be considered, and ongoing placebo-controlled studies are needed to more precisely define the role of tocilizumab in COVID-19 treatment. [19,20]

1.6. The Effect of Tocilizumab on Reducing Hypercoagulability in COVID-19.

Patients with severe COVID-19 have been observed to exhibit a hypercoagulable state and an increased incidence of thromboembolic events. Almskog et al. investigated the effects of interleukin inhibitors, specifically tocilizumab and anakinra, on the coagulation system in hospitalized COVID-19 patients. Two groups received either tocilizumab or anakinra in addition to standard care, while a control group received standard care alone. Coagulation status was assessed using rotational thromboelastometry (ROTEM) and overall hemostatic potential (OHP), with clot morphology visualized by scanning electron microscopy. Secondary outcomes included the evaluation of standard laboratory coagulation parameters. After 29 days of therapy, ROTEM analysis revealed a reduction in hypercoagulability in the tocilizumab-treated group compared to both the anakinra group and controls, characterized by prolonged clot formation time and decreased clot firmness. No significant differences were observed in OHP results. Additionally, plasma fibrinogen levels gradually decreased in the tocilizumab group. In summary, tocilizumab treatment reduces hypercoagulability in hospitalized COVID-19 patients, as evidenced by both coagulation assays and conventional laboratory measurements, compared to anakinra therapy and standard care alone. These findings suggest that tocilizumab may represent a viable therapeutic option for severe COVID-19 patients at high risk of thrombosis. [21]

1.7. IL-6 Levels in Predicting Severity and Response to Tocilizumab in COVID-19.

Interleukin-6 (IL-6) is a key cytokine implicated in the pathogenesis of acute respiratory distress syndrome (ARDS). Galván-Román et al. conducted a retrospective observational study to evaluate whether baseline serum IL-6 levels could predict the need for mechanical ventilation and the response to tocilizumab therapy. IL-6 levels were measured on days 3 and 9 after hospital admission and compared with levels before and after tocilizumab administration. These measurements were then correlated with clinical outcomes, including the requirement for mechanical ventilation, changes in oxygenation, and mortality. Patients who required mechanical ventilation exhibited elevated leukocyte and lymphocyte counts, as well as increased levels of IL-6, C-reactive protein (CRP), and procalcitonin, reflecting a heightened inflammatory state compared to those who did not require ventilation. No significant correlation was observed between IL-6 levels and arterial oxygen partial pressure (PaO2), likely due to augmented oxygen delivery in the most severe cases. Importantly, the study demonstrated that an IL-6 concentration exceeding 30 pg/ml predicts the need for mechanical ventilation. Moreover, improvements in respiratory parameters during tocilizumab treatment may reduce the necessity for mechanical ventilation in COVID-19 patients. [22]

1.8. Reduced Serum Levels of the Inflammatory Marker miR-146a are Associated with Lack of Clinical Response to Tocilizumab in COVID-19 Patients.

COVID-19 poses a significant threat to health and life, particularly among elderly patients with comorbidities who develop hyperinflammatory syndrome. Sabbatinelli et al. hypothesized that the severity of COVID-19 is closely linked to inflammation. They collected serum samples from patients with multifocal interstitial pneumonia due to COVID-19 following tocilizumab administration, as well as from healthy controls. Subsequently, they analyzed a panel of microRNA involved in the regulation of inflammation in these samples. The study found that patients who did not respond to tocilizumab exhibited lower levels of miR-146a-5p. Furthermore, response to tocilizumab was associated with a decrease in IL-6 levels and an increase in miR-146a expression, suggesting that in responders, the drug may restore the balance of the IL-6/miR-146a-5p axis. In conclusion, these findings support the hypothesis that inflammation accelerates COVID-19 progression; however, further large-scale studies are warranted to establish the potential of microRNA as predictive and prognostic biomarkers for tocilizumab therapy in COVID-19 patients. [23]

1.9. Early Administration of Tocilizumab to COVID-19 Patients with Elevated Inflammatory Markers.

The course of COVID-19 is characterized by an imbalanced immune response. Broman et al. hypothesized that patients exhibiting a heightened inflammatory state, reflected by elevated levels of inflammatory biomarkers, would benefit from IL-6 blockade. They focused on four key inflammatory markers: IL-6, C-reactive protein (CRP), ferritin, and D-dimer. Patients were divided into two groups: one received tocilizumab in addition to standard medical care, while the other received standard care alone. Those treated with tocilizumab demonstrated significantly improved clinical recovery and shorter hospital stays compared to the control group, with CRP levels showing a rapid decline following tocilizumab administration. [24]

1.10. Tocilizumab in Patients Hospitalized Due to COVID-19.

The aim of the study was to evaluate the effects of tocilizumab in hospitalized COVID-19 patients with and without hypoxia. The hypoxic group comprised individuals with oxygen saturation (SpO2) below 92% and elevated inflammatory markers. Patients were randomly assigned to two subgroups: one received intravenous tocilizumab at a dose of 400–800 mg, adjusted according to body weight, while the other received standard care alone. Among hypoxic patients, those treated with tocilizumab had a higher likelihood of hospital discharge within 28 days compared to the control group. Furthermore, in patients who did not initially require mechanical ventilation, tocilizumab administration was associated with a reduced probability of progression to mechanical ventilation and a lower risk of mortality. [25]

1.11. Mortality in Patients with Pneumonia in the Course of COVID-19.

Perrone et al. conducted a clinical study to evaluate the impact of tocilizumab on mortality in patients with COVID-19 pneumonia. Participants were selected based on the presence of pneumonia symptoms, a confirmed positive PCR test, oxygen saturation below 93%, or the requirement for mechanical ventilation. Patients in the treatment group received tocilizumab at a dose of 8 mg/kg body weight, up to a maximum of 800 mg. A second dose was administered 12 hours later if no improvement in respiratory function was observed. Among patients treated with tocilizumab, the 30-day mortality rate was reduced; however, this benefit appeared to be limited primarily to the subgroup of patients who did not require mechanical ventilation. [26,27]

2. Conclusion

COVID-19 has become a widespread disease, with the cytokine storm significantly worsening patient outcomes by impairing both quality of life and survival. Tocilizumab, a recombinant humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor, is traditionally indicated for rheumatic diseases such as rheumatoid arthritis, systemic sclerosis, and Still's disease. Recently, emerging evidence has highlighted the potential effectiveness of tocilizumab in treating COVID-19.

The studies reviewed indicate that tocilizumab may offer several clinical benefits in COVID-19 therapy, including reduction of systemic inflammation, improvement of respiratory parameters, and decreased need for mechanical ventilation. These effects contribute to accelerated recovery, shorter hospital stays, and potentially increased survival rates. Clinical improvements are often accompanied by reductions in inflammatory biomarkers and gradual resolution of lung abnormalities visible on computed tomography and chest X-rays. Notably, the most favorable outcomes have been observed in patients with respiratory failure who have not

yet required mechanical ventilation. Additionally, tocilizumab has been reported to reduce hypercoagulability in severe COVID-19 cases at high risk of thrombotic complications.

However, some studies have not demonstrated a significant mortality benefit associated with tocilizumab treatment, underscoring the need for further large-scale, randomized controlled trials to definitively assess its efficacy. This area of research is particularly compelling as it bridges advances in the pharmacology and pharmacokinetics of biological agents with their practical application in modulating ongoing inflammatory processes in COVID-19. Continued progress in medicine and pharmacology will enhance our understanding of these mechanisms and ultimately improve patient outcomes and quality of life.

Disclosures

Author's contribution:
Conceptualization: A.G., M.S., D.N., A.Z.
Formal analysis: J.T., F.Sz., B.Ż., K.K., M.G.
Methodology: A.G., M.S., F.Sz., A.Z., P.M.
Investigation: K.K., D.N., M.G., B.Ż., J.T.
Resources: B.Ż., F.Sz., P.M., A.Z., M.S.
Writing-rough preparation: A.G., K.K., J.T., D.N., M.G.
Writing-review and editing: A.G., B.Ż., M.S., D.N., A.Z., J.T., F.Sz., K.K., P.M.
Supervision: A.G.

All authors have read and agreed with the published version of the manuscript.

Funding statement: Not applicable.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability: Not applicable.
Acknowledgments: Not applicable.
Conflict or interest statement: Authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

During preparing this work the authors have used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

Abbreviations

COVID-19 - Corona-Virus-Disease-2019
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2
RNA - Rybonucleid Acid
ARDS - Acute Respiratory Distress Syndrome
RT-PCR - Reverse Transcription Polymerase Chain Reaction
TNF-α - Tumor Necrosis Factor Alpha
G-CSF - Granulocyte Colony-Stimulating Factor
IL-6 - Interleukin 6
IL-10 - Interleukin 10
IFN-γ - Interferon Gamma
ICU- Intensive Care Unit
PIMS - Pediatric Inflammatory Multisystem Syndrome
CT - Computed Tomography
X-ray - X-ray Image
ROTEM - Rotational Tromboelastometry
OHP - Overall Hemostatic Potential
PaO2 - Partial Pressure of Oxygen in Arterial Blood
miR-146a - MicroRNA 146a
CRP - C-Reactive Protein
PCR - Polymerase Chain Reaction

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