Clinical Management of COVID-19

IL-6 RECEPTOR BLOCKERS FOR COVID-19
Learning objectives

At the end of this module, you will be able to:

• Recognize the role for IL-6 receptor blockers in the management of patients with COVID-19.

• Describe key IL-6 receptor blockers dosing and administration considerations for patients with severe and critical COVID-19.
Special note

Drugs and doses stated here are for illustrative purposes only.

Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient's specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.
IL-6 receptor blockers in COVID-19: summary of recommendations

In July 2021, the following WHO recommendations regarding IL-6 receptor blockers for patients with COVID-19 were released:

**Strong recommendation**: We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe and critical COVID-19.

Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.
IL-6 receptor blockers in COVID-19: recommendation

Population
This recommendation applies only to people with these characteristics:

- Patients with confirmed COVID-19

Disease severity
- Non-severe
  - Absence of signs of severe or critical disease
- Severe
  - Oxygen saturation <90% on room air
  - Signs of pneumonia
  - Signs of severe respiratory distress
- Critical
  - Requires life sustaining treatment
  - Acute respiratory distress syndrome
  - Sepsis
  - Septic shock

IL-6 receptor blockers
Interleukin-6 receptor blockers

Recommendation in favour (strong)

https://doi.org/10.1136/bmj.m3379
Review of IL-6 biology and function
What is IL-6 (Interleukin 6)?

- Cytokines refer to a broad group of small proteins important in cell signaling. Categories of cytokines include interferons, interleukins, tumor necrosis factors and others.

- **Interleukin (IL) 6 is a strong pro-inflammatory cytokine.** It plays an important role in the body’s fight against autoimmune diseases such as Rheumatoid Arthritis.

- IL-6 is important for both systemic and local inflammation and is associated with symptoms such as fever, fatigue and anorexia (decreased appetite).

- Prior to 2020, increased IL-6 levels had been associated with several viral infections, including influenza, hepatitis B, hepatitis C, HIV, Crimean-Congo hemorrhagic fever and Chikungunya. Evidence from clinical studies had shown that increased IL-6 levels worsen clinical outcomes involving viral pathogens. Similar postulations were made for SARS-CoV-2.
The interleukin-6 receptor is a protein complex consisting of two parts: an IL-6 receptor (IL6R) subunit and a glycoprotein.

IL-6 binds to the IL-6 receptor complex. The body’s immune system responds through a variety of immune cascades.

For many years, medicines have been created and tested specifically to target blocking the IL6R and/or glycoprotein subunits for various autoimmune diseases.

Tocilizumab and Sarilumab are two examples of IL6R blockers. They bind to IL6R and thus prevent IL-6 from binding to IL6R.

Tocilizumab is humanized (human-generated) antibody to the IL6R. Sarilumab is a human antibody to the IL6R. Other antibodies to IL6R and IL-6 also exist.
Reviewing the evidence and recommendations regarding IL-6 receptor blockers
The GDG made a **strong recommendation for IL-6 blockers and corticosteroids in severe and critical COVID-19** based on **high certainty of evidence** which showed **reduction in mortality and decreased need for mechanical ventilation** in patients with COVID-19 who are severely or critically ill.
## Understanding the strength of recommendations

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<tr>
<th>Strong</th>
<th>Conditional</th>
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<td>• <strong>For patients</strong>: most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>• <strong>For patients</strong>: The majority of individuals would want the suggested course of action, but many would not.</td>
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<tr>
<td>• <strong>For clinicians</strong>: Most individuals should receive this course of action.</td>
<td>• <strong>For clinicians</strong>: Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient circumstances.</td>
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<td>• <strong>For policymakers</strong>: The recommendation can be adapted as a policy in most situations including for the use as performance indicators.</td>
<td>• <strong>For policymakers</strong>: Policy making will require substantial debates and involvement of many stakeholders. Policies are also likely to vary between regions.</td>
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IL-6R blockers for COVID-19: guideline development process (1/2)

• The WHO Therapeutics and COVID-19 Guideline Development Group (GDG), a group of international content experts, patients, clinicians and methodologists with no conflicts of interest and balanced in terms of gender, geography, expertise, and patient representation, met in mid 2021 to discuss IL-6R blockers.

• The GDG followed standards for trustworthy guideline development using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation), in full compliance with the WHO Handbook for guideline development, 2nd edition.

• The GDG took an individual patient perspective to values and preferences when making decisions. Values considered include:
  - Applicability of the guideline to various populations of patients;
  - Balance of benefits and harms;
  - Resource implications, feasibility, equity and human rights;
  - Acceptability.
Since 2020, WHO has partnered with principal investigators of several ongoing clinical research trials and formed the Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.

WHO REACT conducts prospective meta-analysis (PMA) of randomized trials for therapies such as IL-6R blockers for COVID-19.4

The GDG is presented with the evidence from the PMA and discusses the values and preferences in order to arrive at a recommendation.5
The recommendation for IL-6 receptor blocker use applies only to patients who are severely or critically ill, as per the definitions below.\(^5\)

A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. https://doi.org/10.1136/bmj.m3379
Deeper into the evidence
Summary of the prospective meta-analysis

- The prospective meta-analysis for IL-6 receptor blockers brought together data from 27 randomized clinical trials, totaling 10,930 patients (median 61 years age, 33% women).  

- Mortality risk at 28-days decreased with IL-6 receptor blockers (22%) compared to usual care or placebo (25%). IL-6 receptor blockers were found to be most effective when administered with corticosteroids (21% mortality risk with IL-6RB and steroids vs 25% with steroids alone).
Evidence: IL-6RB vs. SC

The GDG made a **strong recommendation** for IL-6 blockers and corticosteroids in severe and critical COVID-19 based on **high certainty of evidence** which showed reduction in mortality and decreased need for mechanical ventilation in patients with COVID-19 who are severely or critically ill (4).
Clinical considerations when administering IL-6 receptor blockers
IL-6 receptor blockers in COVID-19: treatment

- For COVID-19, only the intravenous formulation of IL-6 receptor blockers should be used. Subcutaneous injections have not been studied for COVID-19.
- IL-6 receptor blockers should be given as **single dose over 1 hour using a dedicated IV line**.
- Avoid IV push or IV bolus.
- If a clinical response is determined to be inadequate after 12-48 hours, a second dose may be considered.

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IL-6 receptor blockers in COVID-19: pre-treatment monitoring

• Prior to initiating IL-6 receptor blocker therapy, routine bloodwork should be checked for the following:
  – Neutrophil count
  – Platelets
  – Transaminases
  – Total bilirubin
  – Lipid profile

• Additional labs such as screening for HIV, hepatitis B and C and other tests may be considered as per clinician discretion.

• Clinicians may choose to avoid IL-6 receptor blocker therapy in patients with history of autoimmune disease such as Rheumatoid Arthritis or giant cell arteritis, especially those who also have abnormal lab findings on routine bloodwork.
IL-6 receptor blockers in COVID-19: post-treatment monitoring

• The evidence of serious adverse events of IL-6 blocker use in COVID-19 is uncertain.

• COVID-19 trials only followed patients for a short interval and cited challenges in accurately capturing adverse events. Evidence summary may under-represent the risks of treatment with IL-6 receptor blockers.

• Serious and potentially fatal infections such as active tuberculosis, invasive fungal, bacterial, viral and other opportunistic infections have been reported in patients receiving tocilizumab for conditions other than COVID-19.

• Use discretion and caution in using IL-6 receptor blockers in patients on concomitant immunosuppressive therapy. Closely monitor patients for signs and symptoms of infection during and after treatment.
Summary
Summary

• Give IL-6 receptor blockers along with oxygen and systemic corticosteroids for patients with severe and critical COVID-19.

• Be aware and monitor for potential adverse events including opportunistic infections, especially due to concomitant corticosteroid administration.
References

7. A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. Published 7 July 2021. [https://www.bmj.com/content/370/bmj.m3379](https://www.bmj.com/content/370/bmj.m3379)
Acknowledgements

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