THE LANCET
Rheumatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kyriazopulou 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* 2021; published online Aug 9. https://doi.org/10.1016/S2665-9913(21)00216-2.

Search Strategy.

PubMed (Date Run: 22/01/2021)		
Step	**Search strategy**	**Found**
#1	(((COVID-19[MeSH Terms]) AND (anakinra[MeSH Terms])) OR ((COVID-19[MeSH Terms]) AND (interleukin blockade[MeSH Terms])) OR ((COVID-19[MeSH Terms]) AND (interleukin-1[MeSH Terms])) OR ((SARS-CoV-2[MeSH Terms]) AND (anakinra[MeSH Terms])) OR ((SARS-CoV-2[MeSH Terms]) AND (interleukin blockade[MeSH Terms])) OR ((SARS-CoV-2[MeSH Terms]) AND (interleukin-1[MeSH Terms])))	95
#2	(((COVID-19[MeSH Terms]) AND (anakinra[MeSH Terms])) OR ((COVID-19[MeSH Terms]) AND (interleukin blockade[MeSH Terms])) OR ((COVID-19[MeSH Terms]) AND (interleukin-1[MeSH Terms])) OR ((SARS-CoV-2[MeSH Terms]) AND (anakinra[MeSH Terms])) OR ((SARS-CoV-2[MeSH Terms]) AND (interleukin blockade[MeSH Terms])) OR ((SARS-CoV-2[MeSH Terms]) AND (interleukin-1[MeSH Terms]))) Filters: Humans, English	92

Cochrane Central Register of Clinical Trials (Date Run: 22/01/2021)		
ID	**Search strategy**	**Found**
#1	(COVID-19):ti,ab,kw OR ("SARS Co-V"):ti,ab,kw	3728
#2	("anakinra"):ti,ab,kw OR ("interleukin-1 blockade "):ti,ab,kw	412
#3	#1 AND #2	30
#4	Removal of dublicates	1

Medrxiv.org (Date Run: 22/01/2021)		
ID	**Search strategy**	**Found**
#1	Anakinra AND COVID-19	10
#2	Interleukin blockade AND COVID-19	6
#3	Interleukin-1 AND COVID-19	7
#4	(Anakinra OR interleukin blockade OR interleukin-1) AND COVID-19	23

Biorxiv.org (Date Run: 22/01/2021)		
ID	**Search strategy**	**Found**
#1	anakinra AND COVID-19	4
#2	Interleukin blockade AND COVID-19	0
#3	Interleukin-1 AND COVID-19	22
#4	(Anakinra OR interleukin blockade OR interleukin-1) AND COVID-19	26

Clinicaltrials.gov (Date Run: 22/01/2021)		
ID	**Search strategy**	**Found**
#1	anakinra AND COVID-19	34
#2	Removal of dublicates	32

eTable 1. Ongoing trials of anakinra administration in patients with pneumonia due to COVID-19.

Study	Country	Inclusion criteria of thrombo-inflammation	Arms of treatment	Number of patients	Primary Endpoint
Anakinra in the Management of COVID-19 Infection (NCT04643678)	Qatar	Signs of cytokine release syndrome	• Anakinra • SOC	80	WHO Clinical Progression score at day 14
Early Treatment of Cytokine Storm Syndrome in Covid-19 (NCT04362111)	Alabama, US	Ferritin >700 ng/ml and fever >38ºC and any 3 of: d-dimer>500 ng/ml; plt <130,000/mm^3; WBC<3500/mm^3; AST or ALT>2x ULN; LDH>2x ULN; CRP>100 mg/L	• Anakinra • Placebo	30	Percentage of patients discharged alive and without need for mechanical ventilation at day 28
suPAR-Guided Anakinra Treatment for Management of Severe Respiratory Failure by COVID-19 (SAVE-MORE) (NCT04680949)	Greece	Plasma suPAR ≥6ng/ml	• Anakinra • Placebo	600	WHO Clinical Progression ordinal Scale at day 28
Anakinra, COVID-19, Cytokine Storm (Sobi) (NCT04603742)	New York, US	Cytokine release syndrome	• Anakinra • Placebo	100	Number of subjects alive without having required mechanical ventilation at day 28
A Trial Using anakinra, tocilizumab Alone or in Association With ruxolitinib in Severe Stage 2b and 3 of COVID19-associated Disease (INFLAMMACOV) (NCT04424056)	France	Early stage: CRP>150mg/l Advanced stage: ferritin>5000ng/ml	• Anakinra +/- Ruxolitinib • Anakinra + ruxolitinib • Tocilizumab +/- ruxolitinib • Tocilizumab + ruxolitinib • SOC	216	Ventilation free days at day 28
The Immunomodulation-CoV Assessment (ImmCoVA) Study (NCT04412291)	Sweden	CRP >70mg/L and ferritin >500µg/L and at least 2 of: lymphocytes <1x 10^9/L; D-dimer ≥0.5mg/L; LDH ≥8microkatal/L.	• Anakinra • Tocilizumab • SOC	120	Time to recovery at day 29
Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to Covid-19 (ANA-COVID-GEAS) (NCT04443881)	Spain	Suspicion of cytokine release syndrome	• Anakinra • SOC	180	Number of patients not requiring mechanical ventilation at day 15

Treatment of COVID-19 Patients With Anti-interleukin Drugs (COV-AID) (NCT04330638)	Belgium	Ferritin >1000 µg/L; or lymphopenia <800 µl and 2 of the following extra: ferritin > 700µg/L or LDH>300 IU/L or D-Dimers >1000 ng/mL or CRP>70mg/L	• Anakinra • Siltuximab • Anakinra + siltuximab • Anakinra + tocilizumab • SOC	342	Time to clinical improvement at day 15
Trial Evaluating Efficacy Of Anakinra In Patients With Covid-19 Infection (CORIMUNO-ANA-2) (NCT04341584)	France	CRP>25mg/L	• Anakinra • SOC	161	WHO Clinical Progression ordinal Scale
Evaluation of Safety and efficacy of anakinra utilization in COVID-19, a randomized controlled clinical trial (IRCT20120703010178N20)	Iran	_	• Anakinra • SOC	30	WHO Clinical Progression ordinal Scale

eTable 2. Risk assessment of included studies according to Newcastle-Ottawa Quality Assessment Scale.

	Selection				Comparability	Outcome			
Ref.	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at study start**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Total**
29	*	*	*	*	**	*	*	*	9
24		*	*	*	**	*	*	*	8
21		*	*	*	**	*	*	*	8
25		*	*	*	**	*	*	*	8
22	*	*	*	*	**	*	*	*	9
27		*	*	*	**	*	*	*	8
28		*	*	*	**	*	*	*	8
23	*	*	*	*	**	*	*	*	9
26	*	*	*	*	**	*	*	*	9

Selection

Representativeness of the exposed cohort (* for a and b) a) truly representative of the average in the community; b) somewhat representative of the average in the community; c) selected group of users eg nurses, volunteers; d) no description of the derivation of the cohort

Selection of the non-exposed cohort (* for a) a) drawn from the same community as the exposed cohort; b) drawn from a different source; c) no description of the derivation of the non-exposed cohort

Ascertainment of exposure (* for a and b) a) secure record (eg surgical records); b) structured interview; c) written self report; d) no description

Demonstration that outcome of interest was not present at start of study (* for a) a) yes; b) no

Comparability

Comparability of cohorts on the basis of the design or analysis a) study controls for the most important factor **; b) study controls for any additional factor*

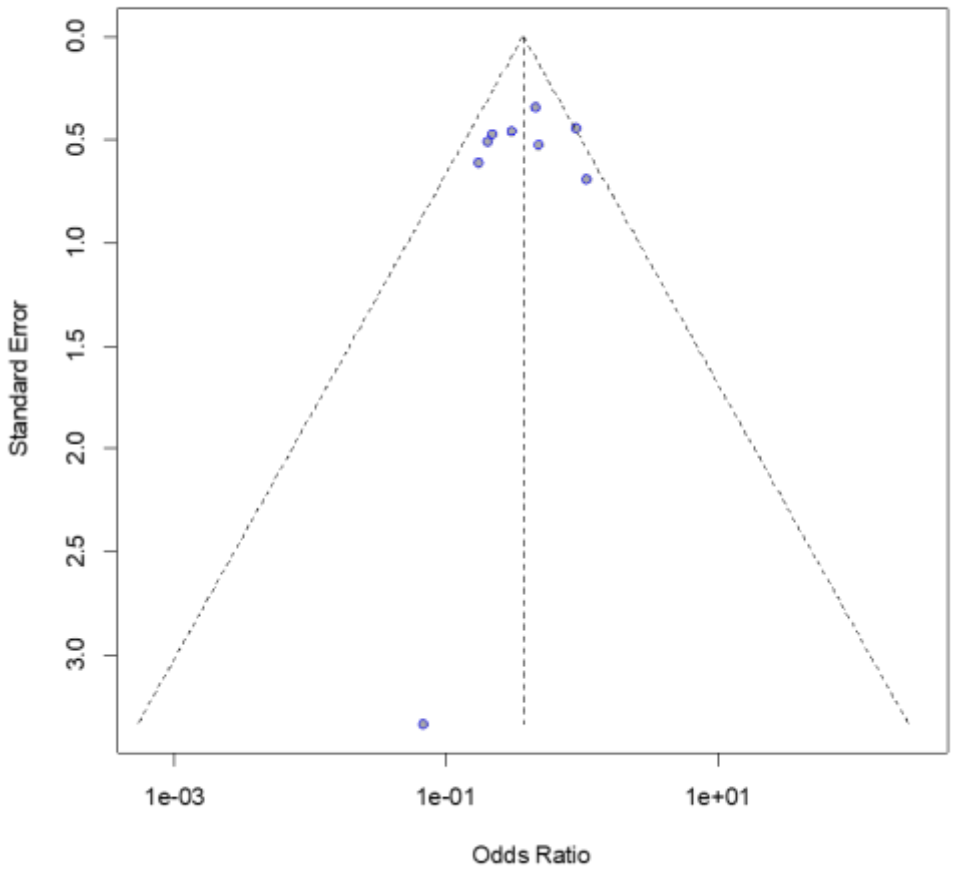
Outcome

Assessment of outcome (* for a and b) a) independent blind assessment; b) record linkage; c) self report; d) no description

Was follow-up long enough for outcomes to occur (* for a) a) yes; b) no

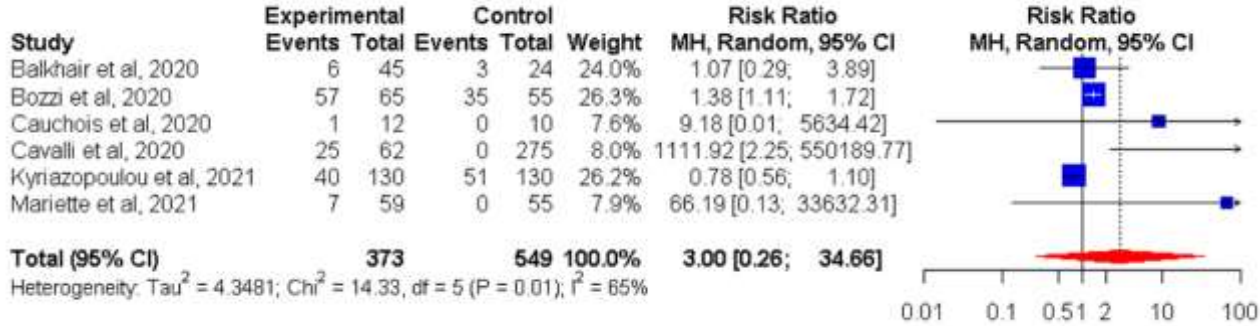
Adequacy of follow up of cohorts (* for a and b) a) complete follow up - all subjects accounted for; b) subjects lost to follow up unlikely to introduce bias - small number lost; c) follow up rate large and no description of those lost; d) no statement

Figure 1. Funnel plot of publication bias for trials included in the analysis of the primary endpoint. Test for funnel plot asymmetry: t = -0.9137, df = 7, p = 0.391



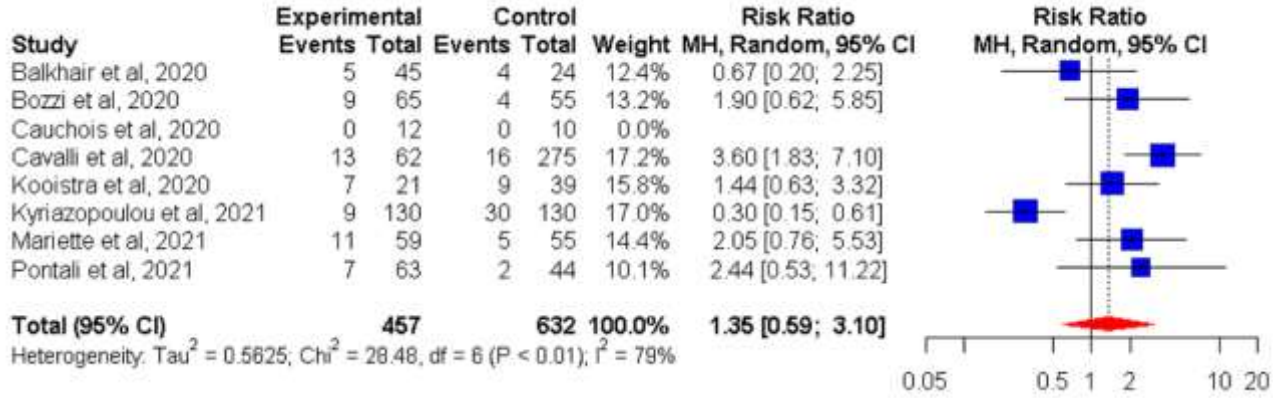
eFigure 2. Forest plot of pooled odds ratio ad respective confidence interval (CI) of onset of adverse events with anakinra treatment versus comparators. A) Elevated liver function tests; B) Leukopenia; and C) Onset of breakthrough infection.

A



B

C



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