INESSS
LE SAVOIR PREND FORME

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COVID-19
USE OF TOCILIZUMAB OR SARILUMAB

This clinical tool is intended mainly for clinicians. It is provided for information purposes only and should not replace the judgement of the clinician who performs the activities reserved under an act or a regulation. Its content are based on a rapid ongoing review of the scientific literature available at the time of its creation and are supported by the knowledge and experience of Québec experts who contributed to its development. Under the circumstances of such a public health emergency, INESSS continues to look for any new data that could cause it to revise 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, mechanical ventilation ($pO_2/FiO_2 < 150$ **OR** $SpO_2/FiO_2 < 200$ [O_2+++]) **OR** vasopressor	Moderate	4 or 5
9. Hospitalized, mechanical ventilation ($pO_2/FiO_2 < 150$ [O_2+++]) **AND** vasopressor **OR** dialysis **OR** ECMO 10. Dead	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 an ambulatory patient.

Acronym 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 a class effect is likely, the data are more robust for tocilizumab than for sarilumab.

A graphical representation of the current scientific data will be available soon.

- Initiation of treatment with a systemic corticosteroid is strongly suggested in people with COVID-19 who require low-flow oxygen therapy, high-flow oxygen therapy, invasive or non-invasive mechanical ventilation, ECMO, or the use of a vasopressor or ionotrope. For recommendations on the use of systemic corticosteroids, see 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.

CLINICAL POSITIONS

IMPORTANT CONSIDERATIONS

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

- individuals under 18 and pregnant women
- clinical benefits of sarilumab

Participation in research efforts is important for documenting the impact of these drugs in the treatment of COVID-19. Thus, for the conditions where uncertainty persists, and if the context allow it, clinical trial enrolment should be favoured.

Considering shortage risks, 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 established. The availability of these biotherapies will need to be preserved for certain indications with no alternative, such as patients with cytokine release syndrome caused by CAR T cell-based immunotherapy.

STAGE	Mild	Moderate O_2 +		Severe to critical O_2 ++	O_2 +++
Score at initiation of treatment with tocilizumab	**1-2-3**	**4**	**5**	**6**	**7-8-9**
Adults			In combination with dexamethasone	In combination with dexamethasone	In combination with dexamethasone
< 18 years					
Pregnancy					

Strongly suggested 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. 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.

Could be initiated for this population **in combination with standard of care including dexamethasone or equivalent corticosteroid, only in the presence of systemic inflammation characterized by elevated C-reactive protein (greater than 75 mg/L) in patients at high risk for complications**, unless contraindicated. 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: low to moderate.

Use is not recommended in this population because of lower biological plausibility, scientific uncertainty about potential benefit based on stage of infection, risks that may outweigh benefits, or because other treatment options may be more beneficial. Level of scientific evidence for efficacy of tocilizumab: insufficient

Populations mainly excluded from studies. Treatment could be considered on a case-by-case basis for these populations if benefits outweigh risks. Enrollment in a research protocol remains an option. Level of scientific evidence regarding the efficacy and safety of biotherapies directed against IL-6 or its receptor in the context of COVID-19: insufficient.

Symbols and Acronym: 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 patients on low-flow oxygen therapy (score 5)			
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 for COVID-19 indication according to studies. Unofficial route of administration according to the Canadian product monograph.
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.

INFORMATION ABOUT THE DRUGS

Contraindications	• History of allergy to any component of the formulation • Severe or latent infection (e.g., tuberculosis) • Septic shock • Pre-existing condition or concomitant therapy (e.g., other biological agent) resulting in immunosuppression • 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) • 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 Events	• Infusion-related reactions • Secondary infections • Elevated liver transaminases • Neutropenia • Thrombocytopenia
Drug Interactions (list not exhaustive)	• Substrates to several CYP450 isoenzymes, including CYP3A4, 2C9, 2D6 and 2C19. • The risk of interactions between tocilizumab (or sarilumab) and remdesivir is unknown.

DISCONTINUATION CRITERIA

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

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