Supplementary Information No 4 Characteristics of included studies

Declercq 2021
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; 9:1427–38

Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
Randomized controlled trial, 2x2 factorial design, open-label, Inpatient	16 hospitals in Belgium	**Patients:** N^{Total}: 118 (with other interventions: 342) A: n = 43[1] C: n = 72 Excluded: Not reported for Anakinra and control only <u>Follow-up:</u> 10-20 weeks after randomization **Inclusion criteria:** − Recent infection with COVID-19 − Presence of hypoxia − Signs of cytokine release syndrome − Chest x-ray and/or CT scan showing bilateral infiltrates within last 2 days − Admitted to specialized COVID-19 ward or an ICU ward taking care of COVID-19 patients − ≥ 18 years − Male or female − Women of childbearing potential must have a negative serum pregnancy test pre-dose on day 1 − Willing and able to provide informed consent or legal representative willing to provide informed consent **Exclusion criteria:** − Patients with known history of serious allergic reactions, including anaphylaxis to any of the study medications, or any component of the product − Mechanical ventilation > 24h at randomization − Patient on ECMO at time of screening − Clinical frailty scale above 3 − Active bacterial or fungal infection − Unlikely to survive beyond 48 h − Neutrophil count below 1500 cells/microliter − Platelets below 50.000/microliter − Patients enrolled in another investigational drug study	**Anakinra** 1x/day 100mg subcutaneously for 28 days or until hospital discharge on top of standard of care If glomerular filtration rate <30 ml/min per 1,73 m2, the dosing was lowered to 100mg once every other day.	**Standard of Care** (not specified)	**Primary outcome:** <u>Time to clinical improvement</u> Number of deaths A: 10/44 (23%) C: 9/74 (12%) **Secondary outcomes:** − Median time until discharge (IQR) A: 14 (9-37) C: 12 (10-20) − Median time until independence from supplemental oxygen or discharge A: 14 (8-20) C: 11 (10-15) − Median time until independence from invasive ventilation A: <50% reached event C: 54 (6-.) − Median time until first use of high-flow oxygen device, ventilation or death A: <50% reached event C: <50% reached event − Number of days in hospital A: 20 (16-25) C: 18 (15-22) − Number of days in ICU A: 12 (7-21) C: 9 (6-14)	No shortening of time to clinical improvement or improvement of supportive endpoints when given early in disease course of hypoxia patients with COVID-19 with evidence of CRS. No increase in infectious adverse events or other safety concerns associated with use of Anakinra. **Comments:** <u>Limitations:</u> − Open-label design − Standard of care could differ among centres and did change during the course of the trial − small sample size − total number of patients screened for eligibility not registered in all centres − decision to exclude patients unlikely to survive beyond 48h made by the individual enrolling physician on clinical grounds without objective criteria beyond the use of a frailty scoring index

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Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		− Patients on high dose systemic steroids − Patients on immunosuppressant or immunomodulatory drugs − Patients on current anti-IL1 or anti-IL6 treatment − Signs of active tuberculosis − Serum transaminase levels >5times upper limit of normal, unless there are clear signs of cytokine release syndrome − History of (non-iatrogenic) bowel perforation or diverticulitis − Pregnant or breastfeeding females **Demographics:** Age, median (IQR): A: 65 (54 - 70) C: 63 (56 - 73) Male, n (%) A: 37 (86) C: 53 (74) **Severity of condition according to respiratory support (n/N (%)):** IMV: A: 8/43 (19); C: 9/72 (13) non-IMV: A: 16/43 (37); C: 23/72 (32) supplemental oxygen only[2]: A: 19/43 (44); C: 39/72 (54) Not requiring supplemental oxygen: A: 0/43 (0); C: 1/72 (1)				

[1]characteristics of the patients at baseline available for A: 43, C: 72; outcomes partially available for A: 44, C: 74
[2]without differentiation between low and high flow

Derde 2021
The REMAPCAP Investigators: Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19 The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial. medRxiv [Preprint] 2021.06.18.21259133; doi: https://doi.org/10.1101/2021.06.18.21259133

Design	Study period and place	Participants	Intervention (Anakinra, A)	Control (C)	Outcomes	Conclusion of study authors
Randomized controlled trial,	19.04.2020 - 10.04.2021,	**Patients:** **s**creened: n = 13,718 randomised to a COVID-19 Immune	**Anakinra (A)** 300mg IV loading dose	**Standard of Care** (not specified)	**Primary outcome[1]:** In-hospital death, n (%)	"Anakinra is not effective in this population" **Comments:**

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Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
open-label, Inpatient, (Preprint)	127 sites (4 sites for Moderate state (3 UK, 1 Australia) & 123 sites for Severe State (110 UK, 11 Netherlands, 3 Ireland, 2 Australia, 2 New-Zealand, 1 Canada, 1 Finland, 1 Italy, 1 Saudi-Arabia)	Modulation Domain intervention: n=2,279 N= 779 A: n = 373 C: n = 406 Excluded: A: 13 C: 12 Follow-up: - 21 d for primary outcome and 90d for secondary outcomes **Inclusion criteria:** − > 18 years − within 24 hours of receiving respiratory or cardiovascular organ support in an ICU − suspected or microbiologically confirmed COVID-19 **Exclusion criteria:** - Patient has already received any dose of one or more of any form of anakinra during this hospitalization or is on long-term therapy with this agent prior to this hospital admission - Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization - Patient has been randomized in a trial evaluating an immune modulation agent for proven or suspected COVID-19 infection, where the protocol of that trial requires ongoing administration of study drug - The treating clinician believes that participation in the domain would not be in the best interests of the patient - Known hypersensitivity to anakinra - Known hypersensitivity o proteins produced by E. coli - Known or suspected pregnancy **Demographics:** Age, mean (SD) Severe state: A: 59.8 (11.9) C: 61.1 (12.9)	100mg every 6 hours for 14 days or until for > 24 h free from IMV or discharge from ICU. creatinine clearance <30ml/min or receiving renal replacement therapy: dosing interval increased to 12 h		A: 145/365 (39.7) C: 150/406 (36.9) **Secondary outcomes:** 90-day mortality, adjusted HR – mean (SD) A: 1.15 (0.16) C: 1 Progression into intubation, ECMO or death, n (%) A: 122/228 (53.5) C: 147/276 (53.3) Time to ICU discharge, adjusted HR – mean (SD) A; 1.10 (0.12) C: 1 Time to hospital discharge, adjusted HR – mean (SD) A: 1.05 (0.12) C: 1	Limitations: − open-label design

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Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
		Moderate State: A: 36.0 (17.0) C: 67.0 (13.7) <u>Male, n (%)</u> Severe state: A: 269 (72.1) C: 285 (70.2) Moderate State: A: 1 (50.0) C: 1 (33.3) **Severity of condition according to respiratory support (n/N (%)):** None / supplemental oxygen only A: 1/373 (0.3) C: 2/406 (0.5) High-flow nasal cannula A: 101/373 (27.1) C: 110/406 (27.1) Non-invasive ventilation only A: 133/373 (35.7) C: 171/406 (42.1) Invasive mechanical ventilation A: 138/373 (37.0) C: 122/406 (30.0) ECMO A: 0/373 (0.0) C: 1/406 (0.2)				
[1] The primary outcome was an ordinal scale that is a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support (Days free from organ support in survivors, median (IQR))						
Kharazmi 2021 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; 10:201–08						
Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
Randomized controlled trial, open-label, Inpatient,	Iran, May 2020 to July 2020	**Patients:** Screening: n = 72 Patients: n = 30 A: n = 15 C: n = 15 Excluded: n = 42	**Anakinra** 1x/day 100mg IV until discharge or a maximum of 14 days	**Standard of Care** (not specified)	**Primary outcome:** <u>Need for invasive mechanical ventilation</u> **Secondary outcomes:**	"Anakinra is effective in improving the respiratory condition and significantly reduces the need for invasive mechanical ventilation in patients with severe COVID-19. "

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Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		Follow-up: for the primary outcome: until endotracheal intubation due to hypoxemia for the secondary outcomes: until hospital discharge **Inclusion criteria:** − confirmed diagnosis of COVID-19 based on reverse transcriptase-polymerase chain reaction − admitted to ICU − > 18 years old − elevated C-reactive protein (CRP) levels − oxygen saturation ≤ 93% measured using a peripheral capillary pulse oximeter − fever (core temperature of 37.8°C or more), or cough or shortness of breath, and PaO2/FiO2 less than 300 **Exclusion criteria:** − Patients who had positive results for tuberculosis (i.e., positive Mendel–Mantoux or QuantiFERON test), − viral hepatitis B or C − hemoglobin < 7.5 g/dl − platelet count < 100,000 cells/µl − serum glutamic–oxaloacetic transaminase or serum glutamic–pyruvic transaminase > five upper limits of normal − untreated active infection − previous administration of anakinumab or anakinra **Demographics:** Age, (SD) A: 49.25 ± 19.12 C: 59.00 ± 1.79 Male, (%) A: 8% C: 7%			Hospital length of stay, Median (IQR) A: 10 (5) C: 28 (15) ICU length of stay, Median (IQR) A: 5 (3) C: 16 (19) Seven categories ordinal scale, n (%) Death A: 5 (33.3) C: 7 (46.7) p = .456 Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation. A: 0 (0) C: 2 (13.3) P = .483 Hospitalized, on non-invasive ventilation or high flow oxygen A: 0 (0) C: 1 (6.7) P = 1.000 Hospitalized, requiring low flow supplemental oxygen A: 0 (0) C: 0 (0) P = 1.000 Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise) A: 0 (0) C: 0 (0) P = 1.000	"The reduction was observed in hospitalization duration, which makes the medication an effective immunomodulatory agent to combat cytokine storm." **Comments:** Limitations: − Open label design − Small sample size

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Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
		Severity of condition according to respiratory support (n/N (%)): IMV or ECMO: A: 2/15 (13); C: 3/15 (20) non-IMV or high flow oxygen: A: 10/15 (67); C: 6/15 (40) low flow supplemental oxygen only: A: 3/15 (20); C: 6/15 (40)			Hospitalized, not requiring supplemental oxygen—no longer required ongoing medical care. A: 0 (0) C: 0 (0) P = 1.000 Not hospitalized A: 10 (66.7) C: 5 (33.3) P = .143 Survival for included patients on day 14	
Kyriazopoulou 2021 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; 27:1752–1760						
Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
Randomized controlled trial; double-blinded, placebo-controlled, Inpatient	23 December 2020 to 31 March 2021 37 study sites (29 in Greece and eight in Italy)	**Patients:** Screening: n=1,060 Patients: n=606 A: n=405 C: n=189 Excluded: n=454 <u>Follow-up:</u> until hospital discharge **Inclusion criteria:** − adult patients of either sex − for women, unwillingness to remain pregnant during the study period − confirmed infection by SARS-CoV-2 by molecular test − findings in chest X-ray or chest computed tomography compatible with lower respiratory tract infection − need for hospitalization − plasma suPAR ≥6 ng ml−l **Exclusion criteria:** − any stage IV malignancy	**Anakinra** 1x/day 100mg subcutaneously at a final volume of 0.67 ml for 7-10 days	**Placebo** 1x/day 0.67 ml of 0.9% sodium chloride	**Primary outcome:** <u>11-point WHO-CPS at day 28, n (%)</u> Fully recovered PCR− A: 204 (50.4) C: 50 (26.5) Asymptomatic PCR+ A: 40 (9.9) C: 6 (3.2) Symptomatic independent A: 93 (23.0) C: 74 (39.2) Symptomatic assistance needed A: 25 (6.2) C. 21 (11.1) Hospitalized with no need for oxygen A: 9 (2.2) C: 3 (1.6) Hospitalized with nasal/mask oxygen A: 8 (2.0)	"In conclusion, the SAVE-MORE trial showed that early start of treatment with anakinra guided by suPAR levels in patients hospitalized with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcome at day 28." **Comments:** <u>Limitations:</u> − the lack of enrollment of patients with critical COVID-19 − the difficulty for application of suPAR in all hospital settings − inclusion of patients with SuPAR ≥ 6 ng ml^{-1} <u>Power-analysis:</u> "To replicate this primary effect size in the SAVE-MORE trial, and with a 90% power at the 5% significance level, a sample size of 200 was needed for the

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Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
		− any do-not-resuscitate order − ratio or partial oxygen pressure to fraction of inspired oxygen less than 150 mmHg − need of NIV (CPAP or BPAP) or MV − any primary immunodeficiency − fewer than 1,500 neutrophils per mm3 − oral or intravenous intake of corticosteroids at a daily dose greater than or equal to 0.4 mg kg−1 of prednisone for a period longer than the last 15 d − any anti-cytokine biological treatment, including JAK inhibitors, during the last 1 month − severe hepatic failure − end-stage renal failure necessitating hemofiltration or peritoneal hemodialysis − pregnancy or lactation. **Demographics (I/B1/B2):** Age, mean (SD) A: 62 (11.4) C: 61.5 (11.3) Male, n (%) A: 236 (58.3) C: 108 (57.1) **Severity of condition according to respiratory support (n/N (%)):** no supplemental oxygen: A:39/405 (10); C:11/189 (6) low or high flow supplemental oxygen: A: 366/405 (90); C: 178/189 (94) suPAR ≥ 6 ng/ml			C: 10 (5.3) Need for HFO or NIV A: 1 (0.2) C: 1 (0.5) MV with P/F > 150 mmHg A: 1 (0.2) C: 1 (0.5) MV with P/F < 150 mmHg or vasopressors A: 5 (1.2) C: 4 (2.1) MV with P/F < 150 mmHg and vasopressors or hemodialysis or ECMO A: 6 (1.5) C: 6 (3.2) Dead A: 13 (3.2) C: 13 (6.9) **Secondary outcomes:** Median time to hospital discharge, d (IQR) A: 11 (7.8) C: 12 (8.5) P = 0.033 Median time of ICU stay, d (IQR) A: 10 (21) C: 14 (22) P = 0.026 At least one serious TEAE, *n* (%) A: 65 (16.0) C: 41 (21.7) P = 0.107 At least one non-serious TEAE, n (%) A: 335 (82.7) C: 156 (82.5) P = 1.00	placebo treatment arm and 400 for the anakinra treatment arm."
Tharaux 2021						

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Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
The CORIMUNO-19 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; 9:295-304						
Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
Randomized controlled trial, open-label, Inpatient	08.04 – 26.04.2020 16 University hospitals in France	**Patients:** Screening: n = 153 Patients: n = 116 A: n = 59 C: n = 57 Excluded: n=37 <u>Follow-up:</u> 14d for primary outcome and 28d or 90d for secondary outcomes **Inclusion criteria:** - adult patients -confirmed SARS-CoV-2 infection (positive on real-time RT-PCR or chest CT scan typical of COVID-19 pneumonia, or both) with mild-to-moderate, severe, or critical pneumonia (ie, receiving oxygen at a flow of >3 L/min via mask or nasal cannula and a score of ≥5 points on the WHO Clinical Progression Scale [WHO-CPS] 10-point ordinal Scale -C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the hospital intensive care unit at the time of admission -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). **Exclusion criteria:** - known hypersensitivity to Anakinra or any of its excipients - pregnancy - current documented bacterial infection - an absolute neutrophil count of $1{\cdot}0 \times 10^9$ per L or less	**Anakinra** 2 x 200 mg (i.v.) daily on days 1–3, followed by 2 x 100 mg (i.v.) daily on day 4 and 100 mg (i.v.) /daily on day 5 In the absence of improvement (reduction in oxygen requirement by >50%) after 3 days, decision by practitioner: 2x 200 mg(i.v.) daily d4-6, then 2x 100 mg (i.v.) d7, then 1x 100 mg (i.v.) d8	**Standard of Care:** Antibiotics, antiviral meds, corticosteroids, vasopressors, anticoagulants (practitioner's choice)	**Co-primary outcomes:** <u>The proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (ie, a score of >5 on the WHO-CPS)</u> A: 21/59 (36%) C: 21/55 (38%) <u>Survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14.</u> median posterior HR: 0·97 (90% CrI 0·62 to 1·52) <u>Non-invasive ventilation, mechanical ventilation or death up to day 14</u> A: 28 (47%; 95% CI 33 to 59) C: 28 (51%; 95% CI 36 to 62) <u>Mortality, at day 90</u> A: 16 (27%) C: 15 (27%) <u>Serious adverse events, n (%), p</u> Patients with at least one serious adverse event 27 (46%) / 21 (38%), 0.45 Patients with multiple serious adverse events 8 (14%) / 5 (9%),	"Anakinra did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia. Further studies are needed to assess the efficacy of anakinra in other selected groups of patients with more severe COVID-19." **Comments:** <u>Limitations</u> − No blinding − usual care could differ among centres and over time − small sample size − wide CrIs and CIs − no provision of an accurate measure of the ratio of partial pressure of oxygen to fractional concentration of oxygen in inspired air, because arterial blood gas measurements were not done − narrow segment of the COVID-19 patient population targeted (patients with a WHO-CPS score of exactly 5 points and requiring at least 3 L/min of oxygen without any ventilatory support regardless of inflammatory status)

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Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		- a platelet concentration of less than 50 G/L - serum aspartate aminotransferase or serum alanine aminotransferase of more than fivetimes the upper limit of normal - severe renal insufficiency defined by an estimated glomerular filtration rate of less than 30 mL/min. **Demographics:** Age, median (IQR): 66 (59 - 76) A: 67 (55.5 –74.3) C: 64,9 (59.5 –78.3) Male, n 80 (70%) **Severity of condition according to respiratory support (n/N (%)):** Low flow supplemental oxygen A: 59/59 (100) C: 55/55 (100)			**Secondary outcomes:** - clinical status assessed with the WHO-CPS at days 4, 7, and 14; Overall survival at days 14, 28, and 90 Mortality at day 14 A: 9 (15%) C: 13 (24%) Adjusted HR: 0·56 (95% CI 0·23 to 1·39) Mortality at day 28 A: 13 (22%) C: 13 (24%) Adjusted HR: 0·77 (95% CI 0·33 to 1·77) Mortality at day 90 A: 16 (27%) C: 15 (27%) Adjusted HR: 0·97 (95% CI 0·46 to 2·04) time to discharge at day 28 A: 34 (58%) C: 34 (62%) Adjusted HR: 0·91 (95% CI 0·56 to 1·48) Time to oxygen supply independency at day 28, n (%), adj. HR (95% CI) 37 (63%) / 38 (69%), 1.01 (95% CI 0.64 to 1.61) time to negative viral excretion not assessed due to paucity of data	

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Design	**Study period and place**	**Participants**	**Intervention**	**Control**	**Outcomes**	**Conclusion**
					biological factors (eg, C-reactive protein concentration Adverse events, n (%), p Patients with at least one adverse event 29 (49%) / 23 (42%), 0.46 Patients with multiple adverse events 19 (32%) / 14 (25%) **Subgroup analysis:** prespecified subgroup analysis according to antiviral drug use at baseline: too few patients were on antivirals at baseline to enable this analysis.	