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Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: two Randomized Controlled Trials of the CORIMUNO-19 Collaborative Group

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Take home message: "In two prospective randomized studies of COVID-19 patients in intensive care unit, anti-IL-6 receptor did not significantly increase early survival without mechanical ventilation. However, due to the small number of patients, no definitive conclusion could be drawn".

Abstract (268 words)

Question

To determine whether anti-IL-6 Receptors improve outcomes of critically ill patients with COVID-19 pneumonia.

Patients and methods

Two cohort-embedded, investigator-initiated, multicenter, open-label, Bayesian randomized controlled clinical trials. Patients were randomly assigned to receive either usual care (UC) or UC+Tocilizumab (TCZ) 8 mg/kg (TOCI-2 trial), or UC or UC+ Sarilumab (SARI) 200 mg (SARI-2 trial), both intravenously on day 1 (D1) and on D3 if clinically indicated.

Results

Between 31 March and 20 April 2020, 97 patients were randomized in the TOCI-2 trial, to receive UC (n=46) or UC+TCZ (n=51). At day 14, numbers of patients who did not need NIV, MV and alive with TCZ or UC were similar (47% versus 42%, median posterior hazard ratio [HR] 1.19, 90% CrI, 0.71 to 2.04), with a posterior probability of HR>1 of 71.4%.

Between 27 March and 4 April 2020, 91 patients were randomized in the SARI-2 trial, to receive UC (n=41) or UC+SARI (n=50). At day 14, numbers of patients who did not need NIV, MV and alive with SARI or UC were similar (38% versus 33%, median posterior hazard ratio [HR] 1.05, 90% CrI, 0.55 to 2.07), with a posterior probability of HR>1 of 54.9%.

Overall, the risk of death up to day 90 was: UC + TCZ vs UC (24% vs 30%, HR 0.67 [0.30 to 1.49]); UC + SARI vs UC (29% vs 39%, (HR 0.74 ([0.35 to 1.58]). Both TCZ and SARI increased serious infectious events.

Conclusion

In critically ill patients with COVID-19, anti-IL-6 Receptors did not significantly increase the number of patients alive without any NIV, MV by D14.

Trial Registration: ClinicalTrials.gov numbers: (NCT04331808 and NCT04324073)

Text (3543 words)

Introduction

COVID-19 is a respiratory disease induced by a novel coronavirus (SARS-CoV-2), having already caused more than 2.5 million deaths over the world [1-4]. Most people with COVID-19 have only mild or uncomplicated symptoms. Still, approximately 10% to 15% have moderate or severe diseases requiring hospitalization and oxygen support, and 3% to 5% require admission to an intensive care unit (ICU) mainly for ventilation assistance [4, 5].

Patients with COVID-19 pneumonia present non-specific inflammatory responses, including edema and inflammatory cell infiltration in the lungs. Besides the specific pathogenic effect of SARS-CoV-2, host immune response, in addition to its role in controlling virus replication, may result in hyper inflammation leading to worsening pulmonary function. It is, at least in part, related to the production of several pro-inflammatory cytokines and chemokines, including interleukin 6 (IL-6). As demonstrated in the RECOVERY collaborative group, dexamethasone (DXM) 6 mg/day for 10 days decreased the 28-day mortality among patients receiving oxygen, including mechanical ventilation (MV), high flow, and non-invasive ventilation (NIV)[6]. Thus, the benefit from glucocorticoids in moderate-to-severe and critically ill patients suggests that an excessive host inflammatory response is responsible for much of the serious illness and death from COVID-19.

At the beginning of the epidemic in France, when no standard of care was defined, including the use of corticosteroids and anticoagulation, we decided to set up the publicly supported CORIMUNO-19 platform dedicated to performing cohort, open-label, randomized clinical trials of immune-modulatory drugs in two well-defined groups of patients: patients hospitalized in medical wards with moderate-to-severe COVID-19 pneumonia and patients hospitalized in intensive medical units (ICU) with non-invasive or invasive ventilation (WHO clinical progression scale (CPS) < 5 with at least 3l O_2/min or >5).

Given the potential deleterious effect of IL-6 in COVID-19 hyperinflammation [7-11], we evaluated the benefit-risk effect of tocilizumab (TCZ) and sarilumab (SARI), two anti-human IL-6 receptor (IL-6R) monoclonal antibodies that inhibit IL-6 signaling. In non-ICU patients, we found an effect of TCZ [12-13] but not of SARI [14] for preventing evolution to

ventilation or death at D14, but no effect on survival at D28 and a trend for a better survival at D90. However, these studies were not designed to evaluate overall survival. In the present two studies, we investigated the effectiveness of TCZ and SARI versus usual care on free-ventilation survival in critically ill patients with COVID-19 on non-invasive or mechanical ventilation

Methods

Trial Design and Study Oversight

At the beginning of the SARS-CoV-2 pandemic, we set up a cohort of COVID-19 patients with moderate, severe, or critical pneumonia (CORIMUNO-19 Cohort, NCT04324047). This cohort was used to perform a series of randomized controlled trials testing different therapeutic regimens in COVID-19 patients. Two separate populations were recruited: patients with moderate or severe pneumonia and patients critically ill. An IRB-approved amendment to the protocol on April 6, 2020, clarified the definition of these 2 populations as follows (see Statistical Analysis Plan (SAP): 1) patients with moderate or severe pneumonia with WHO 10-points Clinical Progression Scale [WHO-CPS] score 5 receiving at least 3L/min O_2 but without high flow oxygen (HFO) (defined by using high flow (Optiflow^{TM}) device with more than 15L/min O_2), non-invasive ventilation (NIV) or mechanical ventilation (MV) and 2) patients with critical pneumonia defined as WHO-CPS score 6 or more (i.e., with HFO, NIV or MV). This article reports on two CORIMUNO, multicenter, open-label, randomized controlled clinical trials in critically ill patients with COVID-19: CORIMUNO-TOCI-2 (Tocilizumab (TCZ) treatment) (NCT04331808, a common identifier with the CORIMUNO-TOCI 1 trial conducted in patients with moderate or severe pneumonia, which has been previously reported [12] and CORIMUNO-SARI-2 (Sarilumab (SARI) treatment) trials (NCT04324073, a common identifier with the CORIMUNO-SARI 1 trial conducted in patients with moderate or severe pneumonia) and also recently reported [14]. Accrual took place in 12 (TOCI-2) and 8 (SARI-2) different French University hospitals. Each center could include patients only in one protocol. Because of the emergency nature of the trial and feasibility issues, no placebo of TCZ and SARI was prepared.

The CORIMUNO Cohort and all embedded trials (i.e., trials using data collected in the CORIMUNO cohort) were approved by an ethics committee (CPP Île-de-France VI) and relevant authorities. Legal issues and trial procedures are presented in detail in SAP. Written informed consent was obtained from all patients or from the patient's legal representative for entering the CORIMUNO Cohort, and longitudinal data (including clinical status, biological data, and outcomes) were recorded as part of their participation in the cohort. In this consent, patients and/or their families were made aware that a number of trials may occur via the

cohort and that they would likely be offered to participate in some of them. In practice, for logistical reasons, only one trial took place at each site at a given time. A specific additional written consent was obtained from eligible patients or their families who were randomly selected to be offered TCZ or SARI. Patients randomized to be offered TCZSARI but who declined to be treated or who could not be treated were analyzed in an intention to treat basis in the arm of randomization (TCZ/SARI). Eligible patients assigned to receive usual care (UC) were not notified about the trial, but their CORIMUNO-cohort data were available for analysis. It is a classical process for Cohort-nested multiple Randomized Controlled Trials [15]. All patients were included in ICU. Thus, numbers of them were not able to give consent. In this situation, according to French law, emergency consent was signed by the physician after approval from the family. When the patients recovered, a pursuit consent had to be signed. If the patient refused to sign it, it was considered a consent withdrawal, and the patient's data could not be analysed. This trial was reported according to CONSORT guidelines.

Patients

Patients were included in the CORIMUNO-19 cohort if they had confirmed SARS CoV-2 infection (positive on RT-PCR and/or typical chest CT scan) with moderate, severe, or critical pneumonia (O_2>3L/min, WHO Clinical Progression Scale [WHO-CPS] score $\geq$ 5 [16] [see SAP]).

Patients from the CORIMUNO-19 cohort were eligible for CORIMUNO-TOCI-2 or SARI-2 trial if they had a WHO-CPS score > 5, including patients with non-invasive ventilation (NIV) or mechanical ventilation (MV). Exclusion criteria are detailed in the SAP.

Randomization and treatments

Participants were randomly assigned in a 1:1 ratio to receive UC+TCZ or UC for TOCI-2 protocol, UC+SARI, or UC for SARI-2 protocol via a web-based secure centralized system. An independent statistician provided a computer-generated assignment randomization list stratified by center and blocked with varying block sizes unknown to the investigators. Centers were eligible to participate either in TOCI-2 or SARI-2 trials but not both. Both trials were performed during the same period.

TCZ was administered intravenously (IV) at 8 mg/kg on day 1 (D1) and SARI was administrated IV at a fixed dose of 400 mg on day 1 (D1). Administration of an additional fixed dose of TCZ 400 mg IV or SARI 400mg on D3 was recommended and left to the treating physician. UC (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the clinicians since, at that time, no standard of care (SOC) was defined, including the use of corticosteroids.

Outcome Measures

The early co-primary outcome is the proportion of patients with a decrease of WHO score of at least 1 point at day 4. Results are presented as the proportion of patients who improved so that effective treatment would be associated with an increase in proportion. The longer-term co-primary outcome is the cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 if patients have been intubated before day 14 or removal of NIV or high flow (for > 48h) if they were included under oxygen by NIV or High flow (score 6) and remained without intubation. Death or new DNR order (if applied after the inclusion of the patient) are considered as a competing event. Both outcomes were consistent with the Core Outcome Set proposed by the WHO [16] (see Statistical Analysis Plan (SAP)). Secondary outcomes were clinical status assessed with the WHO-CPS at D4, D7, and D14, overall survival at D90, time to discharge, time to oxygen supply independence, and change in biological factors such as C-reactive protein level, lymphocytes, and neutrophil counts.

Data Quality Monitoring

Data quality monitoring included both remote data monitoring and on-site monitoring performed by dedicated staff independent of the site investigators, with 100% source data verification performed for all patients recruited at every site for all critical data points.

Statistical Analysis

To maximize information from limited data generated while allowing for a rapid decision, we used Bayesian monitoring and analysis of the trial based on the co-primary outcomes. The sample size was set at 120, with interim analyses presented weekly to the data safety monitoring board (DSMB) and a provision to increase the sample size in case of promising but not conclusive results. We computed that the trial would have frequentist power 97.2% to

detect an increase in primary outcome rate from 0.50 to 0.80 and 73.9% to detect a decrease in event rate from 0.50 to 0.70. For the D4 outcome, we used a beta prior distribution with parameters 1 and 1 for the proportion in each arm. For the D14 outcome, we used a Gaussian prior distribution with mean 0 and variance 10^6 for the log hazard ratio. Sensitivity analyses using a range of prior distribution were then conducted (see SAP). The treatment effect was expressed in terms of absolute risk difference (ARD) for the D4 outcome and sub-distribution hazard ratio (HR) for the D14 outcome. Using Markov chain Monte Carlo Markov methods, posterior probabilities of ARD <0 and HR >1 were computed. According to the protocol, posterior probability >0.99 at the interim analysis or >0.95 at the final analysis indicated efficacy. We also computed posterior probability of ARD < -5.5% and HR >1.18 (i.e. 1/0.85) both denoting moderate or greater effect. Since the decision rules are one-sided, consistent credible intervals (CrIs) would be theoretically. However, we chose to report 2-sided 90% CrIs which have the same lower bound than one-sided 95% CrIs. A subgroup analysis according to antiviral drug use at baseline was pre-specified in the protocol. Analyses according to the use of corticosteroids or DXM and CRP were added post-hoc in light of recent publications. Secondary outcomes were analyzed in a frequentist framework, except the analysis of the WHO-CPS scores as an ordinal variable. The Statistical Analysis Plan and details of the statistical analyses are given in the SAP. In the absence of evidence of statistical heterogeneity, a pooled IL-6 inhibitor effect was used with a one-stage approach (see SAP). Those analyses were carried out in a frequentist framework.

Analyses were performed on an intention-to-treat basis with no correction for multiplicity for secondary outcomes. Thus, results on secondary outcomes should be regarded as exploratory and are reported as point estimates and 95% confidence intervals (CIs). Statistical analyses involved using SAS v9.4 (SAS Institute) and R v3.6.1.

Results

Patients

From March 31 to April 18, and from March 27 to April 4, 2020, 97 and 91 patients were randomized in trial TOCI-2 (51 patients to UC+TCZ and 46 UC alone) and trial SARI-2 (50 patients to UC+SARI and 41 UC alone), respectively. The Data Monitoring Committee DMC did not advise further increasing the sample size and trials were stopped because the number of COVID-19 cases dropped dramatically after mild of April (end of the first epidemic wave in France). Among the 51 and 50 patients assigned to receive TCZ or SARI, two in each protocol withdrew consent and were not analyzed. Among the 46 and 41 patients assigned to receive UC, three in the TOCI protocol and eight in the SARI protocol withdrew consent and were not analyzed. Among the 49 or 45 with TCZ or SARI treatment, 38 (47%) and 26 (58%) received a second injection on D3 (Figure 1). Demographic and baseline clinical and biological characteristics of patients are described in Table 1. The median age was 64.6 or 61.2 years (interquartile range, 58.7 to 70.6 or 53.9 to 66.9 years), and 72% or 77% were men, in TOCI-2 and SARI-2 protocols, respectively. There were no major between-group differences at enrollment in TOCI-2 and SARI-2 protocols.

At randomization, very few patients received antiviral therapy or glucocorticoids, and notably, no patients received dexamethasone (eTable1).

Table 1. Characteristics at randomization.

	TOCI-2 trial		SARI-2 trial	
Characteristic	**Tocilizumab (n=49)**	**Usual care (n=43)**	**Sarilumab (n=48)**	**Usual care (n=33)**
Age (years)	63.2 (59.4–70.9)	65.4 (57.6–70.5)	61.9 (53.8–66.2)	61.2 (55.3–68.5)
Male, n/N (%)	33/49 (67%)	33/43 (77%)	36/48 (75%)	26/33 (79%)
Weight (kg)	80.0 (70.0–95.0)	81.0 (75.0–90.5, n=40)	83.5 (75.5–97.0)	83.5 (71.5–90.0, n=32)
BMI (kg/m²)	27.8 (24.8–31.4, n=47)	28.7 (25.4–31.6, n=37)	28.3 (25.1–33.3, n=38)	26.3 (23.8–30.9, n=25)
BMI ≥30 kg/m², n/N (%)	19/48 (40%)	11/41 (27%)	18/47 (38%)	9/32 (28%)
WHO-CPS score (0–10)	7 (6–8)	8 (6–8)	8 (6–8)	7 (6–8)
WHO-CPS score ≥7, n/N (%)	36/49 (74%)	31/43 (71%)	32/48 (67%)	24/33 (41%)
Body temperature (°C)	37.7 (37.0–38.6)	38.0 (37.0–38.7)	37.7 (37.0–38.5)	37.7 (37.0–38.4)
Respiratory rate (breaths / min)	25.0 (22.0–31.0, n=48)	26.0 (22.0–34.0, n=39)	27.5 (24.0–32.0)	25.0 (20.0–30.0, n=31)
SpO_2 (%)	94.0 (92.0–96.0, n=48)	94.0 (91.0–98.0)	94.0 (93.0–96.0)	92.0 (92.0–97.0)
PaO_2/FiO_2 ratio	128 (100 to 175, n=45)	138 (101 to 187, n=35)	132 (106–204, n=41)	102 (86–155, n=31)
Time from symptoms onset to randomization (days)	11 (9–15, n=47)	11 (9–14, n=42)	11 (9–15)	11 (8–21, n=31)
Time from ICU admission to randomization (days)*	1 (1–2, n=42)	2 (0–4, n=38)	3 (1–4, n=38)	3 (1–4, n=28)
Co–existing conditions, n/N (%)				
Chronic cardiac disease	14/49 (29%)	13/41 (32%)	10/48 (21%)	3/33 (9%)
Diabetes	20/49 (41%)	12/41 (29%)	17/48 (35%)	8/32 (25%)
Chronic kidney disease (stage 1 to 3) or dialysis	3/49 (6%)	3/42 (7%)	6/48 (13%)	5/33 (15%)
Asthma	3/49 (6%)	2/41 (5%)	1/48 (2%)	3/33 (9%)
Chronic pulmonary disease (not asthma)	3/49 (6%)	4/41 (10%)	2/48 (4%)	1/33 (9%)

Active malignant neoplasm	1/49 (2%)	1/41 (2%)	1/48 (2%)	0/33 (0%)
Current or former smoker, n/N (%)	6/44 (14%)	5/41 (12%)	1/44 (2%)	5/29 (17%)
Laboratory values				
C–reactive protein (CRP) (mg/L)	182.0 (123.0–265.0, n=45)	199.0 (108.0–318.0, n=33)	197.0 (137.5–286.0)	200.0 (131.0–273.0, n=31)
D–Dimer (µg/L)	2280 (1475–3912, n=44)	2041 (1000–3420, n=34)	1426 (1065–2528, n=36)	1683 (1169–3245, n=21)
Neutrophil count (G/L)	6.8 (5.3–8.6, n=48)	9.0 (4.8–12.5, n=37)	6.5 (4.9–8.6, n=47)	6.7 (4.6–10.3, n=31)
Lymphocyte count (G/L),	0.8 (0.6–1.3, n=48)	0.9 (0.5–1.3, n=36)	0.8 (0.5–1.2, n=47)	0.9 (0.6–1.2, n=31)
Lymphocytes to neutrophils ratio	0.1 (0.1–0.2, n=48)	0.1 (0.1–0.2, n=36)	0.1 (0.1–0.2, n=47)	0.1 (0.1–0.2, n=31)
Hemoglobin (g/dL)	11.5 (10.1–12.8)	10.7 (9.4–12.4, n=41)	11.5 (10.1–12.5)	11.7 (10.4–12.9)
Platelet count (g/L)	273 (203–352)	255 (191–341, n=41)	243 (181–277, n=47)	253 (182–311)
Creatinine (µmol/L)	79.0 (61.0–109.0, n=48)	77.0 (59.0–112.0, n=42)	81.0 (49.5–141.0)	83.0 (60.0–106.0, n=33)

* Only computed for patients in the ICU at randomization

Values are median [interquartile range] unless stated otherwise.

Primary outcomes

On D4, 35/49 (71%) and 34/48 (71%) patients randomized to receive TCZ and SARI, respectively did not improve by reducing WHO-CPS score by at least 1 point versus 30/43 (70%) and 26/33 (79%) in the UC groups (median posterior ARD +1.7% or -7.3%; 90% CrI, -13.6 to +17.1 or -22.5 to +8.7) (eFigure 1, eTable 2). The posterior probabilities of ARD <0 (TCZ or SARI better than UC) were 42.9% and 77.7% and ARD < -5.5% were 22% and 57.5%, respectively.

At D14, the cumulative incidence of successful tracheal extubation or removal of NIV or high flow (for a duration > 48h) had occurred in 23 (16 intubated and 7 NIV/HFO) or in 18 (11 intubated and 7 NIV/HFO) patients treated with TCZ or SARI, respectively (cumulative incidence of events of 47% or 38%; (95% CI 32% to 60% or 24% to 51%) and in 18 (12 intubated and 6 NIV/HFO) and 11 (6 intubated and 5 NIV/HFO) in patients treated with UC in the TOCI-2 or SARI-2 protocols, respectively (Table 2). The posterior probability of any efficacy of TCZ or SARI (HR >1) was 71.4% and 54.9%, and of moderate or greater efficacy (HR >1.18) was 51.9% and 38.9% (posterior median adjusted HR 1.19; 90% CrI 0.71 to 2.04 or 1.05; 90% CrI 0.55 to 2.07) (eTable 3). Similar results were observed without adjustment for age and center (eTable 4 and eFigure 2). The proportions of patients with the occurrence of the primary event (extubation or removal of NIV or High flow>48h without death) are shown in Figure 2.

Pre-specified (for antiviral drugs) or post-hoc subgroup analyses (for corticosteroids, including DXM) were not performed because the proportion of patients on antiviral drugs or corticosteroids was too low (<5%) in both protocols (eTable 5 (TOCI-2) and eTable 6 (SARI-2)). Additionally, we performed additional post-hoc subgroups analysis according to the

WHO-CPS score and the time from ICU admission to randomization (≤ 1 day vs. > 1 day) and CRP levels (< or >150mg/ml) (eTable 5 and 6).

Table 2. Primary and secondary outcomes.

	TOCI-2 trial			SARI-2 trial		
Outcome	**Tocilizumab (n=49)**	**Usual care (n=43)**	**Treatment effect**	**Sarilumab (n=48)**	**Usual care (n=33)**	**Treatment effect**
Primary outcomes						
No improvement in WHO score at day 4	35 (71%)	30 (70%)	+1.7% (-13.6 to +17.1)**	34 (71%)	26 (79%)	-7.3% (-22.5 to +8.7)**
Posterior probability of any benefit			49.2%			77.7%
Posterior probability of moderate or greater benefit			22.0%			57.5%
Extubation or removal of NIV* >48h at day 14 (95% CI)	47% (32 to 60)	42% (27 to 56)	HR: 1.19 (0.71 to 2.04)**	38% (24 to 51)	33% (18 to 50)	HR: 1.05 (0.55 to 2.07)**
Posterior probability of any benefit			71.4%			54.9%
Posterior probability of moderate or greater benefit			51.9%			38.9%
Secondary outcomes						
Overall survival						
Estimate at day 14 (95% CI)	90% (82 to 99)	79% (68 to 92)	HR: 0.37 (0.12 to 1.15)	75% (64 to 88)	73% (59 to 90)	HR: 0.95 (0.40 to 2.25)
Estimate at day 28 (95% CI)	84% (74 to 95)	77% (65 to 90)	HR: 0.56 (0.22 to 1.46)	71% (59 to 85)	67% (52 to 85)	HR: 0.89 (0.40 to 1.96)
Estimate at day 90 (95% CI)	76% (64 to 89)	70% (57 to 85)	HR: 0.67 (0.30 to 1.49)	71% (59 to 85)	61% (46 to 80)	HR: 0.74 (0.35 to 1.58)
WHO-CPS score (10-point scale)						
Median (IQR) at day 4	7 (7 to 8)	8 (7 to 8)	OR: 0.85 (0.39 to 1.82)†	7 (7 to 8)	8 (7 to 8)	OR: 0.88 (0.38 to 2.02)†
Median (IQR) at day 7	7 (5 to 8)	8 (7 to 8)	OR: 0.69 (0.32 to 1.47)†	8 (7 to 8)	8 (7 to 8)	OR: 1.07 (0.47 to 2.40)†
Median (IQR) at day 14	7 (5 to 8)	7 (5 to 9)	OR: 0.68 (0.32 to 1.43)†	7 (5 to 10)	7 (5 to 10)	OR: 1.13 (0.50 to 2.57)†
Day 2 to day 14 longitudinal analysis	—	—	OR: 0.76 (0.27 to 2.13)‡	—	—	OR: 0.72 (0.21 to 2.41)‡
Day-28 ventilator-free days, mean (SD)	12.8 (10.7)	10.3 (11.1)	MD: -2.5 (-6.9 to +1.7)	10.3 (11.1)	8.7 (11.0)	-1.5 (-6.1 to +3.9)
Patients with WHO-CPS ≥ 7, mean (SD)	9.8 (9.5)	7.2 (9.4)	MD: -2.5 (-6.6 to +2.7)	7.5 (9.5)	4.6 (7.6)	-2.9 (-7.4 to +1.7)
Oxygen supply independency						
Estimate at day 28 (95% CI)	59% (44 to 72)	49% (33 to 63)	HR: 1.44 (0.82 to 2.52)	44% (29 to 57)	36% (20 to 53)	HR: 1.20 (0.59 to 2.44)
Estimate at day 90 (95% CI)	69% (53 to 80)	64% (47 to 77)	HR: 1.28 (0.80 to 2.03)	71% (52 to 83)	56% (35 to 72)	HR: 1.29 (0.74 to 2.25)
Discharge						
Estimate at day 28 (95% CI)	55% (40 to 68)	42% (27 to 56)	HR: 1.45 (0.80 to 2.63)	35% (22 to 49)	30% (16 to 46)	HR: 1.21 (0.55 to 2.66)
Estimate at day 90 (95% CI)	70% (54 to 82)	60% (44 to 74)	HR: 1.35 (0.84 to 2.17)	65% (48 to 77)	52% (33 to 68)	HR: 1.30 (0.71 to 2.37)
ICU discharge††						
Estimate at day 28 (95% CI)	72% (55 to 84)	60% (42 to 74)	HR: 1.28 (0.73 to 2.24)	60% (43 to 74)	71% (50 to 85)	HR: 0.78 (0.42 to 1.44)
Estimate at day 90 (95% CI)	84% (66 to 93)	83% (63 to 93)	HR: 1.15 (0.73 to 1.81)	79% (61 to 89)	82% (57 to 93)	HR: 0.84 (0.49 to 1.47)

All treatment effects are estimates adjusted on age and center, with 95% confidence intervals except otherwise stated.

* Non-invasive ventilation or high-flow oxygen

** Median posterior absolute risk difference with 90% Credible interval (90% CrI).

† Median posterior hazard ratio adjusted for age and center.

‡ Median posterior odds ratio in a proportional odds model, adjusted for baseline WHO-CPS score, age and center.

†† Only for patients in the ICU at randomization (TOCI-2 trial: n=40 in the tocilizumab arm and n=37 in the usual care arm, SARI-2 trial: n=38 in the sarilumab arm and n=28 in the usual care arm).

RD: risk difference; HR: hazard ratio; OR: odds ratio MD: mean difference; 95% CI: 95% confidence interval; IQR: interquartile range.

Secondary outcomes

The evolutions of WHO scores during 14-day follow-up are given eFigure 3 and eTable 7. Although some trends were observed, no significant difference was observed in both TOCI-2 and SARI-2 protocols in Day 28 ventilator free days (eTable 8), oxygen supply independency (59% vs 49% and 44% vs 36%, eTable 9) cumulative incidence of discharge (59% vs 49% and 44% vs 36%) (eTable 10), time to ICU discharge (72% vs 60% or 60% vs 71%) (eTable 11).

Overall, with a median follow-up of 95 days (59-217) and 91 days (36-210), at D90, 12 (24%) and 14 (29%) patients had died in the TCZ or SARI groups versus 13 (30%) and 13 (39%) in their respective UC control groups (adjusted HR 0.67, 95% CI 0.30 to 1.49 and

0.74, 95% CI 0.35 to 1.58) (Figure 2 C and D), eTable 12). Causes of deaths were similar in all groups, mainly due to ARDS, and are summarized in Table 3.

A post hoc pooled analysis of both anti-IL-6 receptor antibodies and UCs are shown for the D14 primary outcome (supplementary Figure 5A) and D90 overall survival (supplementary Figure 5B).

Biological response

Mean C-reactive protein levels decrease rapidly in the TCZ and SARI arms, and lymphocyte count was increased (eFigure 4) mainly in the TCZ but not in SARI arms.

Safety

A total of 33 (67%) or 32 (68%) and 30 (70%) or 22 (68%) patients in the TCZ or SARI and UC groups reported adverse events between randomization and D90, respectively (Table 3). Serious adverse events occurred in 20 (32%) and 29 (43%), respectively (p=0.21) (eTable 13). The number of bacterial and fungal serious infections was higher in the TCZ and SARI groups than in UC groups (27 vs. 13 or 19 vs. 4).

Table 3. Serious adverse events and causes of death.

	TOCI-2 trial		SARI-2 trial	
	Tocilizumab (n=49)	**Usual care (n=43)**	**Sarilumab (n=48)**	**Usual care (n=33)**
Adverse events				
Patients with at least one AE	33 (67%)*	30 (70%)	32 (68%)**	22 (68%)
Patients with multiple AEs	24 (49%)	24 (56%)	18 (38%)	17 (52%)
Total number of AEs	176	177	79	67
Incidence rate per 1000 patient-days (95% CI)	50.9 (32.7-79.3)	60.9 (41.2-89.9)	25.5 (18.6-35.1)	33.7 (23.1-49.2)
Incidence rate ratio (95% CI)	0.84 (0.46-1.51)†	reference	0.76 (0.46-1.24)††	reference
Serious adverse events				
Patients with at least one SAE	31 (63%)‡	27 (63%)	31 (64.6%)‡‡	19 (57.6%)
Patients with multiple SAEs	19 (39%)	10 (23%)	14 (29.2%)	7 (21.2%)
Total number of SAEs	93	55	69	34
Incidence rate per 1000 patient-days (95% CI)	26.9 (16.7-43.3)	18.9 (12.5-28.7)	22.3 (15.1-33.0)	17.1 (10.0-29.3)
Incidence rate ratio (95% CI)	1.42 (0.76-2.68)¶	reference	1.30 (0.67-2.53)¶¶	reference
ARDS	13	15	15	9
Bacterial and fungal sepsis	27	13	19	4
Pulmonary embolism	4	1	2	2
Other ischemic events	3	2	1	1
Hemorrhagic events	5	2	2	2
Renal failure	4	4	4	4
Hepatic toxicity	12	5	5	3
Anemia	7	7	4	2
Thrombopenia	1	0	0	0
Neutropenia	1	0	2	0
Lymphopenia	0	0	2	1
Death	12 (24%)	13 (30%)	14 (29%)	13 (39%)
Causes of death				
ARDS	7	7	11	7
Bacterial sepsis	2	2	0	1
Fungal sepsis	0	1	0	0
Multiple organ failure	0	1	0	5
Hemorrhagic stroke	1	2	1	0
Pulmonary embolism	2	0	1	0
Heart failure	0	0	1	0

* $P = 0.83$ vs usual care (Fisher's exact test)

† $P = 0.55$ vs usual care (Poisson model)

‡ $P = 1.00$ vs usual care (Fisher's exact test)

¶ $P = 0.28$ vs usual care (Poisson model)

** $P = 1.00$ vs usual care (Fisher's exact test)

†† $P = 0.27$ vs usual care (Poisson model)

‡‡ $P = 0.64$ vs usual care (Fisher's exact test)

¶¶ $P = 0.44$ vs usual care (Poisson model)

Discussion

In these two trials embedded in the CORIMUNO-19 cohort, we did not find any efficacy of TCZ and SARI in patients with critical COVID-19 pneumonia requiring high-flow, NIV, or MV, for decreasing the proportion of patients alive with the removal of intubation, NIV, or high flow (for > 48h) at D14. However, a slight numerical (but not statistically significant) increase of survival up to day 90 was found with both anti-IL6 receptor antibodies (76% and 71% vs 70% and 61% with UC, HR 0.67 (0.30 to 1.49) and 0.74 (0.35 to 1.58), respectively, (pooled analysis, HR 0.71; (0.61 to 1.23)). TCZ and SARI did not induce any significant increase in serious adverse events but a numerical increase of serious infections.

In patients in intensive care unit (ICU) requiring high flow, NIV, or mechanical ventilation (WHO-CPS $\geq$6), the only standard of care was DEX [6], which in the RECOVERY trial has been shown to increase D28 overall survival, particularly in patients treated shortly after admission to ICU. The time of IL-6R antagonism introduction seems to be important, as also suggested by a large emulated multicenter trial emulated trial having involved 433 patients that found that in spite of an increased risk of secondary infections, the risk of in-hospital mortality in this study was lower in patients treated with TCZ in the first 2 days of ICU admission compared with patients whose treatment did not include early use of TCZ [17]. TCZ and SARI, two anti-IL6 receptors registered for the treatment of rheumatoid arthritis and cytokines release syndromes (only TCZ), have also been tested extensively in the treatment of COVID-19 patients, and their effects are still a matter of discussion. In non-critically ill patients requiring oxygen (WHO-CPS=5), several studies suggest that TCZ reduces mortality at D28 associated with a reduction of severe adverse events, particularly infections [18]. For SARI, fewer studies have tested its effect, and its efficacy is even uncertain [19].

Our results contrast with those reported recently by REMAP-CAP and to a lesser extent, RECOVERY studies in the same group of critically ill patients [20, 21]. In the REMAP-CAP study, the median number of organ support-free days was superior both for patients assigned to TCZ (median odd ratio 1.64; 95% CI, 1.25 to 2.14) or SARI arms (median odd ratio 1.76; 95% CI, 1.17 to 2.91)), which was associated with better overall survival, and this beneficial effect was observed for all secondary analyses that included WHO scale improvement at D14, and time to discharge [20]. In the RECOVERY trial, TCZ improved overall survival in patients requiring oxygen support. However, although a trend in favor of TCZ was observed

for patients on mechanical ventilation, it did not reach significance (HR 0.94; CI 0.73-1.19)[21]. Interestingly in these two studies, most of the patients received corticosteroids, particularly dexamethasone (>80%), and the effects of TCZ and SARI seem to provide additional benefit to dexamethasone. Additionally, the higher effect observed in the REMAP-CAP study might likely be due to the fact that patients were enrolled and treated within 24h after starting MV. More recently, in the prospective metanalysis of the WHO (that included REMAP-CAP and RECOVERY studies), on 10390 hospitalized patients for pneumonia, randomized in 27 trials, confirming results of REMAP-CAP and Recovery studies, IL-6 antagonists treatment decreased mortality at day 28 (OR, 0.86 [95% CI, 0.79-0.95]; *P* = .003) and these results were even better in the group of patients receiving corticosteroids (ORs, 0.77 (95% CI, 0.68-0.87) for T and 0.92 (95% CI, 0.61-1.38) for SARI [18]. Furthermore, in a subgroup analysis, among 1171 patients (recruited in 9 trials) who were receiving mechanical ventilation at randomization, the weighted mean difference comparing IL-6 antagonists with usual care or placebo in the duration of mechanical ventilation was −0.84 (95% CI, −1.82 to 0.13), favoring IL-6 antagonists (95% of patients receiving TOCI in this analysis). Taken together, the benefit from dexamethasone and possibly of anti-IL-6 receptor inhibitors may be beneficial in some populations at some time points and not too early to inhibit a beneficial immune reaction and may rely on either depression of hyperinflammatory response, or balancing the damage-repairment, or both.

In the TOCI-2 and SARI-2 protocols, dexamethasone was very barely used, and a majority of patients (84/146, 56%) were included and treated after day one of ICU admission, which might be too late, pulmonary lesions being already established.

Even if the primary end-point was not reached, it is interesting and somewhat surprising to observe a non-significant trend in day 90 better overall survival with both anti-IL6 receptor antibodies. It might be due to a slight decrease of ventilator-free days until D28 with TCZ and SARI vs. usual care (-2.5 (-6.9 to +1.7) and -1.5 (-6.1 to +3.9), respectively. Interestingly, the difference of overall survival up to 90 days in our 2 trials between UC and UC + anti-IL-6 receptor antibodies is not far from that observed in the REMAP-CAP study. Indeed in the REMAP-CAP, the hazard ratios of survival up to Day 90 corresponded to 0.63 (95% credible interval, 0.49–0.81) for tociliumab and 0.55 (0.30–0.82) for sarilumab, which was not far from the HRs of death up to day 90 in our study 0.67 (0.30–1.49) for tocilizumab and 0.74 (0.35–1.58) for sarilumab.

Regarding safety, the main difference between these 2 trials in ICU patients and the previous trials of anti-IL6-R antibodies in patients on oxygen in medical wards is a numerical increase

of serious infections in SARI and TCZ arms (n=46) vs. usual care (n=17). This increased risk of serious infections (which was only statistically significant with TCZ) with anti-IL6R antibodies is easily explained by the higher fragility of these patients in ICU compared with patients in medical wards. However, in our study, bacterial sepsis was rarely the cause of death in both arms and thus, the overall benefit of anti-IL6R antibodies in critically ill patients [18] with COVID-19 may be a compromise between reducing deleterious pulmonary hyper inflammation and not increasing too much the risk of bacterial and fungal complications.

Limitations

At the beginning of the first COVID-19 pandemic wave, the CORIMUNO-19 cohort was designed to perform several exploratory clinical trials swiftly and provide information on drug candidates of potential interest quickly. The trial was not blinded since it was logistically impossible to set up a double-blind study quickly enough at the time of the pandemics. However, it is unlikely that in this group of critically ill patients, unblinding could lead to measurement bias since the decision of extubation was based on objective parameters related to Pa02/ Fi02 ratio. Another limitation is that UC could differ among centers and over time. However, the short period of accrual and the stratification of randomization may have limited the impact of such a lack of standardization. Because of the design of the CORIMUNO platform, the sample size, which could not be increased because of the end of the first epidemic wave, was small and not designed to show a difference in survival, credibility intervals were wide, and the treatment effect may be underestimated [22]. The design of our study was also not designed to compare the respective effects of TCZ and SARI that showed here similar effects.

Conclusions

In summary, this study does not bring evidence that TCZ or SARI alone are effective in shortening the time of ventilation support in the group of critically ill patients. However, the recent WHO meta-analysis results are consistent with our results on mortality at day 90, suggesting that anti-IL6 receptor antibodies plus dexamethasone could be an option in patients with critical COVID.

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Conflict of Interest Disclosures:

Olivier Hermine: None related to this work

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Data sharing statement: Authors will share data upon approval by the steering committee of the CORIMUNO-19 platform. Individual deidentified participant data, study protocols, statistical analysis plan, will be shared for any purpose upon approval. Data will be available after publication for 15 years.

Role of the Funders: Funders had no access to the trial data and had no role in the design, conduct, or reporting of the trial. Roche and Sanofi donated TCZ and SARI, respectively in unrestricted grant, and had no role in the trial design or conduct; the collection, management, analysis, interpretation of the data; or in the preparation, review of the manuscript or the approval of the manuscript for submission.

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A steering committee was responsible for the design, conduct, and reporting of the trial, and an independent data and safety monitoring board (DSMB) oversees all CORIMUNO-19 trials (see Appendix 1). The authors vouch for the accuracy and completeness of the data and analyses and the fidelity of the trial to the protocol, which is available with the full text of this article at http://jamanetwork.com.

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Legends to Figures

Figure 1: Flow Chart

A TOCI-2 protocol (treatment with Tocilizumab+UC vs UC)

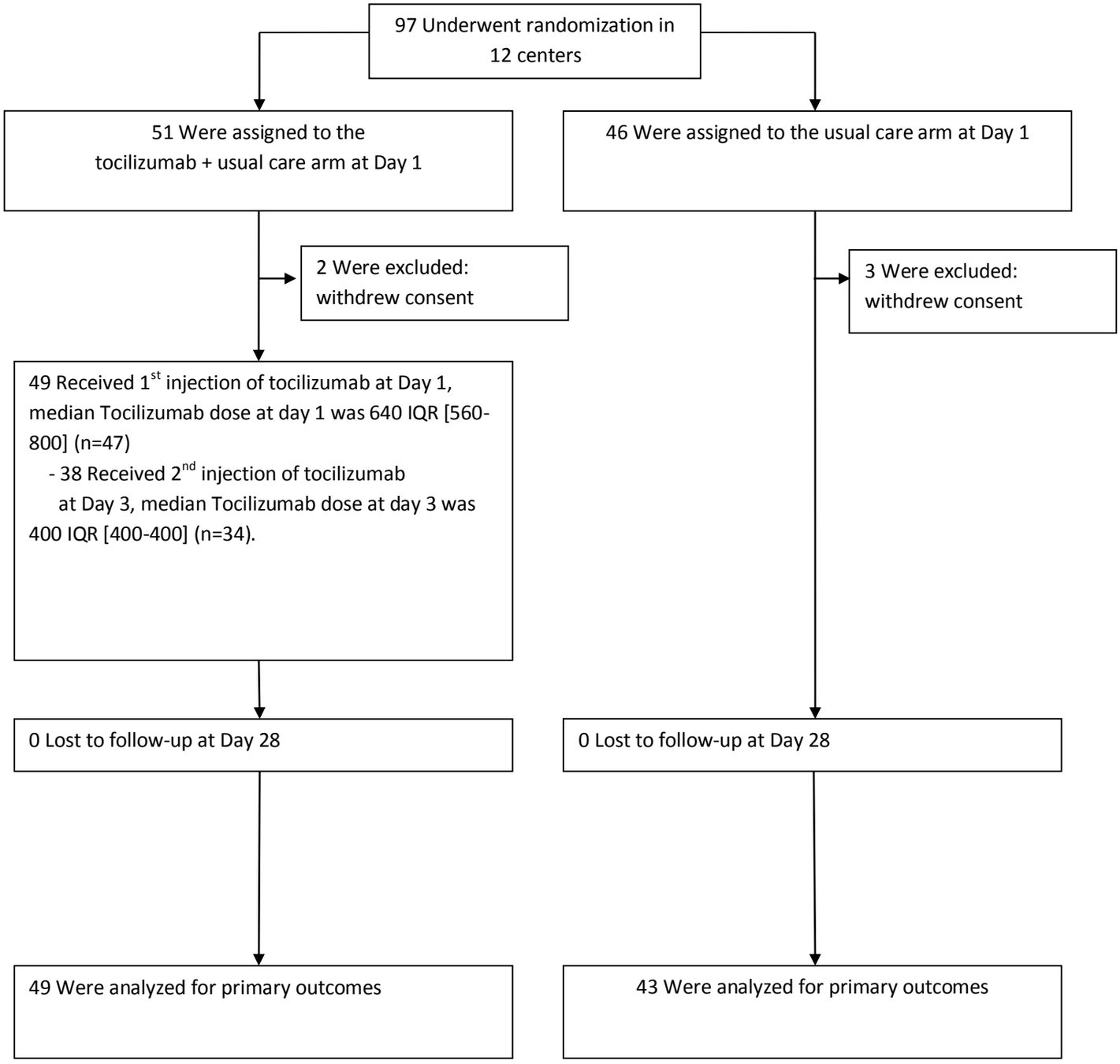
B SARI-2 protocol (Treatment with Sarilumab+UC vs UC)

Figure 2: Occurrence of events during follow-up.

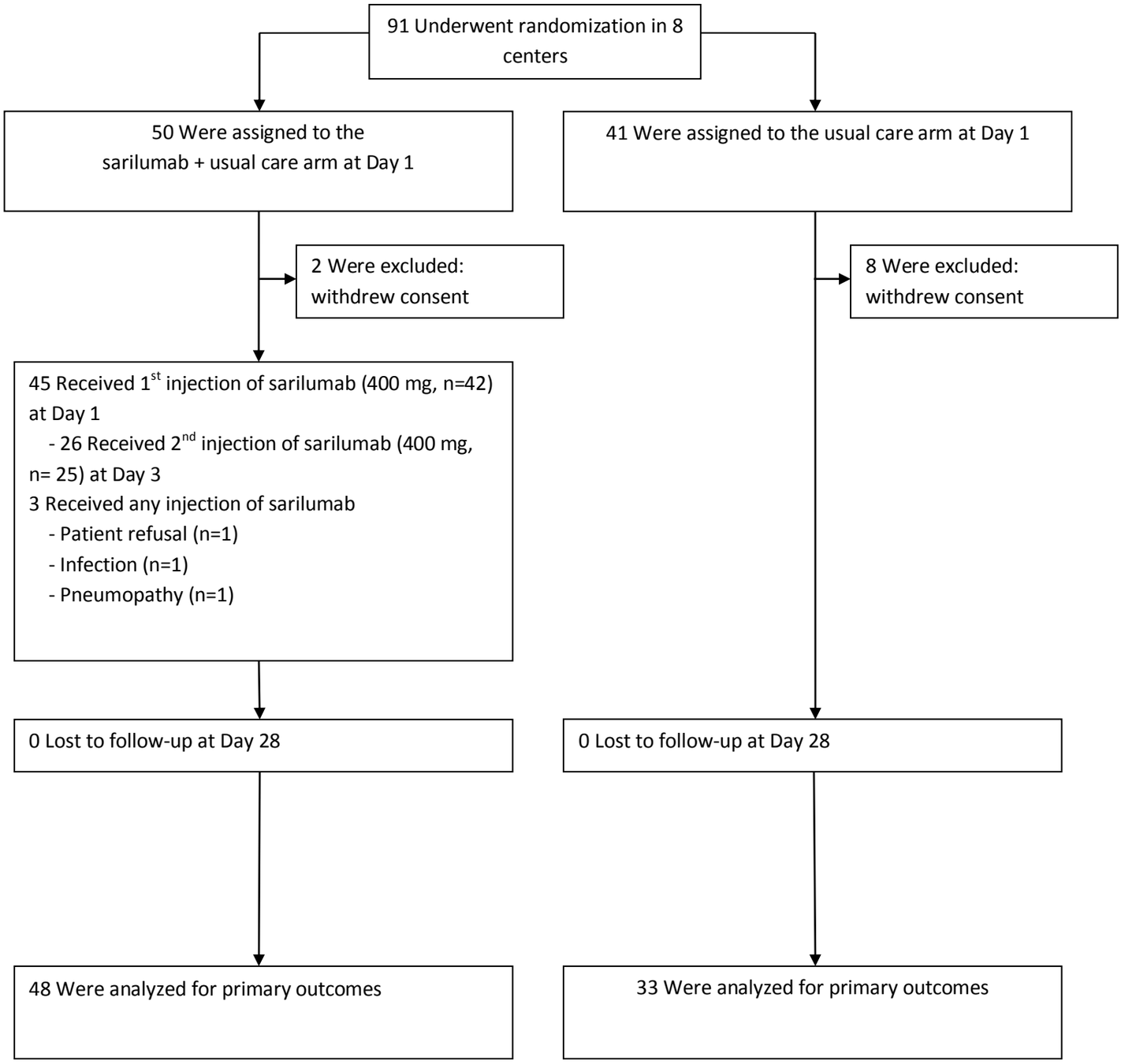
Kaplan-Meier cumulative estimates of the probability of the primary outcome (removal of device (mechanical ventilation, high-flow or non-invasive ventilation support)) and death up to D14 **(A) TOCI-2 protocol** (treatment with tocilizumab) **(B) SARI-2 protocol** (treatment with sarilumab), and overall survival **(C) TOCI-2 protocol** (tocilizumab arm as compared with the usual care arm) **(D) SARI-2 protocol** (sarilumab arm as compared with the usual care arm).

Figure 1: Flow chart of the study.

A TOCILIZUMAB



B SARILUMAB


91 Underwent randomization in 8 centers
50 Were assigned to the sarilumab + usual care arm at Day 1
41 Were assigned to the usual care arm at Day 1
2 Were excluded: withdrew consent
8 Were excluded: withdrew consent
45 Received 1st injection of sarilumab (400 mg, n=42) at Day 1
- 26 Received 2nd injection of sarilumab (400 mg, n= 25) at Day 3
3 Received any injection of sarilumab
- Patient refusal (n=1)
- Infection (n=1)
- Pneumopathy (n=1)
0 Lost to follow-up at Day 28
0 Lost to follow-up at Day 28
48 Were analyzed for primary outcomes
33 Were analyzed for primary outcomes

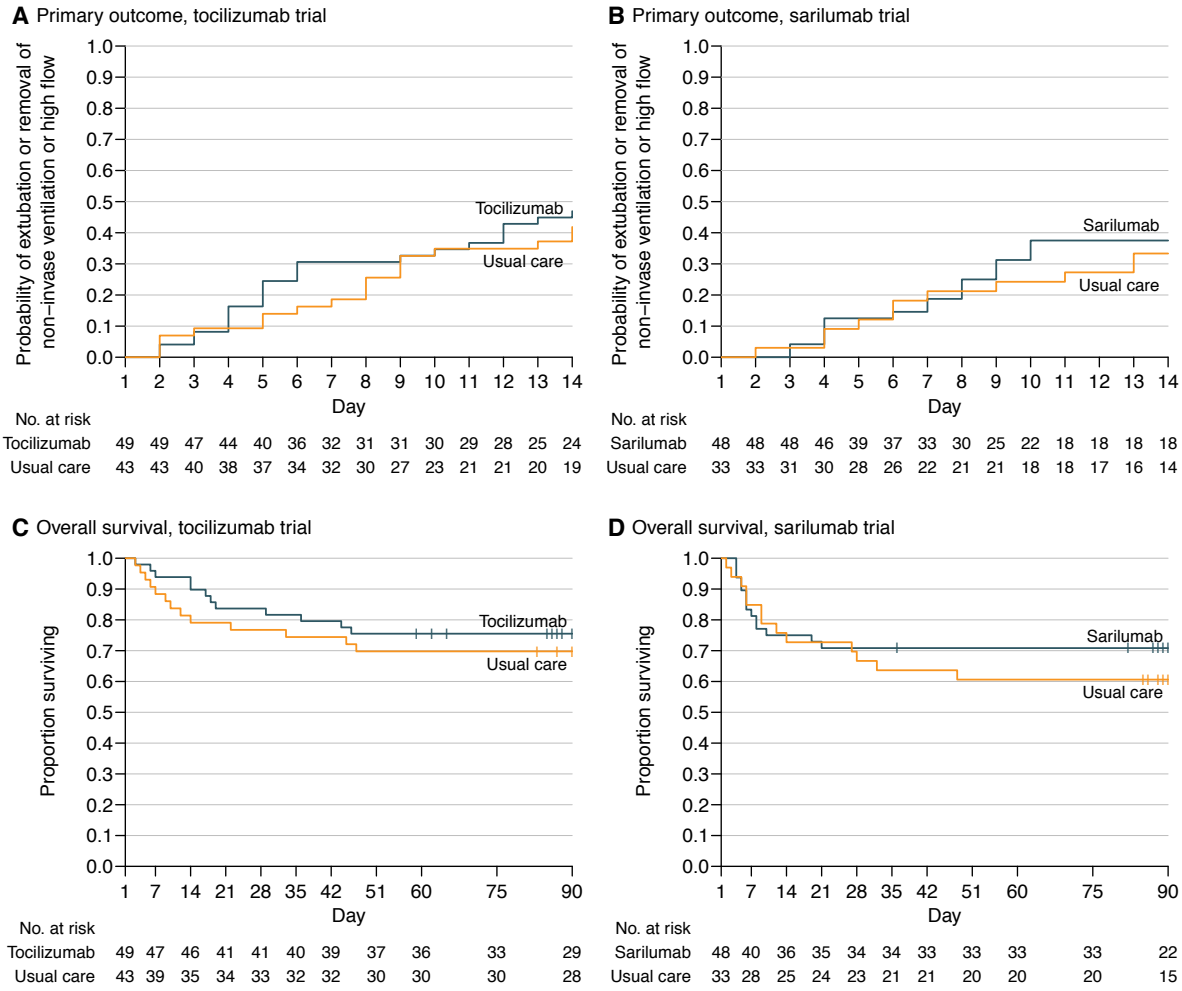


Figure 2: Occurrence of events during follow-up.

Kaplan-Meier cumulative estimates of the probability of the primary outcome (removal of device (mechanical ventilation, high-flow or non-invasive ventilation support)) and death up to D14 **(A) TOCI-2 protocol** (treatment with tocilizumab) **(B) SARI-2 protocol** (treatment with sarilumab), and overall survival **(C) TOCI-2 protocol** (tocilizumab arm as compared with the usual care arm) **(D) SARI-2 protocol** (sarilumab arm as compared with the usual care arm).

Supplementary Table 1 Treatments received before and after randomization until Day 14. Values are n (%**).**

A Tocilizumab.

	Tocilizumab (N=49)			UC (N=43)		
Time from randomization	Before	After	Any	Before	After	Any
Anticoagulants	17 (35)	24 (49)	34 (69)	14 (40)	20 (47)	29(67)
Antibiotics	36 (73)	32 (65)	46 (94)	27 (63)	31 (72)	38 (88)
- Azithromycin	5 (10)	1 (2)	5 (10)	6 (14)	3 (7)	8 (19)
Hydroxychloroquine	10 (20)	0 (0)	10 (20)	6 (14)	0 (0)	6 (14)
Antiviral drugs	5 (10)	3 (6)	8 (16)	3 (7)	2 (5)	4 (9)
- Lopinavir/Ritonavir	2 (4)	3 (6)	5 (10)	1 (2)	1 (2)	2 (5)
- Osteltamivir	3 (6)	0 (0)	3 (6)	2 (5)	1 (2)	2 (5)
Immuno-modulators	0 (0)	0 (0)	0 (0)	0 (0)	1 (2) *	1 (2) *
Corticosteroids	8 (16)	17 (35)	20 (41)	4 (9)	14 (33)	17 (40)
- Dexamethasone	0 (0)	3 (6)	3 (6)	0 (0)	1 (2)	1 (2)

* Tocilizumab provided at day 4 and at day 6

B Sarilumab.

	Sarilumab (N=48)			UC (N=33)		
Time from randomization	Before	After	Any	Before	After	Any
Anticoagulants	26 (55)	29 (62)	43 (91)	17 (52)	19 (58)	30 (91)
Antibiotics	24 (51)	28 (60)	34 (72)	18(55)	23 (70)	30 (91)
- Azithromycin	7 (15)	1 (2)	8 (17)	3 ()	1 (3)	4 (12)
Hydroxychloroquine	3 (6)	3 (6)	6 (13)	2 (6)	1 (3)	3 (9)
Antiviral drugs	2 (4)	1 (2)	3 (7)	1 (3)	0 (0)	1 (3)
- Lopinavir/Ritonavir	2 (4)	1 (2)	3 (7)	1 (3)	0 (0)	1 (3)
Immuno-modulators	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroids	0 (0)	10 (21)	10 (21)	2 (6)	6 (18)	7 (21)
- Dexamethasone	0 (0)	1 (2)	1 (2)	0 (0)	1 (3)	1 (3)

Supplementary Table 2. Day 4 outcome

A TOCILZUMAB

	Tocilizumab	Usual care	Risk Difference	Adjusted Odds Ratio
N	49	43		
N (%) not improved	35 (71%)	30 (70%)		
Posterior Median	70.9%	69.2	+1.7%	1.04
90% CrI			-13.6 to +17.1	0.47 to 2.29
95% CrI	57.5 to 82.1	54.8 to 81.4	-16.4 to +20.0	0.40 to 2.65
Posterior probabilities*				
P(any benefit)			0.429	0.465
P(at least moderate benefit)			0.220	0.333

P(any benefit)=P(RD<0) or P(OR<1), P(at least moderate benefit)=P(RD<5.5%) or P(OR<0.85)

B SARILUMAB

	Sarilumab	Usual care	Risk Difference	Adjusted Odds Ratio
N	48	33		
N (%) not improved	34 (71%)	26 (79%)		
Posterior Median	70.3%	77.7	-7.3%	0.57
90% CrI			-22.5 to +8.7	0.21 to 1.42
95% CrI	56.7 to 81.7	62.1 to 89.3	-25.3 to +11.9	0.17 to 1.69
Posterior probabilities*				
P(any benefit)			0.777	0.846
P(at least moderate benefit)			0.575	0.764

P(any benefit)=P(RD<0) or P(OR<1), P(at least moderate benefit)=P(RD<5.5%) or P(OR<0.85)

Supplementary Table 3. Summary of the posterior distribution of the hazard ratio (HR) adjusted for age and center. A HR>1 indicates efficacy of tocilizumab or sarilumab.

A TOCILIZUMAB

Parameter	Value
Median HR	1.19
90% CrI	0.71 to 2.04
95% CrI	0.64 to 2.27
P(HR > 1)	0.714
P(HR > 1/0.95)	0.656
P(HR > 1/0.85)	0.519
P(HR > 1/0.8)	0.443

B SARILUMAB

Parameter	Value
Median HR	1.05
90% CrI	0.55 to 2.07
95% CrI	0.49 to 2.37
P(HR > 1)	0.549
P(HR > 1/0.95)	0.498
P(HR > 1/0.85)	0.389
P(HR > 1/0.8)	0.334

Supplementary Table 4. Summary of the posterior distribution of the unadjusted hazard ratio (HR). A HR>1 indicates efficacy of tocilizumab or sarilumab

A TOCILIZUMAB

Parameter	Value
Median HR	1.20
90% CrI	0.72 to 2.04
95% CrI	0.65 to 2.27
P(HR > 1)	0.719
P(HR > 1/0.95)	0.662
P(HR > 1/0.85)	0.527
P(HR > 1/0.8)	0.451

B SARILUMAB

Parameter	Value
Median HR	1.17
90% CrI	0.63 to 2.26
95% CrI	0.56 to 2.59
P(HR > 1)	0.662
P(HR > 1/0.95)	0.610
P(HR > 1/0.85)	0.496
P(HR > 1/0.8)	0.433

Supplementary Table 5: Subgroup analyses for the primary outcome (TOCI-2 protocol)
Analyses according to antivirals at baseline were pre-specified in the protocol, but only 8 patients (5 tocilizumab, 3 usual care) were on antivirals at randomization.
Additional analyses according to corticosteroids and dexamethasone were added post-hoc to the SAP hoc in the light of publications or press releases. No patient was on dexamethasone at randomization, and only 12 (8 tocilizumab, 4 usual care) were receiving corticosteroids. Accordingly, no subgroup analysis was performed.
Post-hoc subgroup analyses according to the WHO-CPS score and the time from ICU admission to randomization (≤ 1 day vs. > 1 day) have been performed, as requested by the trial Scientific Committee.

	Tocilizumab (n=49)	Usual care (n=43)		Interaction
Subgroup	N events/N (%)	N events/N (%)	Adjusted HR (95% CI)	P-value
Antivirals at baseline				—
Yes	1/5 (20%)	2/3 (67%)	—	
No	22/44 (50%)	16/40 (40%)	—	
Corticosteroids at baseline				—
Yes	2/8 (25%)	1/4 (25%)	—	
No	21/41 (51%)	17/39 (44%)	—	
Dexamethasone at baseline				—
Yes	0/0 (—)	0/0 (—)	—	
No	23/49 (47%)	18/43 (42%)	—	
Delay from ICU admission*				0.15
≤ 1 day	13/25 (52%)	6/16 (38%)	1.75 (0.63 to 4.83)	
> 1 day	4/17 (24%)	8/22 (36%)	0.58 (0.17 to 1.93)	
WHO-CPS score at randomization				0.65
6	11/13 (85%)	8/12 (67%)	1.60 (0.61 to 4.20)	
≥ 7	12/36 (33%)	10/31 (32%)	1.12 (0.48 to 2.62)	
CRP**				0.002
≤ 150 mg/L	14/19 (74%)	2/13 (15%)	6.60 (2.50 to 17.4)	
> 150 mg/L	9/26 (35%)	11/20 (55%)	0.36 (0.15 to 0.83)	

* Excluded 7 and 4 patients not in the ICU at randomization in the tocilizumab and usual care arm, respectively, and 1 patient with unknown date of ICU admission. ** 4 and 10 missing data in the tocilizumab and usual care arm, respectively.

Supplementary Table 6 : Subgroup analyses for the primary outcome (SARI-2 protocol)
Analyses according to antivirals at baseline were pre-specified in the protocol, but only 3 patients (2 sarilumab, 1 usual care) were on antivirals at randomization.
Additional analyses according to corticosteroids and dexamethasone were added post-hoc to the SAP in the light of publications. No patient was on dexamethasone at randomization, and only 2 (0 sarilumab, 2 usual care) were receiving corticosteroids.
Accordingly, no subgroup analysis stratified on these variables was performed.
Post-hoc subgroup analyses according to the WHO-CPS score and the time from ICU admission to randomization (≤ 1 day vs. > 1 day) have been performed, as requested by the trial Scientific Committee.

Subgroup	Sarilumab (n=48) N events/N (%)	Usual care (n=33) N events/N (%)	Adjusted HR (95% CI)	Interaction *P*-value
Antivirals at baseline				—
Yes	0/2 (0%)	0/1 (0%)	—	
No	18/46 (39%)	11/32 (34%)	—	
Corticosteroids at baseline				—
Yes	0/0 (—)	1/2 (50%)	—	
No	18/48 (38%)	10/31 (32%)	—	
Dexamethasone at baseline				—
Yes	0/0 (—)	0/0 (—)	—	
No	18/48 (38%)	11/33 (33%)	—	
Delay from ICU admission*				0.086
≤ 1 day	1/11 (9%)	3/10 (30%)	0.22 (0.022 to 2.26)	
> 1 day	11/27 (41%)	4/18 (22%)	1.78 (0.54 to 5.80)	
WHO-CPS score at randomization				0.074
6	8/16 (50%)	7/9 (78%)	0.45 (0.16 to 1.30)	
≥ 7	10/32 (31%)	10/24 (17%)	1.84 (0.57 to 4.98)	
CRP**				0.78
≤ 150 mg/L	8/14 (57%)	5/10 (50%)	1.17 (0.41 to 3.32)	
> 150 mg/L	10/34 (29%)	6/21 (29%)	1.00 (0.31 to 3.24)	

* Excluded 10 and 5 patients not in the ICU at randomization in the sarilumab and usual care arm, respectively.
** Two missing data

Supplementary Table 7. WHO scores during follow-up. OR was obtained from Bayesian proportional odds models adjusted for baseline WHO-CPS score, age and center. For longitudinal data, time was used as a main effect in the model. No imputation was performed, but a window of plus/minus 2 days was used for day 14 scores.

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N	Median (IQR)	N	Median (IQR)	Adjusted OR (95% CrI)
Day 1	49	7 (6 to 8)	43	8 (6 to 8)	—
Day 4	49	7 (7 to 8)	43	8 (7 to 8)	0.85 (0.39 to 1.82)
Day 7	48	7 (5 to 8)	43	8 (7 to 8)	0.69 (0.32 to 1.47)
Day 14	48	7 (5 to 8)	43	7 (5 to 9)	0.68 (0.32 to 1.43)
Longitudinal analysis	49	-	43	-	0.76 (0.27 to 2.13)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N	Median (IQR)	N	Median (IQR)	Adjusted OR (95% CrI)
Day 1	48	8 (6 to 8)	33	7 (6 to 8)	—
Day 4	48	7 (7 to 8)	33	8 (7 to 8)	0.88 (0.38 to 2.02)
Day 7	48	8 (7 to 8)	33	8 (7 to 8)	1.07 (0.47 to 2.40)
Day 14	47	7 (5 to 10)	33	7 (5 to 10)	1.13 (0.50 to 2.57)
Longitudinal analysis	48	—	33	—	0.720.21 to 2.41)

Supplementary Table 8. Day 28 ventilator-free days

For patients not ventilated at baseline, the time before ventilation (if it occurred) was considered as ventilator-free. Those never intubated during the first 28 days had 28 ventilator-free days. In all cases, the time horizon (28 days) was counted from randomization. A separate analysis was performed excluding patients not ventilated at randomization (WHO-CPS scores 6). Results are mean (SD). Confidence intervals were obtained by bootstrapping.

A TOCILIZUMAB

	Tocilizumab		Usual care		Mean difference
	N	CIF (95% CI)	N	CIF (95% CI)	(95% CI)
All patients	49	12.8 (10.7)	43	10.3 (11.1)	-2.5 (-6.9 to +1.7)
WHO-CPS ≥ 7	36	9.8 (9.5)	31	7.2 (9.4)	-2.5 (-6.6 to +2.7)

B SARILUMAB

	Sarilumab		Usual care		Mean difference
	N	Mean (SD)	N	Mean (SD)	(95% CI)
All patients	48	10.3 (11.1)	33	8.7 (11.0)	-1.5 (-6.1 to +3.9)
WHO-CPS ≥ 7	32	7.5 (9.5)	24	4.6 (7.6)	-2.9 (-7.4 to +1.7)

Supplementary Table 9. Cumulative incidence of oxygen supply independency until 28 days. CIF: cumulative incidence function.

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	13	26% (15 to 40)	7	16% (7 to 29)	—
Day 28	29	59% (44 to 72)	21	49% (33 to 63)	1.44 (0.82 to 2.52)
Day 90	34	69% (53 to 80)	28	64% (47 to 77)	1.28 (0.80 to 2.03)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	12	25% (14 to 38)	6	18% (7 to 33)	—
Day 28	21	44% (29 to 57)	12	36% (20 to 53)	1.20 (0.59 to 2.44)
Day 90	33	71% (52 to 83)	18	56% (35 to 72)	1.29 (0.74 to 2.25)

Supplementary Table 10. Cumulative incidence of discharge. CIF: cumulative incidence function.

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	13	26% (15 to 40)	7	16% (7 to 29)	—
Day 28	29	59% (44 to 72)	21	49% (33 to 63)	1.44 (0.82 to 2.52)
Day 90	34	69% (53 to 80)	28	64% (47 to 77)	1.28 (0.80 to 2.03)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	12	25% (14 to 38)	6	18% (7 to 33)	—
Day 28	21	44% (29 to 57)	12	36% (20 to 53)	1.20 (0.59 to 2.44)
Day 90	33	71% (52 to 83)	18	56% (35 to 72)	1.29 (0.74 to 2.25)

Supplementary Table 11. Cumulative incidence of ICU discharge for patients in the ICU at inclusion. CIF: cumulative incidence function.

A TOCILIZUMAB

	Tocilizumab (n=40)		Usual care (n=37)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	16	40% (25 to 55)	16	43% (27 to 58)	—
Day 28	29	72% (55 to 84)	22	60% (42 to 74)	1.28 (0.73 to 2.24)
Day 90	33	84% (66 to 93)	30	83% (63 to 93)	1.15 (0.73 to 1.81)

B SARILUMAB

	Sarilumab (n=38)		Usual care (n=28)		
	N events	CIF (95% CI)	N events	CIF (95% CI)	Adjusted HR (95% CI)
Day 14	16	42% (26 to 57)	14	50% (30 to 67)	—
Day 28	23	60% (43 to 74)	20	71% (50 to 85)	0.78 (0.42 to 1.44)
Day 90	30	79% (61 to 89)	23	82% (57 to 93)	0.84 (0.49 to 1.47)

Supplementary Table 12. **Overall survival at 14, 28 and 90 days.**

A TOCILIZUMAB

	Tocilizumab (n=49)		Usual care (n=43)		
	N deaths	OS (95% CI)	N deaths	OS (95% CI)	Adjusted HR (95% CI)
Day 14	5	90% (82 to 99)	9	79% (68 to 92)	0.37 (0.12 to 1.15)
Day 28	8	84% (74 to 95)	10	77% (65 to 90)	0.56 (0.22 to 1.46)
Day 90	12	76% (64 to 89)	13	70% (57 to 85)	0.67 (0.30 to 1.49)

B SARILUMAB

	Sarilumab (n=48)		Usual care (n=33)		
	N deaths	OS (95% CI)	N deaths	OS (95% CI)	Adjusted HR (95% CI)
Day 14	12	75% (64 to 88)	9	73% (59 to 90)	0.95 (0.40 to 2.25)
Day 28	14	71% (59 to 85)	11	67% (52 to 85)	0.89 (0.40 to 1.96)
Day 90	14	71% (59 to 85)	13	61% (46 to 80)	0.74 (0.35 to 1.58)

Supplementary Table 13. Serious adverse events and causes of deaths.

A TOCILIZUMAB

	Tocilizumab (N=49)	**UC (N=43)**	***P***
Adverse events			
- Patients with at least one AE*	33 (67%)	30 (70%)	0.83*
- Patients with multiple AE	24 (49%)	24 (56%)	
- Number of events**	176	177	0.20**
Serious adverse events			
- Patients with at least one SAE	31 (63%)	27 (63%)	1.00*
- Patients with multiple SAE	19 (39%)	23 (9%)	
- Number of events	93	55	0.020**
Angina	1	0	
Arthritis	1	0	
Hemorrhagic stroke	1	2	
Ischemic stroke	1	2	
Hypovolemic shock	1	0	
Diabetes	1	0	
Anemia	7	7	
Hepatic cholestasis	3	2	
Hepatic cytolysis	9	3	
Pneumothorax	1	1	
Pulmonary embolism	4	1	
Thrombophlebitis	1	0	
Thrombopenia	1	1	
ARDS	13	15	
Bacterial sepsis	25	12	
Fungal sepsis	2	1	
Severe acute pancreatis	1	0	
Thrombopenia	1	0	
Neutropenia	1	0	
Renal failure	4	4	
Adrenal insufficiency	1	0	
Hyperleukocytosis	1	0	
Arterial hypertension	1	0	
Metabolic acidosis	1	0	
Guillain Barré syndrome	1	0	
Hemoptysis	1	0	
Gastrointestinal bleeding	1	0	
Bleeding	1	0	
Limb ischemia	1	0	
Neuropathy	1	0	
Acute pulmonary oedema	2	0	
Tracheotomy	1	1	
Psoas hematoma	1	0	
Bradycardia	0	1	
Heart failure	0	1	

	Tocilizumab (N=49)	UC (N=43)	*P*
Facial paralysis	0	1	
Death	12 (24%)	13 (30%)	
- Causes			
ARDS	7	7	
Bacterial sepsis	2	2	
Fungal sepsis	0	1	
Multiple organ failure	0	1	
Hemorrhagic stroke	1	2	
Pulmonary embolism	2	0	

* Fisher's exact test
** Poisson model

B SARILUMAB

	Sarilumab (N=48)	UC (N=33)	*P*
Adverse events			
- Patients with at least one AE*	32 (68%)	22 (68%)	1.00*
- Patients with multiple AE	18 (38%)	17 (52%)	
- Number of events**	79	67	0.2062**
Serious adverse events			
- Patients with at least one SAE	31 (64.6%)	19 (57.6%)	0.6426*
- Patients with multiple SAE	14 (29.2%)	7 (21.2%)	
- Number of events	69	34	0.1119**
Acidosis	1	0	
Allergy to sarilumab	1	0	
Severe constipation	1	0	
Accidental extubation	1	0	
Cerebral hemorrhage	1	0	
Hyperkalemia	1	0	
Lymphopenia	2	1	
Neuromuscular abnormalities acquired in ICU	2	1	
Cardiac rythm disorder	2	0	
Diabetes	2	0	
Anemia	4	2	
Hepatic cytolysis	5	3	
Pulmonary embolism	2	2	
ARDS	15	9	
Bacterial sepsis	18	4	
Fungal sepsis	1	0	
Neutropenia	2	0	
Renal failure	4	4	
Gastrointestinal bleeding	1	2	
Lower limbs ischemia	1	0	
Heart failure	2	0	
Complication of tracheostomy	0	1	
Bone fracture	0	1	
Hypoalbuminemia	0	1	
Hypotension	0	2	
Transient ischemic attack	0	1	
Death	14 (29%)	13 (39%)	
- Causes			
ARDS	11	7	
Bacterial sepsis	0	1	
Multiple organ failure	0	5	
Cerebral hemorrhage	1	0	

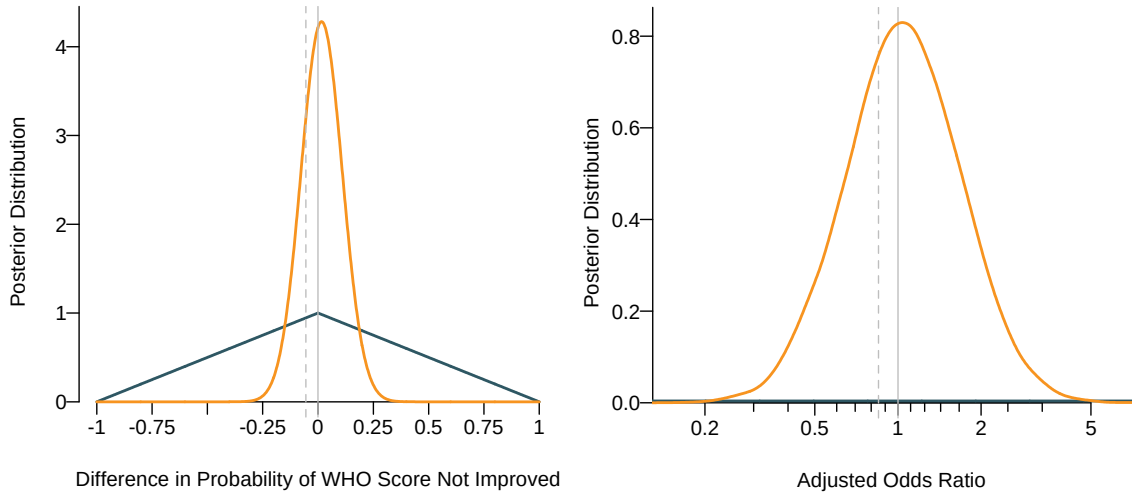
	Sarilumab (N=48)	UC (N=33)	*P*
Pulmonary embolism	1	0	
Heart failure	1	0	

* Fisher's exact test

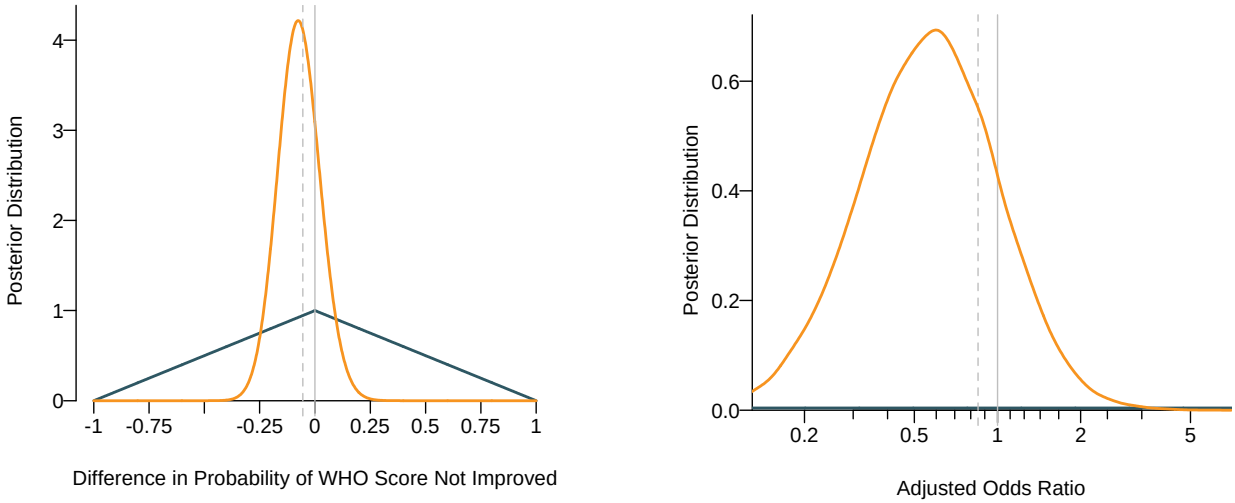
** Poisson model

Supplementary Figure 1 A (TOCI-2) and B (SARI-2).
Posterior density of the risk difference and adjusted odds ratio for the day 4 outcome (golden line). The dark blue line represents the minimally informative priors. The solid gray lines indicates an RD of 0 or an OR of 1, representing no treatment effect, and the dashed gray lines indicate a moderate benefit (RD = 5.5%, OR=0.85).

A TOCILIZUMAB

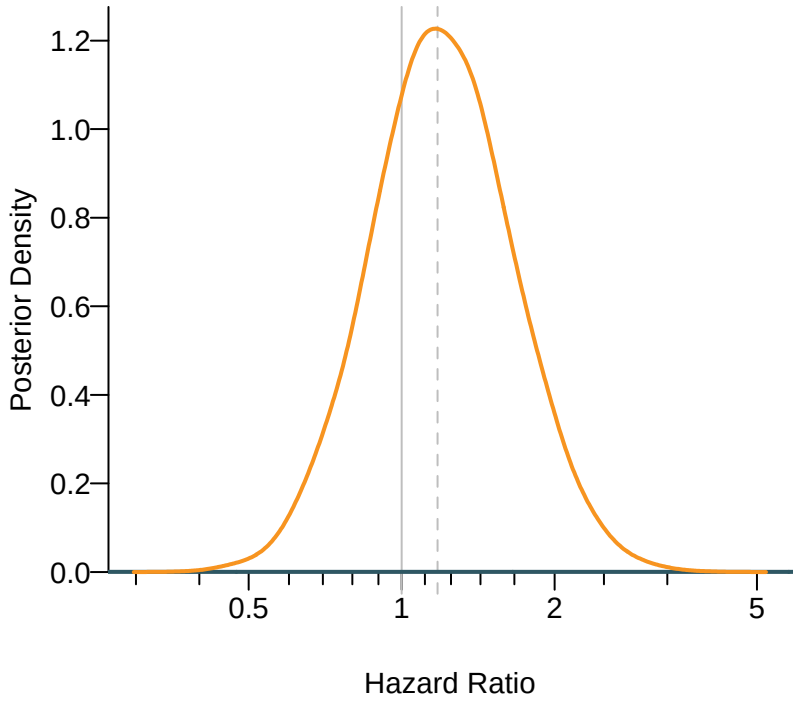


B SARILUMAB

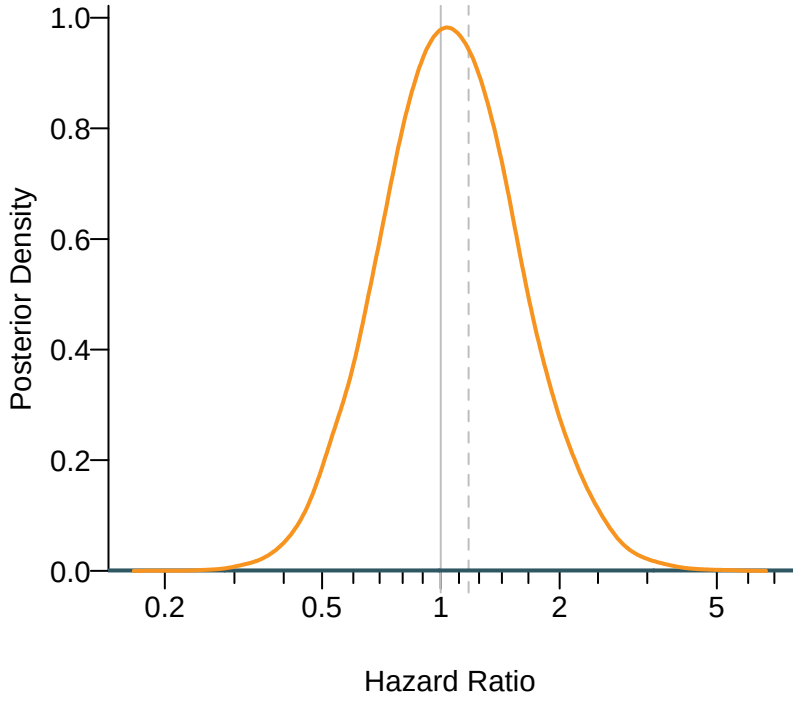


Supplementary Figure 2 A (TOCI-2) and B (SARI-2). Posterior density of the adjusted hazard ratio for the primary outcome (golden line). The dark blue line represents the minimally informative prior. The solid gray line indicates a HR of 1 representing no treatment effect. The dashed gray line indicates a HR of 1.18 (1/0.85) indicating a moderate benefit.

A TOCILIZUMAB

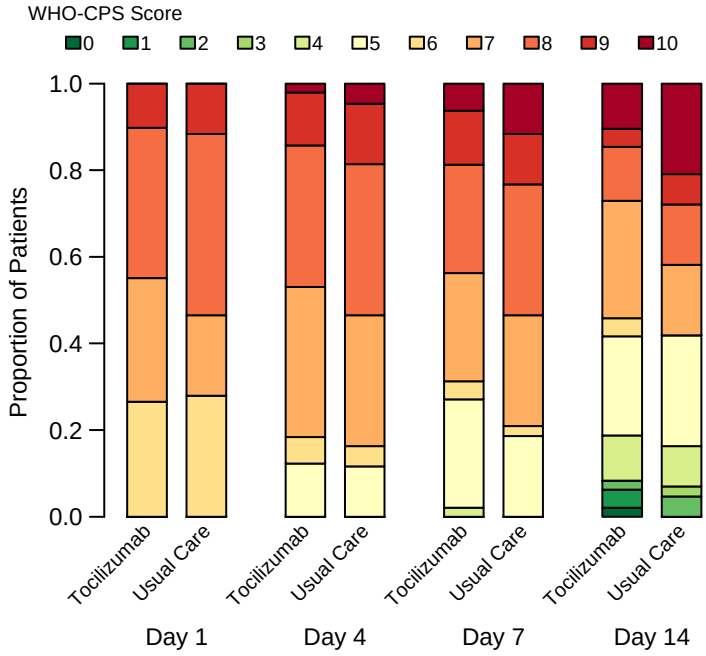


B SARILUMAB

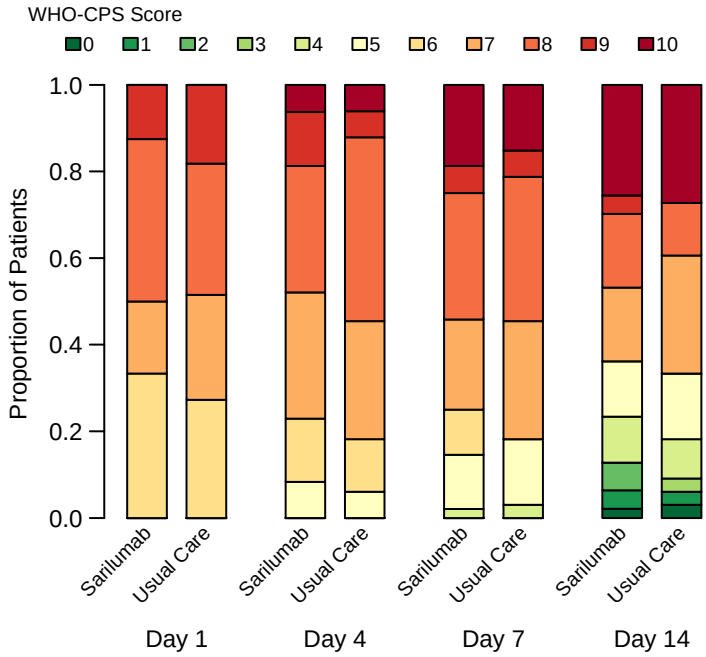


Supplementary Figure 3. WHO score during follow-up. (TOCI-2) and B (SARI-2).

A TOCILIZUMAB

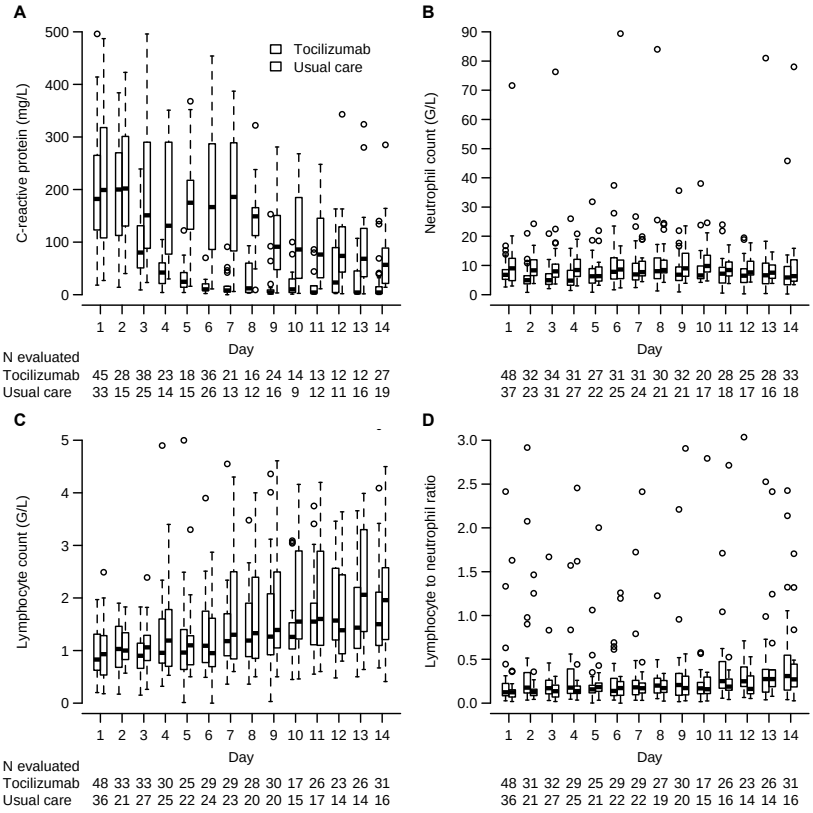


B SARILUMAB

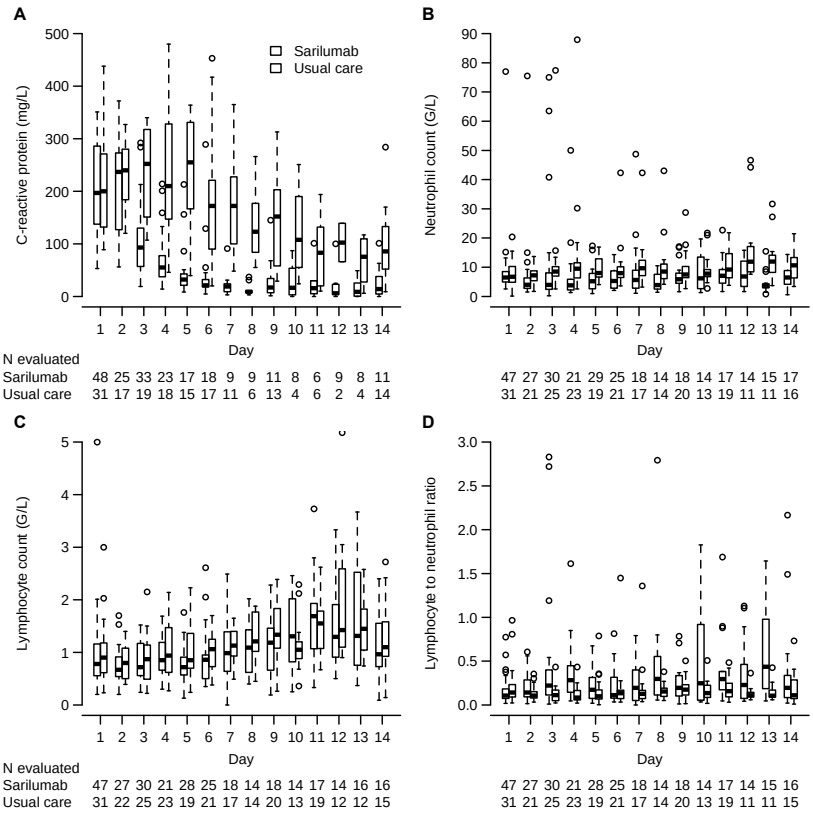


Supplementary Figure 4. Evolution of biological parameters TOCI-2 and SARI-2 protocols

A TOCILIZUMAB



B SARILUMAB

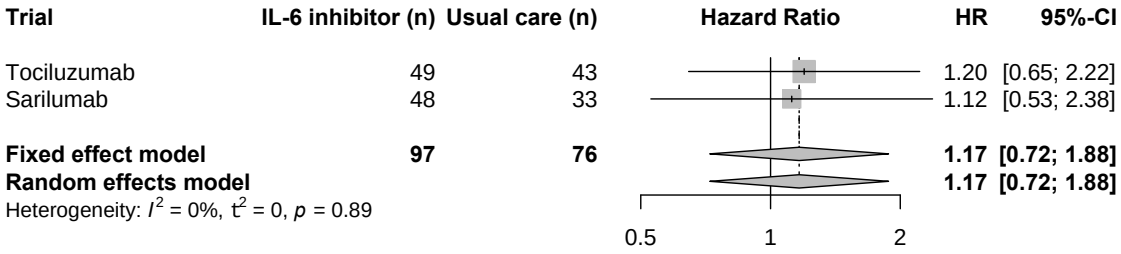


Supplementary Figure 5

(A) Forest plot of the two-stage pooled analysis of the day 14 co-primary outcome. A HR > 1 indicates the efficacy of tocilizumab/sarilumab compared to usual care. No heterogeneity was found ($\tau^2 = 0$).

(B) Forest plot of the two-stage pooled analysis of the day 90 survival outcome. A HR < 1 indicates the efficacy of tocilizumab/sarilumab compared to usual care. No heterogeneity was found ($\tau^2 = 0$).

A



B