INESSS
LE SAVOIR PREND FORME

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COVID-19
USE OF TOCILIZUMAB OR SARILUMAB

This clinical tool is intended primarily for clinicians. It is provided for information purposes only and should not replace the judgment of the clinician who performs activities reserved under a statute or a regulation. The contents are based on a rapid ongoing review of the scientific literature available when it was being developed and it is supported by the knowledge and experience of Québec clinicians who contributed to its development. INESSS remains on the lookout for any new data that might warrant changes to this tool, which is intended to complement other INESSS publications. For further details, go to **inesss.qc.ca/en/covid-19**.

CLINICAL PRESENTATION

- For a list of symptoms and signs of the 2019 coronavirus disease (COVID-19), see the table here.
- Severe forms of the disease include a viral pneumonia that can progress to an acute respiratory distress syndrome (ARDS) and complications associated with elevated levels of pro-inflammatory cytokines.

CLINICAL PROGRESSION SCALE

WHO Ordinal Scale[1]	Classification	
	Stage	Score
1. Ambulatory, asymptomatic, viral RNA detected 2. Ambulatory, symptomatic, independent 3. Ambulatory, symptomatic, assistance needed 4. Hospitalized, no oxygen therapy[2]	Mild	1, 2 or 3
5. Hospitalized, oxygen by mask or nasal prongs (O_2+) 6. Hospitalized, oxygen by noninvasive ventilation (NIV) **OR** high-flow oxygen (O_2++) 7. Hospitalized, intubation **AND** mechanical ventilation ($pO_2/FiO_2 \geq 150$ **OR** $SpO_2/FiO_2 \geq 200$ [O_2+++]) 8. Hospitalized, invasive mechanical ventilation ($pO_2/FiO_2 < 150$ **OR** $SpO_2/FiO_2 < 200$ [O_2+++]) **OR** vasopressor	Moderate	4 or 5
9. Hospitalized, invasive mechanical ventilation ($pO_2/FiO_2 < 150$ [O_2+++]) **AND** vasopressor **OR** dialysis **OR** ECMO 10. Deceased	Severe to critical	6, 7, 8 or 9

1. *WHO Working Group. A minimal common outcome measure set for COVID-19 clinical research. The Lancet Infectious diseases 2020;20(8):e192-e7.*
2. If the patient is hospitalized for isolation only (oxygen therapy or medical care not required), classify him or her as ambulatory.

Acronyms and Symbols: pO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; SpO_2: oxygen saturation; ECMO: extracorporeal membrane oxygenation

BIOTHERAPIES DIRECTED AGAINST THE IL-6 RECEPTOR

- Tocilizumab and sarilumab are monoclonal antibodies directed against the interleukin-6 (IL-6) receptor.
- To perform its functions, IL-6 first binds to its receptor. The resulting complex associates with the transmembrane glycoprotein 130, which has several intracellular signaling patterns whose activation leads to the gene expression of inflammatory markers.
- The involvement of IL-6 in the inflammatory response observed in patients who have developed a severe form of COVID-19 is relatively well established.
- The results of a systematic review with meta-analyses showed that patients who developed a severe or critical form of the disease have IL-6 levels nearly three times higher than those of patients with moderate disease. There is a significant association between elevated IL-6 levels and adverse clinical outcomes such as ICU admission, ARDS and death.

TREATMENT RELATED LABORATORY TESTS

- For the relevant laboratory tests in the context of COVID-19 in adults, consult the table available here.

LABORATORY TESTS BEFORE AND AFTER INITIATING TREATMENT WITH TOCILIZUMAB OR SARILUMAB

Test	Before initiation	After initiation
C-reactive protein (CRP)[2]	✓	PRN[1]
Liver function test	✓	PRN[1]
Complete blood count (CBC)	✓	PRN[1]

1. Unless required by the patient's condition, it is preferable to limit the frequency of certain tests that are normally ordered and to combine blood draws to reduce the risk of exposure for the staff who collect the samples and to rationalize the use of personal protective equipment and medical supplies.
2. The use of these biotherapies could modulate inflammatory marker measurements and conceal classic signs of infection.

Québec

TREATMENT PRINCIPLES

- Based on the current state of knowledge, the use of tocilizumab would reduce the need for respiratory or cardiovascular support and mortality in:
  - Patients hospitalized with COVID-19 on oxygen therapy and with systemic inflammation characterized by elevated CRP (greater than 75 mg/L) at initiation of therapy (RECOVERY study)
  - Patients who have been hospitalized for less than 14 days with COVID-19 and whose respiratory or cardiovascular support[1] began very recently (ideally within the last 24 hours[2]) at initiation of therapy (REMAP-CAP trial).
- The effect of tocilizumab adds to that of systemic corticosteroids when given concomitantly.
- Although the data are more robust for tocilizumab than for sarilumab, a class effect is likely and the therapeutic equivalence criterion of sarilumab and tocilizumab was achieved for mortality[3].

A graphical representation of the current scientific data is available here.

- Treatment with a systemic corticosteroid should be initiated in persons with COVID-19 who require low-flow oxygen therapy, high-flow oxygen therapy, invasive or noninvasive mechanical ventilation, ECMO, or the use of a vasopressor or an ionotrope. For the recommendations regarding the use of systemic corticosteroids, consult the corresponding clinical tool.
- In the event of shortage or restricted access, baricitinib, a janus kinase (JAK) inhibitor, should be preferred for people with COVID-19 whose condition requires low-glow or high flow oxygenation, or who use non-invasive mechanical ventilation. For the recommendations regarding the use of baricitinib, consult the corresponding clinical tool.
- Other drugs with immunomodulatory properties (e.g., biotherapies against the IL-1 pathway or against granulocyte-macrophage colony-stimulating factor [GM-CSF]) are currently being investigated. For the current state of scientific knowledge regarding different therapeutic drugs, go to inesss.qc.ca/en/covid-19.

1. High-flow oxygen therapy, invasive or non-invasive mechanical ventilation, vasopressor or ionotrope.
2. The principle is to treat the patients who could benefit most as soon as possible.
3. https://www.remapcap.org/covid19publications

CLINICAL POSITIONS

IMPORTANT CONSIDERATIONS

Due to the lack of available clinical data, scientific uncertainties remain regarding:

- persons under 18 years of age and pregnant women

Considering the risks of shortage, the use of tocilizumab, or alternatively sarilumab, in patients with severe forms of COVID-19 should be reserved for circumstances in which their clinical benefits have been clearly demonstrated. The availability of these biotherapies will have to be preserved for certain indications without any other replacement option, such as patients suffering from a cytokine release syndrome caused by CART cell-based immunotherapy and pregnant women with COVID-19 in moderate to critical stage.

In the event of shortage or a difficulty in supplying these biotherapies, the prioritization of patients should be based, beyond the clinical parameters, on ethical benchmarks for equitable drug allocation and a tool to guide deliberation and decision-making in matter of prioritization.

Regardless of the shortage risk, participation in research efforts remain important and should be encouraged if the context so permits, especially in academic settings. Acquiring and consolidating knowledge are key to identifying and positioning value-added therapies within the therapeutic arsenal against COVID-19.

STAGE	Mild	Moderate O_2 +		Severe to critical O_2 ++	O_2 +++
Score at initiation of treatment with tocilizumab or sarilumab	**1-2-3**	**4**	**5**	**6**	**7-8-9**
Adults	✗	✗	Prioritize baricitinib if tocilizumab or sarilumab restricted ✓ In combination with dexamethasone if CRP ≥ 75 mg/L	Prioritize baricitinib if tocilizumab or sarilumab restricted ✓ In combination with dexamethasone	✓ In combination with dexamethasone
< 18 years	✗	✗	?	?	?
Pregnancy	✗	✗	?	?	?

✓ Should be initiated for this population **in combination with standard of care including dexamethasone or equivalent corticosteroid**, ideally when the patient has been hospitalized for less than 14 days as a result of COVID-19 and there is roughly 24 h or less between initiation of therapy and initiation of respiratory support, unless contraindicated or a life expectancy of less than 24 hours as judged by the clinician. Based on current knowledge: clinical benefit in terms of clinical course, length of hospital stay, admission rate and length of ICU stay, and mortality; low risk of major adverse events. Level of scientific evidence for efficacy of tocilizumab: moderate to high. Level of scientific evidence for efficacy of sarilumab: weak.

✗ Use is not recommended for this population because of lower biological plausibility, scientific uncertainty regarding the potential benefits according to the stage of the infection, risks that could outweigh the benefits, or because other treatment options could be more beneficial. Level of scientific evidence for the efficacy of tocilizumab and sarilumab : insufficient.

? Populations mainly excluded from studies. Treatment, **in combination with standard of care**, could be considered on a case-by-case basis for these populations in exceptional situations if the benefits outweigh the risks. Enrollment in a research study remains, however, an option. Level of scientific evidence for the efficacy and safety of biotherapies directed against IL-6 or its receptor in the context of COVID-19: insufficient.

Symbols and acronym: CRP: C-reactive protein, O_2+: oxygen therapy by mask or nasal prongs; O_2++: high-flow nasal oxygen therapy OR noninvasive mechanical ventilation ; O_2+++: oxygen therapy with invasive mechanical ventilation or ECMO

CONDITIONS OF USE

Drug	Dosage	Duration of treatment	Infusion[3]
PREFERRED OPTIONS			
Tocilizumab[1]	**> 30 kg and ≤ 40 kg :** 8 mg/kg[2] **> 40 kg and ≤ 65 kg :** 400 mg **> 65 and ≤ 90 kg :** 600 mg **> 90 kg :** 800 mg **Other dosage:** 8 mg/kg (max. 800 mg)	Single injection[8]	Dilution[4] in 100 ml of 0.9% NaCl Duration : 60 minutes[5]
	< 30 kg : 12 mg/kg[2]	Single injection[8]	Dilution[4] in 50 ml of 0.9% NaCl Duration : 60 minutes[5]
ALTERNATIVE OPTION [6] Except for pregnant women who meet eligibility criteria unless discussed with a suitability committee			
Sarilumab[1,6,7]	**> 40 kg:** 400 mg	Single injection[8]	Dilution[4] in 100 ml of 0.9% NaCl Duration: 60 minutes[5]

1. Off-label use.
2. For those under 40 kg, extrapolation of CAR T use.
3- In the presence of minor reactions (nausea, mild pruritus, headache, mild chills or facial flushing): stop the infusion and resume at 50% of the rate after resolution of symptoms. If moderate to severe reaction, stop the infusion.
4. Preparation of the infusion solution: Since tocilizumab and sarilumab vials do not contain preservatives, reconstitution and dilution of the product must be performed using aseptic technique. Although stable for 24 hours after reconstitution, the prepared solution should ideally be administered immediately. Gently agitate the mixture of tocilizumab, or sarilumab, with 0.9% NaCl to avoid foaming of the product and potential damage to the antibodies.
5. The following infusion rate is recommended: 10 mL/hr for the first 15 minutes, then 130 mL/hr for the remaining 45 minutes followed by a 20 mL saline flush.
6. In case of tocilizumab shortage, in patients who have not yet received tocilizumab for COVID-19.
7. Intravenous administration from the solution for subcutaneous injection (practice performed in clinical trials).
8. A single injection should be preferred given the uncertainty regarding the evidence of additional clinical benefit of a second dose and the need to maximize available supply.

⚠ For exceptional use in a child, consult a pediatric specialist.

⚠ For exceptional use in a pregnant woman, consult a maternal fetal medicine specialist.

INFORMATION ON DRUGS

Contraindications	• History of allergy to any component of the formulation • Severe or latent infection (tuberculosis, for example) • Septic shock • ALT or AST greater than 5 times the upper normal limit • Platelets < 50 x 10^9/L • Neutrophils < 0,5 x 10^9/L
Precautions	• Pregnant or breastfeeding woman • Latent infection (possibility of reactivation) • Pre-existing condition or concomitant therapy (e.g., other biological agent) resulting in immunosuppression • History of diverticulitis or gastrointestinal tract ulceration (risk of gastrointestinal perforation) • Active liver disease or liver failure • Platelets < 100 x 10^9/L • Neutrophils < 2 x 10^9/L
Most Common Adverse effects	• Infusion-related reactions • Secondary infections • Elevated liver transaminases • Neutropenia • Thrombocytopenia
Drug Interactions (list not exhaustive)	• The IL-6 regulated activation pathway has been shown to suppress the expression / activity of CYP3A4, CYP2C19, CYP2C9 and CYP1A2. Tocilizumab, or sarilumab have no inhibitory or inducing effect on cytochromes. They normalize cytochrome activity via inhibition of the IL-6 pathway.

DISCONTINUATION CRITERIA

➔ Administration of tocilizumab or sarilumab should be discontinued in the following situations:
- If a minor reaction occurs (nausea, mild pruritus, headache, mild chills or facial flushing)
- If a moderate to severe reaction occurs (hypotension, bronchospasm, skin erythema, generalized urticaria, chills, dyspnea, swelling of the tongue or throat, vomiting

MAIN REFERENCES

Recovery Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397(10285):1637-45.

Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med 2021.

Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med 2021.

Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2020.

Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. New England Journal of Medicine 2020.

Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, Group C-C. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Internal Medicine 2020.

Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Internal Medicine 2020.

Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. Bmj 2021;372:n84.

Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021.

Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med 2021;

Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Front Med 2021:1-9.

NHS. Interim Clinical Commissioning Policy: Tocilizumab for hospitalised patients with COVID-19 pneumonia (adults) [website]. 2021. Available at: https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-tocilizumab-for-hospitalised-patients-patients-with-covid-19-pneumonia-adults/ (consulted may 17, 2021).

NHS. Interim Clinical Commissioning Policy: Sarilumab for critically ill patients with COVID-19 pneumonia (adults) [website]. 2021. Available at: https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-sarilumab-for-critically-ill-patients-with-covid-19-pneumonia-adults/ (consulted may 17, 2021).

NICE. COVID-19 rapid guideline: managing COVID-19 [website]. 2021. Available at: https://app.magicapp.org/#/guideline/L4Qb5n/section/E5BJJj (consulted may 17, 2021).

BCCDC. Clinical Reference Group Recommendations: Therapies for COVID-19 [website]. 2021. Available at: http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments (consulted may 17, 2021).

IDSA. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection [website]. 2021. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (consulted may 17, 2021).

NIH. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [website]. 2021. Available at: https://www.covid19treatmentguidelines.nih.gov/ (consulted may 17, 2021).

Van lerssel S, Dauby N, Bottieau E, Huits R. Interim Clinical Guidance For Adults With Suspected Or Confirmed Covid-19 In Belgium [website]. Belgium : 2021. Available at: https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf (consulted may 17, 2021).

National COVID-19 Clinical evidence taskforce. Australian guidelines for the clinical care of people with COVID-19 [site Web]. National Health and Medical Research Council (NHMRC); 2021. Available at: https://app.magicapp.org/#/guideline/L4Q5An/section/L0OPkj (consulted may 17, 2021).