NICE National Institute for Health and Care Excellence

Sarilumab for COVID-19

Evidence review

20 January 2021

This evidence review sets out the best available evidence on sarilumab for treating COVID-19. It should be read with the evidence summary, which gives the likely place in therapy and factors for decision making.

Commissioned by NHS England.

Disclaimer

The content of this evidence review was up to date in January 2021.

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Contents

Background

COVID-19 is a disease caused by a novel coronavirus that emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold. COVID-19 manifests as a respiratory illness, of widely varying clinical severity. At the most severe end of the spectrum, it results in severe pneumonia and respiratory failure. Acute respiratory distress syndrome (ARDS) is often the preterminal event in people with COVID-19. Severe COVID-19 is often associated with release of proinflammatory cytokines, which may cause or exacerbate lung injury leading to life-threatening disease.

As of 10 January 2021, the World Health Organization COVID-19 dashboard reports 88,828,387 confirmed cases of COVID-19, with 3,017,413 confirmed cases and 80,868 deaths in the UK.

Intervention

Sarilumab is a monoclonal antibody that is an antagonist to the membrane-bound and soluble interleukin-6 (IL-6) receptor. IL-6 is a proinflammatory cytokine that is a key driver behind the cytokine-release syndrome seen in people with severe COVID-19. By targeting IL-6 receptors, sarilumab may mitigate the cytokine-release syndrome and prevent progression of disease.

Sarilumab has marketing authorisation for moderate to severe rheumatoid arthritis in adults whose condition has not responded adequately to 1 or more disease modifying antirheumatic drugs. It is licensed for use in combination with methotrexate, or as monotherapy if methotrexate is inappropriate or not tolerated. In rheumatoid arthritis the recommended dosage of sarilumab is 200 mg once every 2 weeks administered as a subcutaneous injection. A reduced dosage of 150 mg once every 2 weeks is recommended for the management of neutropenia, thrombocytopenia and liver enzyme elevations (summaries of product characteristics for sarilumab).

The marketing authorisations for sarilumab do not cover use in COVID-19. This use is therefore off label, and the prescriber should follow relevant professional guidance

and take full responsibility for the decision. See the General Medical Council's good practice in prescribing and managing medicines and devices for further information.

The dosage of sarilumab used in the REMAP-CAP study (NCT02735707) was a single dose of 400 mg as an intravenous infusion. This evidence review only considers this dose and route. The dosage of sarilumab used in unpublished studies for COVID-19 has varied. Subcutaneous or intravenous doses of 150 mg to 400 mg have been used, usually as a single dose (sometimes a further dose has been given after 24 hours if no improvement).

The most commonly reported adverse drug reactions with sarilumab include neutropenia, deranged liver enzymes, upper respiratory tract infections and urinary tract infections (summaries of product characteristics for sarilumab).

Clinical problem

The UK and Europe are currently experiencing a second wave of COVID-19, with the peak of the first wave having occurred in April 2020 in the UK. Initial UK hospital data suggest that increasing age over 50 years is a strong predictor of mortality in hospital (hazard ratio 2.6 for 50 to 59 years, 5.0 for 60 to 69 years, 8.5 for 70 to 79 years and 11.1 for 80 years or over; Docherty et al. 2020). UK primary care record data from 17.3 million patients linked to 10,926 COVID-19-related deaths in hospital showed that mortality was strongly associated with male gender, greater age, black or South Asian ethnicity, deprivation, obesity, diabetes, cardiovascular and respiratory comorbidities (Williamson et al. 2020). The Chinese Centre for Disease Control and Prevention reported that cardiovascular disease, hypertension, diabetes, respiratory disease and cancers are risk factors for mortality (Deng et al. 2020). Children and young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions in this age group (Lu et al. 2020).

Between 1 March and 31 August 2020, the Intensive Care National Audit Research Centre (ICNARC) was notified of 10,904 patients who were admitted to critical care with COVID-19 in England, Wales and Northern Ireland. From 1 September to 4 December 2020, there have been a further 6,388 patients with confirmed COVID-19 admitted to critical care in these areas, with daily admissions showing an upward trend.

Objective

This evidence review aims to review the best available evidence on the effectiveness and safety of sarilumab in adults and children hospitalised with moderate, severe or critical suspected or confirmed COVID-19.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NHS England for the topic (see appendix A for more information). The review questions for this evidence review are:

1. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the clinical effectiveness of sarilumab compared with placebo or standard care?

2. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of sarilumab compared with placebo or standard care?

3. From the evidence selected, are there any subgroups of patients who may benefit (or be harmed) from sarilumab more than the wider population of interest?

4. From the evidence selected, what dose or regimen of sarilumab did patients receive?

5. From the evidence selected, which treatments had patients received as standard care?

Summary of included studies

A literature search for sarilumab identified 159 references (see appendix E for full details). These references were screened using their titles and abstracts, and no references met the PICO criteria. Therefore, no full-text references were obtained and assessed for relevance.

The prepublication study results from the nationally prioritised platform study, REMAP-CAP (study NCT02735707) are included in this evidence summary. This study included 450 adults with severe COVID-19 who were critically ill and receiving

respiratory or cardiovascular organ support in intensive care (71% having non-invasive or mechanical ventilation). A summary of the included study is shown in appendix B. Quality assessment of the included study is in appendix C.

No studies were excluded after full text review. See appendix F.

Effectiveness and safety

Full details of the results are in appendix D.

Review question 1: In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the clinical effectiveness of sarilumab compared with placebo or standard care?

Mortality

REMAP-CAP found that, in adults with severe COVID-19 who were critically ill and receiving respiratory or cardiovascular organ support in an intensive care setting (71% on non-invasive or mechanical ventilation), there were fewer in-hospital deaths in the sarilumab group (10/45, 22.2%) compared with the standard care group (142/397, 35.8%).

There was a statistically significant improvement in-hospital survival (median adjusted odds ratio [aOR] 2.01, 95% credible interval [CrI] 1.18 to 4.71, 99.5% probability of superiority) and 90-day survival (median adjusted hazard ratio [aHR] 1.82, 95% CrI 1.22 to 3.38, probability of superiority 99.8%) with sarilumab compared with standard care.

Organ support

REMAP-CAP found that, in adults with severe COVID-19 who were critically ill, the median number of days free of organ support (respiratory or cardiovascular support) up to 21 days was statistically significantly higher in the sarilumab group (11 days, inter-quartile range [IQR] 0 to 16) compared with the standard care group (0 days, IQR -1 to 15). The median aOR was 1.76 (95% CrI 1.17 to 2.91, probability of superiority 99.5%). Days free of organ support was a composite ordinal outcome that included death during acute hospital admission. All deaths within hospital were assigned -1.

The median number of days free of organ support in survivors (excluding all people who died during hospital admission) up to 21 days was 15 (IQR 6.5 to 17) in the sarilumab group and 13 (IQR 4 to 17) in the standard care group

Time to discharge (critical care or hospital)

REMAP-CAP found that, in adults with severe COVID-19 who were critically ill, there was a statistically significant reduction in time to intensive care discharge (median aHR 1.64, 95% CrI 1.21 to 2.45, probability of superiority 99.9%) and time to hospital discharge (median aHR 1.60, 95% CrI 1.17 to 2.40, probability of superiority 99.8%) with sarilumab compared with standard care.

Disease progression or change in clinical status

REMAP-CAP found that, in adults with severe COVID-19 who were critically ill, there was a statistically significant improvement in the World Health Organization (WHO) scale at day 14 (median aOR 1.86, 95% CrI 1.22 to 2.91, probability of superiority 99.6%). The WHO scale ranges from 0 (no disease) to 8 (death).

In adults who were not intubated at baseline (310/450, 69%), statistically significantly fewer people progressed to invasive mechanical ventilation, extracorporeal membrane oxygenation, or death in the sarilumab group (13/37, 35.1%) compared with the standard care group (114/273, 52.7%; median aOR 1.74, 95% CrI 1.01 to 3.14, probability of superiority 97.7%).

Review question 2: In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of sarilumab compared with placebo or standard care?

Adverse events

There was no statistically significant difference in the number of adults with at least 1 serious adverse event between sarilumab (0/48, 0.0%) and standard care (11/402, 2.7%) in REMAP-CAP.

See the summaries of product characteristics for sarilumab for contraindications, cautions and a general summary of the safety profile.

Review question 3: From the evidence selected, are there any subgroups of patients that may benefit (or be harmed) from sarilumab more than the wider population of interest?

In the prepublication study results from REMAP-CAP, there was insufficient detail to accurately assess subgroups of interest.

Review question 4: From the evidence selected, what dose or regimen of sarilumab did patients receive?

In REMAP-CAP, sarilumab was given as a single dose of 400 mg by intravenous infusion.

Review question 5: From the evidence selected, which treatments had patients received as standard care?

In REMAP-CAP, standard care included corticosteroids in most patients and remdesivir in about a third of patients.

Limitations of the evidence

This evidence review includes 1 prepublication study only. Although REMAP-CAP is a nationally prioritised platform study, the data included in this evidence review are preliminary and the study results have not been peer reviewed. There was insufficient detail available to accurately assess the statistical approach taken. No published randomised controlled trials were identified, so it is possible that the findings may change if further evidence becomes available.

REMAP-CAP investigated adults with severe COVID-19 who were critically ill and receiving organ support in an intensive care setting (71% receiving non-invasive or mechanical ventilation). Patients had to be randomised within 24 hours of starting organ support. The benefits and harms of treatment with sarilumab in people with less severe disease or who have been receiving organ support for more than 24 hours cannot be determined from the available evidence.

In REMAP-CAP, risk of bias was rated as 'some concerns'. The study was open label, therefore could be subject to bias. However, a lack of blinding is unlikely to

have affected the composite primary outcome of organ support-free days and mortality. Although, it may have affected safety outcomes, including reporting of adverse events.

The number of patients randomised to sarilumab in REMAP-CAP was small (n=48). The authors of the study explain that sarilumab only became available later in the study timeline. REMAP-CAP is an ongoing trial, and future results will likely include higher patient numbers for sarilumab.

REMAP-CAP allowed concomitant standard care in both groups, including corticosteroids in most patients and remdesivir in around one-third. There were no apparent differences in demographics or baseline comorbidities between groups in REMAP-CAP.

The primary outcome of REMAP-CAP was reported at 21 days, with secondary outcomes reporting up to 90 days, and some patients were still in hospital at the time of reporting. Therefore, the long-term effects of sarilumab in COVID-19 beyond this timepoint are not known.

REMAP-CAP included adults only, so it is not possible to say what the efficacy or safety of sarilumab is in children or young people.

References

Deng G, Yin M, Chen X et al. (2020) Clinical determinants for fatality of 44,672 patients with COVID-19. Critical Care 24: 179 doi.org/10.1186/s13054-020-02902-w

Docherty A, Harrison E, Green C et al. (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study British Medical Journal 369: m1985

Lu X, Zhang L, Du H et al. (2020) SARS-CoV-2 infection in children. New England Journal of Medicine 382: 1663–5 doi:10.1056/NEJMc2005073

The REMAP-CAP investigators. (2021) Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report (9 Jan 2021). medRxiv 2021.01.07.21249390, doi: https://doi.org/10.1101/2021.01.07.21249390

Williamson EJ, Walker AJ, Bhaskaran K. et al. (2020) Factors associated with COVID-19-related death using OpenSAFELY. Nature 584: 430–6 doi.org/10.1038/s41586-020-2521-4

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Details of expert advisers and any declarations of interest

Name, job title, organisation	Declaration of interests
Dr Daniele Bryden, consultant in intensive care medicine, Sheffield NHS Foundation Trust; vice dean, Faculty of Intensive Care Medicine	No direct interests
Dr James Watts, consultant in anaesthesia and critical care, East Lancashire Hospitals NHS Trust	No direct interests
Professor Mike Morgan, consultant respiratory physician, University Hospitals of Leicester NHS Trust	No direct interests
Dr Natasha Ratnaraja , consultant in infection, University Hospitals Coventry and Warwickshire NHS Trust	No direct interests

Appendices

Appendix A: PICO table

Population, Intervention, Comparator and Outcomes (PICO) table

Criteria	Details
Population and indication	Adults and children hospitalised with moderate, severe or critical suspected or confirmed COVID-19 (COVID-19 infection is the acute clinical syndrome caused by SARS-CoV-2 virus). Subgroups: • adults >50 years • children <12 years • disease severity (moderate, severe or critical) • gender • ethnic background • pregnant women • comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • time from symptom onset.
Intervention	Sarilumab delivered as a subcutaneous injection or intravenous infusion
Comparators	Placebo with standard care or standard care alone. Standard care comprises best supportive care and, in certain circumstances, additional drugs (such as dexamethasone, remdesivir).

Outcomes	Critical to decision making:
	• mortality
	• requirement for or duration of:
	  ○ mechanical ventilation
	  ○ non-invasive ventilation (continuous positive airway pressure, non-invasive ventilation or high-flow oxygen therapy)
	  ○ organ support (extracorporeal membrane oxygenation,

Criteria	Details

	vasopressors, renal replacement treatment)
	• serious adverse events (grade 3 or 4).
	
	Important to decision making:
	• time to recovery or SARS-CoV-2 RT-polymerase chain reaction negativity
	• length of stay (hospital or critical care)
	• disease progression or change in clinical status, to include:
	  ○ initiation of ventilation
	  ○ transfer or admission to critical care.
	Adverse events.

Inclusion criteria	-
Study design	Systematic reviews of randomised controlled trials and randomised controlled trials
Language	English
Patients	Human studies only
Age	All ages
Date limits	2019-2020
Exclusion criteria	-
Publication type	Preprints before peer review. Apart from: • peer-reviewed journal publications (including in-press, preproof or epub-ahead-of-print articles) or • prepublication study results that meet minimum dataset requirements from Department of Health and Social Care nationally prioritised platform studies, such as RECOVERY or REMAP-CAP.
Study design	Controlled clinical trials, observational studies including case series and case reports

Appendix B: Summary of included studies

Summary of included studies table

Study	Number of patients	Population	Intervention	Comparison	Outcomes
REMAP-CAP 2020 (NCT02735707) Prepublication open-label randomised controlled trial Global, mainly UK	n=450	Adults with severe suspected or confirmed COVID-19 who were critically ill and receiving respiratory or cardiovascular organ support in an intensive care setting. Patients were randomised within 24 hours after starting organ support, and treatment was started immediately after allocation was revealed. Baseline respiratory support: None or supplemental oxygen only (0.4%) High-flow nasal cannula (28.2%) Non-invasive ventilation (42.7%) Mechanical ventilation (28.7%) Patients were excluded where there was a presumption	Sarilumab 400 mg intravenous infusion, single dose only (n=48)	Standard care including corticosteroids in most patients and remdesivir in about a third of patients (n=402)	Primary outcome: Composite of organ support-free days up to day 21 and in-hospital deaths Secondary outcomes: In-hospital deaths Organ support-free days in survivors

Study	Number of patients	Population	Intervention	Comparison	Outcomes
		that death was imminent.			

Mechanical (invasive) ventilation: the patient is anesthetised, and a tube is inserted into the trachea and attached to a mechanical ventilator.

Non-invasive ventilation: breathing support is given through a face mask, nasal mask, or helmet.

In REMAP-CAP patients were included who had suspected or proven pandemic (COVID-19) infection of a severe disease state. This was defined by the patient receiving respiratory or cardiovascular organ failure support in an intensive care unit. Respiratory organ support was defined as non-invasive or mechanical ventilation including via high-flow nasal cannula, if the flow rate was greater than 30 litre/min and fraction of inspired oxygen (FiO2) greater than 0.4. Pandemic surge capacity meant that provision of advanced organ support may have occurred in locations that do not usually provide intensive care. Therefore, an intensive care unit was defined as an area of the hospital repurposed to be able to deliver organ support.

Appendix C: Quality assessment of included studies

Quality assessment of REMAP-CAP (based on prepublication manuscript)

Question	REMAP-CAP
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Probably no
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Risk of bias judgement	Low risk
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Not applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable

Question	REMAP-CAP
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably yes
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No information
Risk of bias judgement	Some concerns
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No
Risk of bias judgement	Low
Overall risk of bias judgement	Some concerns

Checklist used: Cochrane risk of bias 2 tool.

Appendix D: Results tables

Results table for REMAP-CAP

Outcome	Sarilumab	Standard care	Analysis
Primary outcome	**n=48**	**n=402**	**-**
Organ support-free days up to 21 days (median) This is a composite outcome comprising • mortality during the acute hospital admission (scored as -1 days) and • number of study days for which the patient did not require organ failure support while admitted to an intensive care unit up until the end of study day 21	11 (IQR 0 to 16)	0 (IQR -1 to 15)	Median aOR 1.76 (95% CrI 1.17 to 2.91, 99.5% posterior probability of superiority)
Hospital survival (survival during hospital admission)	-	-	Median aOR 2.01 (95% CrI 1.18 to 4.71, 99.5% posterior probability of superiority)
Secondary outcomes	**n=48**	**n=402**	**-**
In-hospital deaths (subcomponent of 'organ support-free days') Timescale not reported	10/45 (22.2%)	142/397 (35.8%)	-
Organ support-free days in survivors (median; (subcomponent of 'organ support-free days') 21 days	15 (IQR 6.5 to 17)	13 (4 to 17)	-
Survival (time to event) 90 days	-	-	Median aHR 1.82 (95% CrI 1.22 to 3.38, 99.8% posterior probability of superiority)
Time to discharge from intensive care 90 days	-	-	Median aHR 1.64 (95% CrI 1.21 to 2.45, 99.9% posterior

			probability of superiority)
Time to hospital discharge 90 days	-	-	Median aHR 1.60 (95% CrI 1.17 to 2.40, 99.8% posterior probability of superiority)
World health organization (WHO) scale At day 14	-	-	Median aOR 1.86 (95% CrI 1.22 to 2.91, 99.6% posterior probability of superiority)
Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation, or death (in patients not intubated at baseline)	13/37 (35.1%)	144/273 (52.7%)	Median aOR 1.74 (95% CrI 1.01 to 3.14, 97.7% posterior probability of superiority)
Safety outcomes	**n=48**	**n=402**	**-**
Serious adverse events (number of patients with at least 1 event)	0/48 (0.0%)	11/402 (2.7%)	Median aOR 2.10 (95% CrI 0.51 to 10.77, probability of superiority 84.0%)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CrI, credible interval; IQR, inter-quartile range

The World Health Organization (WHO) scale ranges from 0 (no disease) to 8 (death).

Median organ support-free days include days free of respiratory and cardiovascular organ support and death, where all deaths were assigned a value of -1.

Appendix E: Literature search strategy

Database	Platform	Segment searched
MEDLINE ALL	Ovid	Ovid MEDLINE(R) ALL 1946 to January 06, 2021
Embase	Ovid	Embase 1974 to January 06, 2021
Cochrane Library	Wiley	Issue 1 of 12, January 2021
WHO COVID-19 database	WHO website	-

Source	No. of results
MEDLINE ALL	37
Embase	143
Cochrane Library - CDSR	0
Cochrane Library - Central	6
WHO COVID-19 database	13
Total results	199
Total after deduplications	159

Database search strategies

MEDLINE ALL

1 sarilumab.af. (184)
2 kevzara.af. (16)
3 ("regn 88" or regn88).af. (3)
4 ("sar 153191" or sar153191).af. (2)
5 "1189541-89-7".af. (0)
6 or/1-5 (185)
7 exp coronavirus/ (45387)
8 exp Coronavirus Infections/ (49625)
9 COVID-19/ (9242)
10 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (2626)
11 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (61003)
12 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (85861)
13 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (311)
14 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (96)
15 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (557)
16 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (348)
17 "severe acute respiratory syndrome*".ti,ab,kw,kf. (15555)
18 or/7-17 (112001)

19 limit 18 to yr="2019 -Current" (92585)
20 6 and 19 (64)
21 randomized controlled trial.pt. (520231)
22 random*.mp. (1427565)
23 placebo.mp. (221425)
24 controlled clinical trial/ (94003)
25 clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ (52305)
26 equivalence trial/ (697)
27 pragmatic clinical trial/ (1600)
28 trial.tw. (625354)
29 trials.tw. (580966)
30 intervention.tw. (628550)
31 interventions.tw. (481884)
32 or/21-31 (2813243)
33 20 and 32 (37)
34 (MEDLINE or pubmed).tw. (224959)
35 systematic review.tw. (174439)
36 systematic review.pt. (142470)
37 meta-analysis.pt. (124597)
38 intervention$.ti. (157430)
39 or/34-38 (496252)
40 20 and 39 (7)
41 33 or 40 (37)

Embase

1 sarilumab/ (849)
2 sarilumab.af. (881)
3 kevzara.af. (51)
4 ("regn 88" or regn88).af. (28)
5 ("sar 153191" or sar153191).af. (17)
6 "1189541-89-7".af. (0)
7 or/1-6 (889)
8 exp Coronavirinae/ (22773)
9 exp Coronavirus infection/ (24377)
10 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (78614)
11 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (2078)
12 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (61251)
13 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (82885)
14 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (385)
15 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (102)
16 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (615)
17 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (161)
18 "severe acute respiratory syndrome*".ti,ab,kw. (15467)
19 or/8-18 (117235)
20 limit 19 to yr="2019 -Current" (93803)
21 limit 20 to medline (22378)
22 20 not 21 (71425)
23 7 and 22 (312)

24 random:.tw. (1622328)
25 placebo:.mp. (468148)
26 double-blind:.tw. (216967)
27 exp randomized controlled trial/ (641075)
28 trial.tw. (902752)
29 trials.tw. (805582)
30 intervention.tw. (934252)
31 interventions.tw. (600003)
32 or/24-31 (3754540)
33 23 and 32 (133)
34 (MEDLINE or pubmed).tw. (283016)
35 exp systematic review/ or systematic review.tw. (332726)
36 meta-analysis/ (205348)
37 intervention$.ti. (211016)
38 or/34-37 (706953)
39 23 and 38 (31)
40 33 or 39 (143)

Cochrane Library (CDSR and CENTRAL)

#1 sarilumab:ti,ab,kw 248
#2 kevzara:ti,ab,kw 15
#3 ("regn 88" or regn88):ti,ab,kw 26
#4 ("sar 153191" or sar153191):ti,ab,kw 34
#5 "1189541-89-7":ti,ab,kw 0
#6 {or #1-#5} 261
#7 [mh "COVID-19"] 0
#8 MeSH descriptor: [Coronavirus] explode all trees 139
#9 MeSH descriptor: [Coronavirus Infections] explode all trees 567
#10 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw 182
#11 (coronavirus* or coronovirus* or coronavirinae* or CoV):ti,ab,kw 2363
#12 ("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid):ti,ab,kw 3810
#13 (respiratory* near/2 (symptom* or disease* or illness* or condition*) near/5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 29
#14 (("seafood market" or "seafood markets" or "food market" or "food markets") near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 5
#15 (pneumonia* near/3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 39
#16 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 4
#17 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes"):ti,ab,kw 678
#18 {or #7-#17} 4133
#19 #6 and #18 28
#20 (trialsearch OR clinicaltrials):so 352906
#21 #19 not #20 6

Also browsed Cochrane collections on evidence relevant to critical care and rapid reviews in response to COVID-19. No relevant results found.

Covid-19 databases and collections

Name	**BMJ Best Practice Coronavirus disease 2019 (COVID-19)**
URL	https://bestpractice.bmj.com/topics/en-gb/3000168
Search info including how the results were selected	Browsed emerging treatments section. No mention of sarilumab as a treatment, nor is it mentioned withing the interleukin-6 (IL-6) inhibitors section.
Results (number)	0

Name	**World Health Organization Global research on coronavirus disease (COVID-19)**
-	"WHO is gathering the latest scientific findings and knowledge on coronavirus disease (COVID-19) and compiling it in a database. We update the database daily from searches of bibliographic databases, hand searches of the table of contents of relevant journals, and the addition of other relevant scientific articles that come to our attention."
URL (WHO landing page)	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov
URL (search page)	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
Search info including how the results were selected	Searched for (sarilumab OR kevzara OR regn88 OR (regn 88) OR (sar 153191) OR sar153191) Returned 44 results. Limited source databases using on-screen filters to: WHO COVID; ELSEVIER; LILACS; Grey literature. This was done in order to remove as many Medline or pre-print references as possible since these are either not required or covered elsewhere in the searches. 13 results remained after filters applied.
Results (number)	13

Name	**Cochrane COVID-19 living evidence project**
URL	https://covid-nma.com/living_data/index.php
-	"The project includes two main parts: living mapping of ongoing research followed by living synthesis of study results as soon as they are available."
Search info including how the results were selected	Browsed under: Living Evidence Synthesis > Pharmacological Treatments > Monoclonal Antibodies
Results	0

Evidence reviews and guidance

Name	**MHRA**
URL	https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19
Search info including how the results were selected	Browsed landing page and conducted a general gov.uk site search for sarilumab
Results	0

Name	**Norwegian Institute of Public health – map of COVID-19 evidence**
URL	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
Search info including how the results were selected	Searched the pharmaceutical and non-pharmaceutical interventions section for sarilumab. 9 articles returned. Cross checked against Eppi database, 3 not already listed so added manually
Results	3

Name	**Centre for Evidence-based medicine (CEBM) COVID-19 Evidence Service**
URL	https://www.cebm.net/oxford-covid-19-evidence-service/
Search info including how the results were selected	Searched site for sarilumab. No results
Results	0

Appendix F: Excluded studies

There were no excluded studies (no studies were requested for full text review).