

CADTH Reference List

Anakinra Therapy for Inflammatory Response Syndromes

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Authors: Camille Santos, Alison Adams

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Key Messages

- One randomized controlled trial and 3 non-randomized studies were identified regarding the clinical effectiveness of anakinra therapy for inflammatory response syndromes.
- No evidence was identified regarding the cost-effectiveness of anakinra therapy for inflammatory response syndromes.

Research Questions

1. What is the clinical effectiveness of anakinra therapy for inflammatory response syndromes?
2. What is the cost-effectiveness of anakinra therapy for inflammatory response syndromes?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, 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 anakinra therapy and inflammatory response syndromes. No filters were applied to limit the retrieval by study type. Comments, newspaper articles, editorials, and conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2011, and December 12, 2021. Internet links were provided, where available.

Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed.

Results

One randomized controlled trial¹ and 3 non-randomized studies²⁻⁴ were identified regarding the clinical effectiveness of anakinra therapy for cytokine storm or cytokine release syndrome. No literature was identified regarding the cost-effectiveness of anakinra therapy for inflammatory response syndromes. Additionally, no health technology assessments, systematic reviews, and economic evaluations were found.

Table 1: Selection Criteria

Criteria	Description
Population	Individuals (of all ages) with the following inflammatory response syndromes: systemic inflammatory response syndrome (SIRS), multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A), cytokine storm or cytokine release syndrome (CRS)
Intervention	Anakinra therapy
Comparators	Standard care (corticosteroids, IV immunoglobulin, cyclosporine, methotrexate and/or etoposide), Tocilizumab, Emapalumab, Cyclosporine, Etoposide, Alemtuzumab, placebo
Outcomes	Q1: Clinical effectiveness (e.g., mortality, end organ failure, hospital-acquired infections), safety (e.g., adverse events, serious adverse events, sepsis) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-years)
Study designs	Health technology assessments, systematic reviews, randomized-controlled trials, non-randomized studies, economic evaluations

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

References

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

1. Declercq J, Van Damme KFA, De Leeuw E, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. *Lancet Respir Med*. 12 2021;9(12):1427-1438. [PubMed](#)

Non-Randomized Studies

2. Narain S, Stefanov DG, Chau AS, et al. Comparative survival analysis of immunomodulatory therapy for coronavirus disease 2019 cytokine storm. *Chest*. 03 2021;159(3):933-948. [PubMed](#)
3. Iglesias-Julian E, Lopez-Veloso M, de-la-Torre-Ferrera N, et al. High dose subcutaneous Anakinra to treat acute respiratory distress syndrome secondary to cytokine storm syndrome among severely ill COVID-19 patients. *J Autoimmun*. 12 2020;115:102537. [PubMed](#)
4. Langer-Gould A, Smith JB, Gonzales EG, et al. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. *Int J Infect Dis*. Oct 2020;99:291-297. [PubMed](#)

Economic Evaluations

No literature identified.

Appendix 1: References of Potential Interest

Systematic Reviews and Meta-Analyses

Comparator Not Specified

- Panda PK, Sharawat IK, Natarajan V, Bhakat R, Panda P, Dawman L. COVID-19 treatment in children: A systematic review and meta-analysis. *J Family Med Prim Care*. Sep 2021;10(9):3292-3302. [PubMed](#)

Alternative Population – COVID-19 Patients (Unclear Diagnosis of Inflammatory Response Syndrome)

- Barkas F, Filippas-Ntekouan S, Kosmidou M, Liberopoulos E, Lontos A, Milionis H. Anakinra in hospitalized non-intubated patients with coronavirus disease 2019: a Systematic review and meta-analysis. *Rheumatology (Oxford)*. 12 01 2021;60(12):5527-5537. [PubMed](#)
- Kyriazopoulou E, Huet T, Cavalli G, et al. Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis. *Lancet Rheumatol*. Oct 2021;3(10):e690-e697. [PubMed](#)

Alternative Population (COVID-19 Patients With Unclear Diagnosis of Inflammatory Response Syndrome) and Unclear Comparator

- Khan FA, Stewart I, Fabbri L, et al. Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19. *Thorax*. 01 Sep 2021;76(9):907-919. [PubMed](#)
- Kyriakoulis KG, Kollias A, Poulakou G, et al. The effect of anakinra in hospitalized patients with COVID-19: an updated systematic review and meta-analysis. *J Clin Med*. Sep 28 2021;10(19):4462. [PubMed](#)
- Cantini F, Goletti D, Petrone L, Najafi Fard S, Niccoli L, Foti R. Immune therapy, or antiviral therapy, or both for COVID-19: a systematic review. *Drugs*. Dec 2020;80(18):1929-1946. [PubMed](#)

Randomized Controlled Trials

Alternative Population – COVID-19 (Unclear Diagnosis of Inflammatory Response Syndrome)

- Kharazmi AB, Moradi O, Haghighi M, et al. A randomized controlled clinical trial on efficacy and safety of anakinra in patients with severe COVID-19. *Immun Inflamm Dis*. Nov 11 2021;10.1002/iid3.563. [PubMed](#)

Alternative Population – Cardiac Patients (Unclear Diagnosis of Inflammatory Response Syndrome)

- Abbate A, Trankle CR, Buckley LF, et al. Interleukin-1 blockade inhibits the acute inflammatory response in patients with ST-segment-elevation myocardial infarction. *J Am Heart Assoc*. 03 03 2020;9(5):e014941. [PubMed](#)
- Van Tassel BW, Canada J, Carbone S, et al. Interleukin-1 blockade in recently decompensated systolic heart failure: Results from REDHART (Recently Decompensated Heart Failure Anakinra Response Trial). *Circ Heart Fail*. 2017;10(11):e004373. [PubMed](#)

Non-Randomized Studies

Alternative Population – COVID-19 Patients (Unclear Diagnosis of Inflammatory Response Syndrome)

- Aomar-Millan IF, Salvatierra J, Torres-Parejo U, et al. Anakinra after treatment with corticosteroids alone or with tocilizumab in patients with severe COVID-19 pneumonia and moderate hyperinflammation. A retrospective cohort study. *Intern Emerg Med*. 06 2021;16(4):843-852. [PubMed](#)
- Bozzi G, Mangioni D, Minoia F, et al. Anakinra combined with methylprednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: An observational cohort study. *J Allergy Clin Immunol*. Feb 2021;147(2):561-566.e4. [PubMed](#)
- Cavalli G, Larcher A, Tomelleri A, et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. *Lancet Rheumatol*. Apr 2021;3(4):e253-e261. [PubMed](#)
- Franzetti M, Forastieri A, Borsa N, et al. IL-1 receptor antagonist anakinra in the treatment of COVID-19 acute respiratory distress syndrome: a retrospective, observational study. *J Immunol*. 2021;206(7):1569-1575. <https://www.jimmunol.org/content/206/7/1569>. Accessed 2021 Dec 15. [PubMed](#)
- Kyriazopoulou E, Panagopoulos P, Metallidis S, et al. An open label trial of anakinra to prevent respiratory failure in COVID-19. *eLife*. 03 08 2021;10:e66125. [PubMed](#)
- Monti G, Campochiaro C, Zangrillo A, et al. Immunosuppressive strategies in invasively ventilated ARDS COVID-19 patients. *Minerva Anesthesiol*. August 2021;87(8):891-902. [PubMed](#)
- Borie R, Savale L, Dossier A, et al. Glucocorticoids with low-dose anti-IL1 anakinra rescue in severe non-ICU COVID-19 infection: A cohort study. *PLoS ONE*. 2020;15(12):e0243961. [PubMed](#)
- Cauchois R, Koubi M, Delarbre D, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc Natl Acad Sci U S A*. 08 11 2020;117(32):18951-18953. [PubMed](#)
- Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. Jun 2020;2(6):e325-e331. [PubMed](#)

23. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol*. Jul 2020;2(7):e393-e400. [PubMed](#)
24. Kooistra EJ, Waalders NJB, Grondman I, et al. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care*. 12 10 2020;24(1):688. [PubMed](#)

Case Series

25. Della Paolera S, Valencic E, Piscianz E, et al. Case report: use of anakinra in multisystem inflammatory syndrome during COVID-19 pandemic. *Front Pediatr*. 2021;8:624248. [PubMed](#)
26. Fouriki A, Fougere Y, De Camaret C, et al. Case report: case series of children with multisystem inflammatory syndrome following SARS-CoV-2 infection in Switzerland. *Front Pediatr*. 2021;8:594127. [PubMed](#)
27. Navarro-Millan I, Sattui SE, Lakhnpal A, Zisa D, Siegel CH, Crow MK. Use of anakinra to prevent mechanical ventilation in severe COVID-19: a case series. *Arthritis Rheumatol*. 12 2020;72(12):1990-1997. [PubMed](#)

Case Reports

28. Aggarwal A, Cohen E, Figueira M, et al. Multisystem inflammatory syndrome in an adult with COVID-19—a trial of anakinra: a case report. *Infect Dis Clin Pract (Baltim Md)*. Nov 2021;29(6):e420-e423. [PubMed](#)
29. Cattaneo P, Volpe A, Cardellino CS, et al. Multisystem inflammatory syndrome in an adult (MIS-A) successfully treated with anakinra and glucocorticoids. *Microorganisms*. Jun 28 2021;9(7):1393. [PubMed](#)
30. Trpkov C, MacMullan P, Feuchter P, et al. Rapid response to cytokine storm inhibition using anakinra in a patient with COVID-19 myocarditis. *CJC Open*. Feb 2021;3(2):210-213. [PubMed](#)
31. Cirks BT, Geracht JC, Jones OY, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case report on managing the hyperinflammation. *Mil Med*. Nov 26 2020;usaa508. [PubMed](#)
32. Nemchand P, Tahir H, Mediwake R, Lee J. Cytokine storm and use of anakinra in a patient with COVID-19. *BMJ Case Rep*. Sep 15 2020;13(9):e237525. [PubMed](#). [PM32933914](#) [PubMed](#)