Anakinra

Section last reviewed and updated on 5/4/2023

Last literature search conducted 3/31/2023

Recommendation 1: In hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests against the routine use of anakinra. (Conditional recommendation, Low certainty of evidence)

Severity definitions:

*Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

Why is anakinra considered for treatment?

Anakinra is a recombinant IL-1 inhibitor that is currently FDA approved for rheumatoid arthritis, cryopyrin-associated Periodic Syndromes, and Deficiency of IL-1 Receptor Antagonist. IL-1β is a pro-inflammatory cytokine, and in conjunction with other pro-inflammatory cytokines and interferon, can trigger hyperinflammation and ARDS which is often seen in severe COVID-19. Throughout the pandemic, Anakinra has been evaluated in numerous retrospective and randomized controlled trials for COVID-19. It was recently granted emergency use authorization by the US FDA for use in hospitalized adults with COVID-19 who require supplemental oxygen and who are at risk for progression to severe disease and are likely to have an elevated plasma suPAR (soluble urokinase plasminogen activator receptor) [1]. This authorization was based on results of the SAVE-MORE trial which utilized serum levels of the biomarker suPAR of ≥6 ng/mL to guide initiation of treatment with anakinra. The suPAR assay is not commercially available in the United States.

Summary of the evidence

Our search identified six RCTs that reported on hospitalized patients with severe COVID-19 who received treatment with either anakinra or no anakinra reporting on the outcomes of mortality, progression to mechanical ventilation, duration of hospital stay and serious adverse events [2-7].

Benefits

Hospitalized patients treated with anakinra showed a trend towards reduced progression to mechanical ventilation (RR: 0.69; 95% CI: 0.33, 1.44; low CoE). Anakinra appears to have trivial or no effect on mortality or duration of hospitalization (RR: 0.98; 95% CI: 0.57, 1.70; low CoE and MD: -0.93; 95% CI: -1.74, -0.11; low CoE, respectively).

Harms

Serious adverse events may not be meaningfully different among hospitalized patients treated with anakinra or not (RR: 0.93; 95% CI: 0.74, 1.19; low CoE).

Other considerations

The panel determined the certainty of evidence of treatment with anakinra for hospitalized patients with severe COVID-19 to be low due to concerns with imprecision, as effects failed to show or exclude a beneficial effect for mortality or duration of hospitalization. One study reported a reduction in mortality from treatment with anakinra used the suPAR scale to try to identify patients most likely to benefit from the treatment; however, this scale is not available in the US, restricting the feasibility of identifying the most appropriate patient group [4].

The guideline panel made a conditional recommendation against routine treatment with anakinra.

Conclusions and research needs for this recommendation

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The guideline panel suggests against anakinra for the routine treatment of hospitalized patients with severe COVID-19. Research is needed to identify which patients are most likely to benefit from this drug in settings where suPAR testing is not available (e.g. the US). There are several therapies recommended for use in this population (link to Bari/Steroids?); however, this is a conditional recommendation against the use of anakinra based on low certainty of evidence, so in situations when other agents are not available patients who put a high value on the possible reduction in hospital stay and a low value on the uncertain effect on mortality would reasonably select treatment with anakinra.

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Table 1. GRADE evidence profile, Recommendation 1

Question: Anakinra compared to no anakinra for hospitalized patients with severe COVID-19

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anakinra	no anakinra	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
6[1-6]	randomized trials	not serious	not serious	not serious	very serious [a]	none	50/600 (8.3%)	46/407 (11.3%)	**RR 0.98** (0.57 to 1.70)	**2 fewer per 1,000** (from 49 fewer to 79 more)	⨁⨁◯◯ LOW	CRITICAL
Mechanical ventilation (follow-up: range 14 days to 28 days)												
4[3-6]	randomized trials	not serious	not serious	not serious	very serious [a,b]	none	20/514 (3.9%)	19/291 (6.5%)	**RR 0.69** (0.33 to 1.44)	**20 fewer per 1,000** (from 44 fewer to 29 more)	⨁⨁◯◯ LOW	CRITICAL
Duration of Hospitalization (assessed with: days)												
3[1,3,4]	randomized trials	not serious	serious [c]	not serious	serious [d]	none	460	244	-	MD **0.93 days fewer** (1.74 fewer to 0.11 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events												
5[1-6]	randomized trials	not serious	not serious	not serious	very serious [b,e]	none	118/585 (20.2%)	88/392 (22.4%)	**RR 0.93** (0.74 to 1.19)	**16 fewer per 1,000** (from 58 fewer to 43 more)	⨁⨁◯◯ LOW	CRITICAL

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 95% CI cannot exclude the potential for both meaningful benefit or harm.
b. Few events suggest fragility of the estimate.
c. High I2 (97%).
d. 95% CI cannot exclude no meaningful reduction in duration of hospitalization.
e. 95% CI cannot exclude the potential for no meaningful harm.

References

1. Elmekaty E, Maklad A, Abouelhassan R, et al. Efficacy of Anakinra in the Management of Patients with COVID-19 Infection: A Randomized Clinical Trial. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.07.04.22277207 [Preprint 6 July 2022].
2. 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 **2021**; 9(12): 1427-38.
3. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med **2021**; 27(10): 1752-60.
4. 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 **2022**; 10(2): 201-8.
5. Corimuno-Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med **2021**; 9(3): 295-304.
6. Audemard-Verger A, Le Gouge A, Pestre V, et al. Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial. PLoS One **2022**; 17(8): e0269065.

References

1. Swedish Orphan Biovitrum. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Kineret. Available at: https://www.fda.gov/media/163075/download. Accessed 21 April 2023.
2. Elmekaty E, Maklad A, Abouelhassan R, et al. Efficacy of Anakinra in the Management of Patients with COVID-19 Infection: A Randomized Clinical Trial. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.07.04.22277207 [Preprint 6 July 2022].
3. 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 **2021**; 9(12): 1427-38.
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7. Audemard-Verger A, Le Gouge A, Pestre V, et al. Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial. PLoS One **2022**; 17(8): e0269065.

Supplementary Materials

Study characteristics

- **Table s1.** Should hospitalized patients with severe COVID-19 receive anakinra vs. no anakinra?

Forest plots

- **Figure s1a.** Outcome of mortality for anakinra vs. no anakinra in hospitalized patients
- **Figure s1b.** Outcome of hospitalization duration for anakinra vs. no anakinra in hospitalized patients
- **Figure s1c.** Outcome of mechanical ventilation for anakinra vs. no anakinra in hospitalized patients
- **Figure s1d.** Outcome of adverse events (mild to severe) for anakinra vs. no anakinra in hospitalized patients

Risk of bias

- **Table s2a.** Randomized control studies (anakinra vs. no anakinra)

Table s1. Should hospitalized patients with severe COVID-19 receive anakinra vs. no anakinra?

Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Audemard-Verger 2022 [6]	France/ 20 University and General Hospitals	RCT	71 (37/34)	26.8	Mean (SD): Intervention: 71 (15) Control: 70 (14)	Positive rRT-PCR and/or typical chest or CT scan of COVID 19 pneumonia and required oxygen therapy	Anakinra IV 400 mg/day (100 mg every 6 hrs) x 3 days then 200 mg/day (100 mg ever 12 hrs) x 7 days	SoC	SoC included antiviral drugs, hydroxychloroquine, corticosteroid, anticoagulants, hydration, nutrition, extra-renal purification, oxygen therapy and vasopressive drugs	Treatment success at day 14 (patient being alive and not requiring invasive mechanical ventilation or ECMO) Clinical status (WHO Clinical Progression Scale) National Early Warning Score Biological parameters (lymphocytes count, CRP, ferritin, d-dimers, fibrinogen levels) Overall survival Time to hospital discharge Time to ICU admission	Endowment fund of the university hospital of Tours

Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Time to ventilatory support Time to oxygen supply withdrawal over 28-day follow-up Adverse and serious adverse events	
CORIMUNO-19 2021 [5]	France/ 16 University hospitals	RCT	116 (59/57)	29.8	Median (IQR): Intervention: 67.0 (55.5-74.3) Control: 64.9 (59.5-78.3)	Mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving at least 3 L/min of oxygen but without ventilation assistance (eg, high-flow oxygen, non-invasive ventilation, or mechanical ventilation	Anakinra IV 200 mg twice a day (total 400 mg) on days 1-3, then 100 mg twice a day on day 4 (total 200 mg), then 100 mg once on day 5 If no improvement was seen on morning of day 4 (reduction in requirement of oxygen of more than 50%, but the decision was left to the treating physician), 3 supplementary days of treatment at 400 mg per day were done on days 4–6, followed by a	SoC	Antibiotic drugs, antiviral drugs, corticosteroid, vasopressor support, anticoagulants	Proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (score of >5 points on WHO-CPS) Survival with no need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14 Clinical status assessed with WHO-CPS at days 4, 7, and 14	The Ministry of Health Programme Hospitalier de Recherche Clinique Foundation for Medical Research AP-HP Foundation

Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
							decrease to 200 mg per day on day 7 and 100 mg per day on day 8			Overall survival at days 14, 28, and 90 Time to discharge from hospital Time to oxygen supply independency Biological factors (eg, CRP concentration) Adverse events Time to discharge and at day 28 Time to oxygen supply independency at day 28	
Declercq 2021 [2]	Belgium/ 16 hospitals	RCT	342 (112/230)	N/A	Median (IQR): Intervention: 67 (56-74) Control: 64 (54-72)	Symptoms between 6 and 16 days, PaO_2:FiO_2 < 350 mm Hg on room air or > 280 mm Hg on supplemental oxygen and bilateral	Anakinra 100 mg once daily SC for 28 days or until hospital discharge	SoC	Antibiotics, remdesivir, HCQ, glucocorticoids, methylprednisolone equivalents	Time to clinical improvement or to discharge from hospital alive Median time until discharge Median time until independence	Belgian Health Care Knowledge Center

Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						pulmonary infiltrates				from invasive ventilation Median time until first use of high-flow oxygen device Ventilation or death Number of days in hospital Number of days in ICU Number of days in ICU in patients ventilated at day of randomization Number of days in ICU, relative to number of days alive the first 28 days after randomization Number of days without supplemental oxygen use up to 28 days after randomization	

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Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Number of invasive ventilator days Number of invasive ventilator days in patients ventilated at day of randomization Number of invasive ventilator days, relative to number of days alive the first 28 days after randomization Number of invasive ventilator-free days up to 28 days after randomization Number of invasive ventilator-free days up to 28 days after randomization in patients ventilated at day of randomization	

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Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Death Serious adverse events	
Elmekaty 2022 [1]	Qatar/ 3 clinical sites	RCT	80 (40/40)	17.5	Mean (SD): 49.9 (11.7)	Positive SARS-CoV2 PCR test and associated presence of respiratory distress [defined as: $PaO_2/FiO_2 \leq$ 300 mm Hg or respiratory Rate ≥24 breaths/min or $SpO_2 \leq 94\%$ at room air], and signs of cytokine release syndrome	Anakinra 100 mg SC injection evert 12 hrs for 3 days, then 100 mg SC once daily from day 4 to 7	SoC	Remdesivir, favipravir, corticosteroid, convalescent plasma, azithromycin, ceftriaxone, anticoagulants	Treatment success on day 14 (WHO Clinical Progression score of ≤3) Duration of mechanical ventilation in ventilated patients up to 14 days Changes in WHO Clinical Progression Score between day 1 and 7 Viral burden (change in PCR cycle threshold) at day 7 and day 10-14 Time to ICU admission up to 28 days Adverse events	Medical Research Center at Hamad Medical Corporation, Qatar

Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Length of hospital stay up to 28 days All-cause mortality rate at hospital discharge or at 28 days	
Kharazmi 2022 [4]	Iran/ Imam Hossein Medical Center	RCT	30 (15/15)	36.7	Mean (SD) Intervention: 49.25 (19.12) Control: 59.00 (1.79)	Elevated CRP levels, oxygen saturation ≤ 93% measured using a peripheral capillary pulse oximeter, fever, or cough or shortness of breath, and $PaO_2/FiO_2 < 300$	Anakinra 100 mg IV once daily until discharge or maximum of 14 days	SoC	Remdesivir, lopinavir/ritonavir, interferon, favipiravir, and corticosteroid, oxygen supplementation, ventilation support, fluid, and electrolyte correction, vasoactive agents and antibiotic administration, and renal replacement support if appropriate	Need for endotracheal intubation due to hypoxemia Hospital length of stay ICU length of stay Seven categories ordinal scale (includes hospitalization, mechanical ventilation) Survival on day 14	Not specified
Kyriazopoulou 2021 [3]	Greece	RCT	594 (405/189)	42.1	Mean (SD): 61.9 (12.1)	Confirmed infection by SARS-CoV-2 by molecular test; findings in chest X-ray or chest CT	Anakinra 100 mg SC once daily in for 7–10 days	Placebo	Remdesivir, dexamethasone (severe patients)	Frequencies of the scores from the 11-point WHO-CPS on day 28	Hellenic Institute for the Study of Sepsis

Study/ year	Country/ Hospital	Study design	N subjects (intervention / comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						compatible with lower respiratory tract infection; need for hospitalization; and plasma suPAR ≥6 ng ml^{-1}				Changes of WHO-CPS scores at days 14 and 28 from the baseline Change of SOFA score at day 7 from baseline Time until hospital discharge Time of stay in the ICU Comparison of biomarkers	Swedish Orphan Biovitrum

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Figure s1a. Outcome of mortality for convalescent plasma vs. no convalescent plasma in hospitalized patients

	Anakinra		No anakinra			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Audemard-Verger 2022	9	37	3	34	13.1%	2.76 [0.81, 9.35]
CORIMUNO-19 2021	13	59	13	55	23.6%	0.93 [0.47, 1.83]
Declercq 2021	10	44	9	74	20.2%	1.87 [0.82, 4.24]
Elmekaty 2022	0	40	1	40	2.8%	0.33 [0.01, 7.95]
Kharazmi 2021	5	15	7	15	18.5%	0.71 [0.29, 1.75]
Kyriazopoulou 2021	13	405	13	189	21.8%	0.47 [0.22, 0.99]
Total (95% CI)		**600**		**407**	**100.0%**	**0.98 [0.57, 1.70]**
Total events	50		46			

Heterogeneity: Tau² = 0.21; Chi² = 9.82, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 0.06 (P = 0.95)

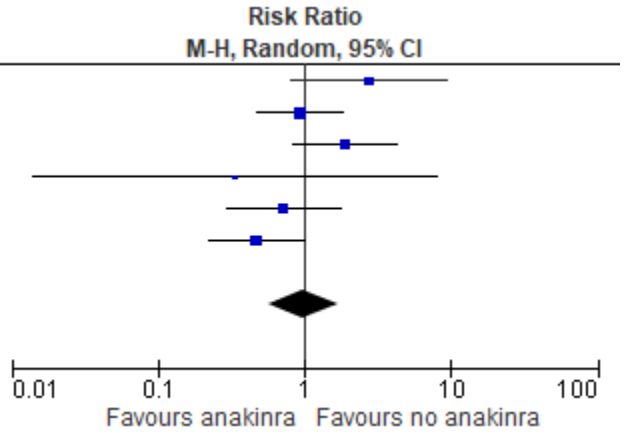

Figure s1b. Outcome of hospitalization duration for anakinra vs. no anakinra in hospitalized patients

	Anakinra			No anakinra				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Elmekaty 2022	10	2.96	40	10	2.96	40	39.3%	0.00 [-1.30, 1.30]
Kharazmi 2021	10	3.7	15	28	11.1	15	1.9%	-18.00 [-23.92, -12.08]
Kyriazopoulou 2021	11	5.78	405	12	6.3	189	58.8%	-1.00 [-2.06, 0.06]
Total (95% CI)			**460**			**244**	**100.0%**	**-0.93 [-1.74, -0.11]**

Heterogeneity: Chi² = 33.92, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.24 (P = 0.03)

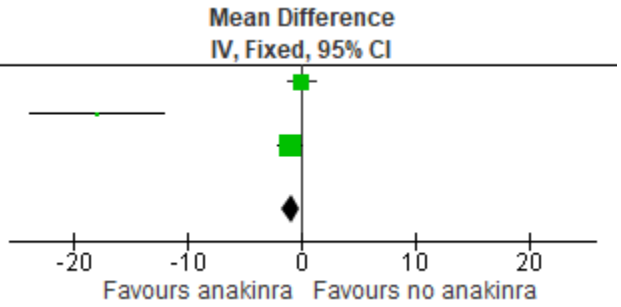

Figure s1c. Outcome of mechanical ventilation for anakinra vs. no anakinra in hospitalized patients

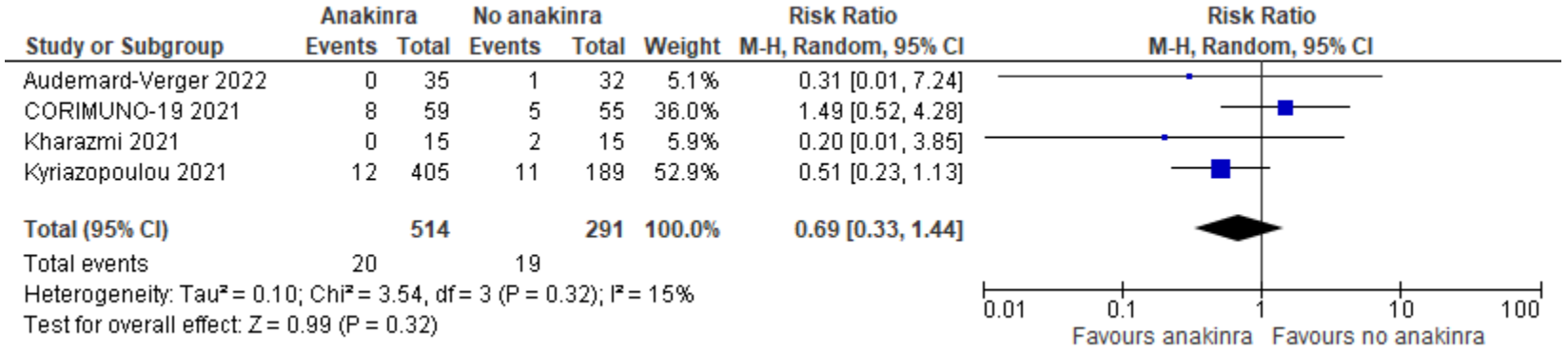

Figure s1d. Outcome of adverse events (mild to severe) for anakinra vs. no anakinra in hospitalized patients

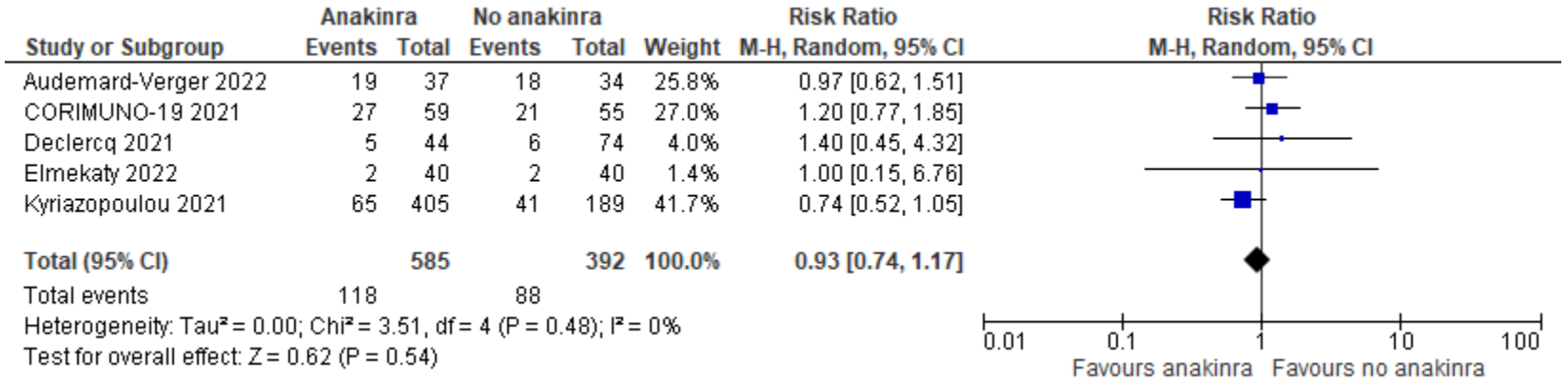

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Table s2. Randomized control studies (anakinra vs. no anakinra)

Study	Randomization process	Deviation from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result
Audemard-Verger 2022 [6]					
CORIMUNO-19 2021 [5]					
Declercq 2021 [2]					
Elmekaty 2022 [1]					
Kharazmi 2022 [4]					
Kyriazopoulou 2021 [3]					

Low	High	Some concerns

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References for Supplementary Materials

1. Elmekaty E, Maklad A, Abouelhassan R, et al. Efficacy of Anakinra in the Management of Patients with COVID-19 Infection: A Randomized Clinical Trial. medRxiv **2022**: Available at: https://doi.org/10.1101/2022.07.04.22277207 [Preprint 6 July 2022].
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