

COVID-19 CADTH HORIZON SCAN

CADTH Emerging Health Technology for COVID-19: Sarilumab

**This report was published on
September 2, 2020.**

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

Version: 1.0
Publication Date: September 2020
Report Length: 10 Pages

Authors: Amanda Manoharan, Christine Perras, Tarry Ahuja, Aleksandra Grobelna

Cite As: *CADTH Emerging Health Technology for COVID-19: Sarilumab*. Ottawa: CADTH; 2020 September. (CADTH horizon scan).

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

- Sarilumab is an interleukin-6 receptor antagonist that is approved, in Canada, for rheumatoid arthritis. It has emerged as a potential candidate for treating COVID-19.
- One unpublished, phase II/III randomized controlled trial (NCT04315298) assessed the efficacy and safety of sarilumab compared to placebo in adult patients hospitalized with COVID-19. The trial has stopped because of a failure to meet primary and key secondary end points.
- Two published studies evaluated the safety and efficacy of sarilumab for the treatment of COVID-19. An open-label, non-randomized, controlled study investigated sarilumab plus standard of care (n = 28) compared with standard of care alone (n = 28) in patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There was no difference in clinical improvement in the sarilumab plus standard of care group compared to the standard of care group. The data are limited because of the lack of randomization and blinding.
- A case series included eight patients hospitalized with SARS-CoV-2 who received treatment with sarilumab in addition to standard daily therapy of hydroxychloroquine, azithromycin, darunavir, cobicistat and enoxaparin. Seven patients reported an improvement in the oxygen saturation to fraction of inspired oxygen ratio (SpO₂/FiO₂), as well as a reduction in the echocardiographic assessment of valve suitability (Echo Score) that resulted in discharge within 14 days of hospitalization. The study is small and lacked a control group.
- There are ongoing randomized controlled trials investigating sarilumab monotherapy versus placebo or sarilumab combination therapies for the treatment of COVID-19.
- Overall, the published two non-randomized studies demonstrated poor-quality evidence on the efficacy and safety of sarilumab for the treatment of COVID-19.

Background

The Technology

Sarilumab (Kevzara, Sanofi and Regeneron Pharmaceuticals, Inc.) is an interleukin-6 receptor antagonist used for treatment in rheumatoid arthritis and has emerged as a potential candidate to treat COVID-19. Sarilumab inhibits the release of cytokines and the inflammatory response that follows.¹

Regulatory Status

Sarilumab is indicated for rheumatoid arthritis in Canada² and is not approved for the treatment of COVID-19.

Methods

A limited literature search was conducted by an information specialist on key resources including Ovid MEDLINE, Ovid Embase, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of

Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were sarilumab and COVID-19. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 01, 2019 and July 21, 2020.

Clinical trial registries were searched: the U.S. National Institutes of Health's clinicaltrials.gov, COVID-19 studies from the WHO database through clinicaltrials.gov, and Health Canada's Clinical Trials Database.

This CADTH Horizon Scan is not a systematic review and does not involve a critical appraisal or include a detailed summary of study findings.

Summary of the Evidence

One published open-label, non-randomized study³ and a case series⁴ evaluated the efficacy and safety of sarilumab for the treatment of COVID-19.

Of note, an unpublished, adaptive phase II/III, randomized, double-blind, placebo-controlled study assessed the efficacy and safety of sarilumab in adult patients hospitalized with COVID-19 (NCT04315298).⁵ The trial has stopped because of failure to meet primary and key secondary end points, and will not be reviewed in this horizon scan.⁶

Study Design and Patient Population

One open-label, non-randomized, controlled study was conducted in a hospital in Italy between March 14, 2020 and April 2, 2020. Patients that met the following inclusion criteria were enrolled: confirmed SARS-CoV-2 via a polymerase chain reaction test on nasal-pharyngeal swabs, bilateral pneumonia, and severe hyperinflated COVID-19. Patients who were hospitalized beyond 14 days, who had a history of using concomitant medications or immunosuppressive agents, or who were mechanically ventilated were excluded. There were 28 patients who received treatment with sarilumab plus standard of care (SoC) and 28 patients in the comparison group who received SoC. The groups were concomitantly matched according to age, sex, comorbidities, inflammatory markers, respiratory parameters, and radiological findings from lung CT scans. The total sample size included 56 patients who were prospectively followed up to day 28 of hospitalization, intensive care unit admission, discharge, or death — whichever occurred first.³

One case series conducted in a hospital in Italy included patients hospitalized with SARS-CoV-2 that was confirmed via a reverse transcription polymerase chain reaction test.⁴ The exclusion criteria, time period of the study, and duration of follow-up were not specified.

Intervention and Comparator

The open-label, non-randomized, controlled study investigated sarilumab 400 mg administered intravenously over one hour. Treatment with sarilumab was administered to patients within 24 hours of enrolment in the study. All patients received SoC, which included lopinavir-ritonavir 400 mg/100 mg orally twice daily and hydroxychloroquine 200 mg orally twice daily unless contraindicated. Patients with community- or hospital-acquired pneumonia received either daily intravenous ceftriaxone at a dose of 2 g or azithromycin at a dose of 500 mg. Supportive therapies including supplemental oxygen and/or non-invasive

ventilation with continuous positive airway pressure were available to patients at the discretion of the treating clinician.³

In the case series, patients received treatment with sarilumab 400 mg intravenously in a one-hour infusion after 24 hours of hospitalization and daily therapy with hydroxychloroquine 400 mg, azithromycin 500 mg, darunavir 800 mg, cobicistat 150 mg, and enoxaparin 100 units per kg. Subsequently, patients received treatment with 200 mg of sarilumab intravenously at 48 hours and 96 hours post-hospitalization.⁴

Outcomes

In the open-label, non-randomized, controlled study, the outcomes assessed included the following: changes in oxygen support requirement, overall survival, clinical improvement, mechanical ventilation (MV)-free survival, hospital discharge, and death, using a six-category ordinal scale recommended by the WHO R&D Blueprint. This six-point ordinal scale is categorized, as follows: 1) discharged; 2) hospitalized, not requiring supplemental oxygen; 3) hospitalized, requiring supplemental oxygen; 4) hospitalized, requiring nasal high-flow oxygen therapy, non-invasive ventilation, or both; 5) hospitalized, requiring MV, extracorporeal membrane oxygenation (ECMO), or both; and 6) death. Clinical improvement was reached if patients were discharged from hospital, had a decrease of at least two points from baseline on the six-point ordinal scale, or both. Adverse events that occurred among patients during the study treatment were reported.³

In the case series, the primary end point was the improvement in respiratory function, which included the following criteria: a reduction in $\geq 30\%$ from baseline in oxygen requirement, an improvement in oxygenation according to an increase in oxygen saturation to a fraction of the inspired oxygen ratio (SpO_2/FiO_2) by ≥ 50 compared to the nadir SpO_2/FiO_2 , for a minimum of 48 hours and improvement in ultrasound imaging. The secondary end points investigated various laboratory values at different time points.⁴ An echocardiographic assessment of valve suitability (Echo Score) and mortality were also reported. Adverse events were not assessed.

Population Characteristics and Demographics at Baseline

In the open-label, non-randomized, controlled study, the median age of patients in the sarilumab plus SoC group was 56 years (interquartile range [IQR] = 49 to 60) compared to 57 years (IQR 52 to 60) in the SoC group ($P = 0.37$). The proportion of males was slightly higher in the sarilumab plus SoC group ($n = 24$, 85%) compared to the SoC group ($n = 20$, 71%) ($P = 0.32$). The median duration of symptoms prior to study enrolment was seven days each in the sarilumab plus SoC group (IQR 6 to 10) and the SoC group (IQR 7 to 10). The median number of days of hospitalization before enrolment in the sarilumab plus SoC group and the SoC group was 2 days (IQR 1 to 3) and 3 days (IQR 1 to 3), respectively ($P = 0.51$). The most common coexisting condition among patients was hypertension reported in six patients (21%) in the sarilumab plus SoC group and 11 patients (39%) in the SoC group ($P = 0.24$).³ Overall, there were no differences between the sarilumab plus SoC group and the SoC group across baseline demographics, respiratory status, laboratory values, and radiological features.

The case series included six men and two women with a mean age of 62 years.⁴ Other baseline patient demographics were not reported.

Efficacy

The key efficacy outcome results from the open-label, non-randomized, controlled study are subsequently summarized.

At day 28 after treatment initiation, there were four patients (14%) on either MV or ECMO in the sarilumab plus SoC group compared to two patients (7%) in the SoC group.³

The hazard of death was lower in the sarilumab plus SoC group compared to the SoC group (hazard ratio [HR] = 0.36; 95% confidence interval [CI], 0.1 to 1.7); this improvement in survival in the sarilumab plus SoC group was not different from the SoC group (P = 0.21). Similarly, there was no difference between the sarilumab plus SoC group and the SoC group in MV-free survival (P = 0.52). The HR and 95% CI for MV-free survival were not reported.³

At day 28 after treatment initiation, there was no difference in clinical improvement between the sarilumab plus SoC group (n = 17, 60%) and the SoC group (n = 18, 64%) (P = 0.94). Similarly, there was no difference in mortality between the sarilumab plus SoC group (n = 2, 7%) and SoC group (n = 5, 18%) (P = 0.42). The causes of death in the sarilumab plus SoC group were refractory hypoxia in one patient and multiorgan failure in another patient. In the SoC group, one patient died from massive pulmonary embolism and two patients each died from refractory hypoxia and multiorgan failure, respectively.³

In the case series, seven patients reported an improvement in the SpO₂/FiO₂ ratio, as well as a reduction in the Echo Score.⁴ Patients received treatment with sarilumab in combination with other drugs; therefore, it cannot be determined if sarilumab had a clinical impact over the other treatments.

Safety

In the open-label, non-randomized, controlled study, the total number of adverse events reported at day 28 was higher in the sarilumab plus SoC group (n = 12, 43%) compared to the SoC group (n = 10, 36%). In the sarilumab plus SoC group, six patients (21%) reported bacterial infections while in the intensive care unit, four patients (14%) each reported neutropenia and an increase in liver enzymes, and two patients (7%) experienced thromboembolism. In the SoC group, five patients (18%) acquired a bacterial infection while in the intensive care unit and two patients (7%) experienced a thromboembolism.³ The type of adverse events experienced by three patients in the SoC group were not reported.

In the case series, adverse events were not assessed. One patient died 13 days after hospitalization.⁴

Ongoing Trials

Ongoing randomized controlled trials investigating sarilumab monotherapy versus placebo or sarilumab combination therapies for the treatment of COVID-19 are outlined in Appendix 1. The randomized controlled trials described in that table are based on the information posted on the ClinicalTrials.gov registry.⁷ The results were tabulated according to the phase of clinical development and are presented in order of estimated primary trial completion dates (the earliest first).

Of note, there may be reporting errors in the study records posted on ClinicalTrials.gov and not all ongoing trials are posted to this website. Therefore, there may be ongoing clinical trials related to COVID-19 that are missing.

References

1. Crisafulli S, Isgro V, La Corte L, Atzeni F, Trifiro G. Potential role of anti-interleukin (IL)-6 drugs in the treatment of COVID-19: rationale, clinical evidence and risks. *Biodrugs*. 2020;15:15.
2. Kevzara (sarilumab): solution for subcutaneous injection, 150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled pen interleukin-6 (IL-6) receptor antagonist [product monograph]. Laval (QC): Sanofi-aventis Canada Inc.; 2019 Aug 8.
3. Della-Torre E, Campochiaro C, Cavalli G, et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann Rheum Dis*. 2020;03:03.
4. Benucci M, Giannasi G, Cecchini P, et al. COVID-19 pneumonia treated with Sarilumab: a clinical series of eight patients. *Journal of medical virology*. 2020;30.
5. NCT04315298: Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19. Bethesda (MD): U.S. National Library of Medicine; 2020: <https://clinicaltrials.gov/ct2/show/NCT04315298>. Accessed 2020 Aug 17.
6. Sanofi and Regeneron provide update on Kevzara® (sarilumab) phase 3 U.S. trial in COVID-19 patients. 2020 Jul 2; <https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00>. Accessed 2020 Aug 17.
7. ClinicalTrials.gov. Bethesda (MD): U.S. National Library of Medicine: <https://clinicaltrials.gov/>.

Appendix 1: Ongoing Studies

Table 1: Sarilumab — Ongoing Randomized Controlled Trials (Current as of July 21, 2020)

Interventions	Trial title	Study design, country, sample size	Estimated trial primary completion date ^a	Population	ClinicalTrials.gov reference
Phase III					
Sarilumab versus placebo	An Adaptive Phase 3, Randomized, Double-blind, Placebo-controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients With COVID19	DB, PC Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russian Federation, Spain N = 409	July 30, 2020	Patients ≥18-years-old with SARS-CoV-2	NCT04327388
Phase II/III					
Sarilumab versus placebo	An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients With COVID-19	DB, PC US N = 1, 912	July 24, 2020	Patients ≥18-years-old with SARS-CoV-2	NCT04315298
Sarilumab versus best standard of care	Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Sarilumab Trial - CORIMUNO-19 - SARI	MC, OL France N = 239	May 27, 2021	Patients ≥18-years-old with moderate, severe pneumonia associated with COVID-19	NCT04324073
Phase II					
Sarilumab (200 mg) versus Sarilumab (400 mg) versus best available treatment	Clinical Trial of Sarilumab in Adults Hospitalized With COVID-19 Presenting Cytokine Release Syndrome	OL Spain N = 120	July 27, 2020	Patients ≥18-years-old to 75-years-old with COVID-19	NCT04357860

Interventions	Trial title	Study design, country, sample size	Estimated trial primary completion date ^a	Population	ClinicalTrials.gov reference
Sarilumab plus standard of care versus standard of care	Randomized Open Pilot Study to Evaluate the Efficacy of Subcutaneous Sarilumab in Patients With Moderate-severe COVID-19 Infection	SC, OL Spain N = 30	December 2020	Patients ≥18-years-old with SARS-CoV-2	NCT04357808
Tocilizumab IV versus tocilizumab SC versus sarilumab versus standard medical care	Effectiveness of Interleukin-6 Receptor Inhibitors in the Management of Patients With Severe SARS-CoV-2 Pneumonia: An Open-Label, Multicenter Sequential and Cluster Randomized Trial	OL, MC Denmark N = 200	June 1, 2021	Patients ≥18-years-old with SARS-CoV-2	NCT04322773
Sarilumab versus standard of care	Sarilumab for Patients With Moderate COVID-19 Disease: A Randomized Controlled Trial With a Play-The-Winner Design	OL US N = 120	April 2022	Patients ≥18-years-old with moderate COVID-19	NCT04359901

DB = double-blind; SC = single centre; MC = multi-centre; OL = open-label; PC = placebo-controlled; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous,

^aThe date on which data collection is completed for all the primary outcome measures.