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Effect of interleukin-6 receptor antagonists in critically ill adult patients with COVID-19 pneumonia: two randomised controlled trials of the CORIMUNO-19 Collaborative Group

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Shareable abstract (@ERSpublications)
In two prospective randomised studies of COVID-19 patients in the ICU, 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. https://bit.ly/3GoFAJV

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Abstract

Background Our objective was to determine whether anti-interleukin (IL)-6 receptors improve outcomes of critically ill patients with coronavirus disease 2019 (COVID-19) pneumonia. We report on two cohort-embedded, investigator-initiated, multicentre, open-label, Bayesian randomised controlled clinical trials.

Methods Patients were randomly assigned to receive either usual care (UC) or UC+tocilizumab (TCZ) 8 mg·kg^{-1} (TOCI-2 trial) or UC or UC+sarilumab (SARI) 200 mg (SARI-2 trial), both intravenously on day 1 and, if clinically indicated, on day 3.

Results Between 31 March and 20 April 2020, 97 patients were randomised 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 noninvasive ventilation (NIV) or mechanical ventilation (MV) and were alive with TCZ or UC were similar (47% *versus* 42%; median posterior hazard ratio (HR) 1.19, 90% credible interval (CrI) 0.71–2.04), with a posterior probability of HR >1 of 71.4%. Between 27 March and 4 April 2020, 91 patients were randomised 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 or MV and were alive with SARI or UC were similar (38% *versus* 33%; median posterior HR 1.05, 90% CrI 0.55–2.07), with a posterior probability of HR >1 of 54.9%. Overall, the risk of death up to day 90 was: UC+TCZ 24% *versus* UC 30% (HR 0.67, 95% CI 0.30–1.49) and UC+SARI 29% *versus* UC 39% (HR 0.74, 95% CI 0.35–1.58). 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 or MV by day 14.

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease induced by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)), having already caused more than 2.5 million deaths worldwide by February 2021 [1–4]. Most people with COVID-19 have only mild or uncomplicated symptoms. Still, ∼10–15% have moderate or severe disease requiring hospitalisation and oxygen support, and 3–5% require admission to an intensive care unit (ICU) mainly for ventilation assistance [4, 5].

Patients with COVID-19 pneumonia present nonspecific inflammatory responses including oedema and inflammatory cell infiltration in the lungs. Besides the specific pathogenic effect of SARS-CoV-2, the host immune response, in addition to its role in controlling virus replication, may result in hyperinflammation leading to worsening pulmonary function. It is, at least in part, related to the production of several pro-inflammatory cytokines and chemokines, including interleukin (IL)-6. As demonstrated by the RECOVERY Collaborative Group, dexamethasone (DXM) 6 $mg \cdot day^{-1}$ for 10 days decreased 28-day mortality among patients receiving oxygen, including mechanical ventilation (MV), high-flow oxygen (HFO) and noninvasive 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, randomised clinical trials of immune-modulatory drugs in two well-defined groups of patients: patients hospitalised in medical wards with moderate-to-severe COVID-19 pneumonia and patients hospitalised in intensive medical units (ICUs) with NIV or invasive ventilation (World Health Organization Clinical Progression Scale (WHO-CPS) score <5 with at least 3 $L \cdot min^{-1}$ O_2 or score >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 signalling. 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 day 14, but no effect on survival at day 28 and a trend for a better survival at day 90. 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 (UC) on free-ventilation survival in critically ill patients with COVID-19 on NIV or MV.

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; ClinicalTrials.gov: NCT04324047). This cohort was used to perform a series of randomised controlled trials testing different therapeutic regimens in COVID-19 patients. Two separate populations were recruited: patients with moderate or severe pneumonia and critically ill patients. An Institutional Review Board-approved amendment to the protocol on 6 April 2020 clarified the definition of these two populations as follows (see the statistical analysis plan (SAP) in the supplementary material): 1) patients with moderate or severe pneumonia with 10-point WHO-CPS score 5 receiving at least 3 $L \cdot min^{-1}$ O_2 but without HFO (defined by using a high-flow device (Optiflow; Fisher & Paykel, Auckland, New Zealand) with >15 $L \cdot min^{-1}$ O_2), NIV or MV, and 2) patients with critical pneumonia defined as WHO-CPS score ⩾6 (*i.e.* with HFO, NIV or MV). This article reports on two CORIMUNO-19, multicentre, open-label, randomised controlled clinical trials in critically ill patients with COVID-19: CORIMUNO-TOCI-2 (TCZ treatment) (ClinicalTrials.gov: 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 (SARI treatment) (ClinicalTrials.gov: 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 eight (SARI-2) different French university hospitals. Each centre 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-19 cohort and all embedded trials (*i.e.* trials using data collected in the CORIMUNO-19 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 the SAP in the supplementary material. Written informed consent was obtained from all patients or from the patient's legal representative for entering the CORIMUNO-19 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 randomised to be offered TCZ/SARI but who declined to be treated or who could not be treated were analysed on an intention-to-treat basis in the arm

of randomisation (TCZ/SARI). Eligible patients assigned to receive UC were not notified about the trial, but their CORIMUNO-19 cohort data were available for analysis. This is a classical process for cohort-nested multiple randomised controlled trials [15]. All patients included were in the ICU and thus some 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. Trials are reported according to CONSORT guidelines.

Patients

Patients were included in the CORIMUNO-19 cohort if they had confirmed SARS-CoV-2 infection (positive on reverse transcriptase-PCR and/or typical chest computed tomography scan) with moderate, severe or critical pneumonia (O_2 >3 L·min^{-1}, WHO-CPS score ⩾5; see the SAP in the supplementary material [16]).

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

Randomisation and treatments

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

TCZ was administered intravenously at 8 mg·kg^{-1} on day 1 and SARI was administrated *i.v.* at a fixed dose of 400 mg on day 1. Administration of an additional fixed dose of TCZ 400 mg *i.v.* or SARI 400 mg *i.v.* on day 3 was recommended and left to the treating physician. UC (antibiotic agents, antiviral agents, corticosteroids, vasopressor support and anticoagulants) was provided at the discretion of the clinicians since, at that time, no standard of care was defined, including the use of corticosteroids.

Outcome measures

The early co-primary outcome was the proportion of patients with a decrease of WHO-CPS 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 was the cumulative incidence of successful tracheal extubation (defined as duration of extubation >48 h) at day 14 if patients have been intubated before day 14 or removal of NIV or HFO (for >48 h) if they were included under oxygen by NIV or HFO (score 6) and remained without intubation. Death or new do-not-resuscitate order (if applied after the inclusion of the patient) was considered as a competing event. Both outcomes were consistent with the Core Outcome Set proposed by the WHO (see the SAP in the supplementary material) [16]. Secondary outcomes were clinical status assessed with the WHO-CPS at days 4, 7 and 14, overall survival at day 90, time to discharge, time to oxygen supply independence, and change in biological factors such as C-reactive protein (CRP) 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 maximise 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 and Safety Monitoring Board 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 day 4 outcome, we used a β prior distribution with parameters 1 and 1 for the proportion in each arm. For the day 14 outcome, we used a Gaussian prior distribution with mean 0 and variance 10^6 for the log hazard ratio (HR). Sensitivity analyses using a range of prior distribution were then conducted (see the SAP in the supplementary material). The treatment effect was expressed in terms of absolute risk difference

(ARD) for the day 4 outcome and subdistribution HR for the day 14 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 one-sided 95% CrIs. However, we chose to report two-sided 90% CrIs which have the same lower bound as 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 [11]. Secondary outcomes were analysed in a frequentist framework, except the analysis of WHO-CPS scores as an ordinal variable. The SAP and full details of the statistical analyses are provided in the supplementary material. In the absence of evidence of statistical heterogeneity, a pooled IL-6 inhibitor effect was used with a one-stage approach (see the SAP in the supplementary material). 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 were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.1 (www.r-project.org).

Results

Patients

From 31 March to 18 April 2020 and from 27 March to 4 April 2020, 97 and 91 patients were randomised in the TOCI-2 trial (51 patients to UC+TCZ and 46 to UC alone) and SARI-2 trial (50 patients to UC +SARI and 41 to UC alone), respectively. The Data and Safety Monitoring Board did not advise further increasing the sample size and trials were stopped because the number of COVID-19 cases dropped dramatically after the middle 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 analysed. Among the 46 and 41 patients assigned to receive UC, three in the TOCI-2 protocol and eight in the SARI-2 protocol withdrew consent and were not analysed. Among the 49 or 45 with TCZ or SARI treatment, 38 (47%) and 26 (58%), respectively, received a second injection on day 3 (figure 1). Demographic and baseline clinical and biological characteristics of patients are described in table 1. The median (interquartile range (IQR)) age was 64.6 (58.7–70.6) and 61.2 (53.9–66.9) years, and 72% and 77% were men, in the TOCI-2 and SARI-2 protocols, respectively. There were no major between-group differences at enrolment in the TOCI-2 and SARI-2 protocols.

At randomisation, very few patients received antiviral therapy or glucocorticoids, and notably, no patients received DXM (supplementary table S1).

Primary outcomes

On day 4, 35 out of 49 (71%) and 34 out of 48 (71%) patients randomised to receive TCZ and SARI, respectively, did not improve by reducing the WHO-CPS score by at least 1 point *versus* 30 out of 43 (70%) and 26 out of 33 (79%) in the UC groups (median posterior ARD +1.7% (90% CrI −13.6 to +17.1) or −7.3% (90% CrI −22.5 to +8.7) (supplementary figure S1 and supplementary table S2). The posterior probabilities of ARD <0 (TCZ or SARI better than UC) were 42.9% and 77.7% and of ARD <−5.5% were 22% and 57.5%, respectively.

At day 14, the cumulative incidence of successful tracheal extubation or removal of NIV or HFO (for a duration >48 h) had occurred in 23 (16 intubated and seven NIV/HFO) or in 18 (11 intubated and seven NIV/HFO) patients treated with TCZ or SARI, respectively (cumulative incidence of events of 47% (95% CI 32–60%) or 38% (95% CI 24–51%) and in 18 (12 intubated and six NIV/HFO) and 11 (six intubated and five 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 0.71–2.04) and 1.05 (90% CrI 0.55–2.07)), respectively (supplementary table S3). Similar results were observed without adjustment for age and centre (supplementary table S4 and supplementary figure S2). The proportions of patients with occurrence of the primary event (extubation or removal of NIV or HFO >48 h 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

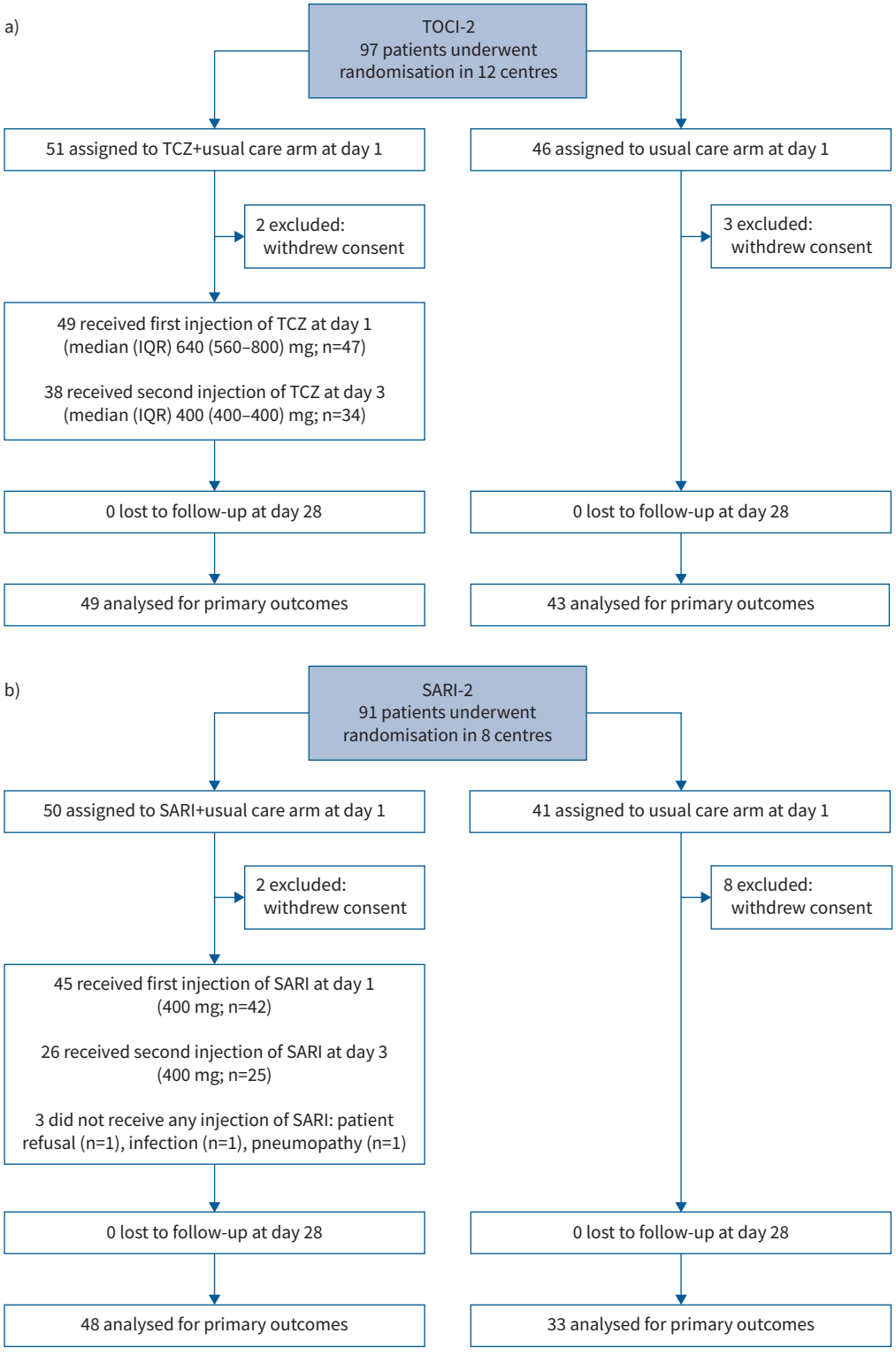


FIGURE 1 Flowchart. a) TOCI-2 protocol (treatment with tocilizumab (TCZ)+usual care *versus* usual care). b) SARI-2 protocol (treatment with sarilumab (SARI)+usual care *versus* usual care). IQR: interquartile range.

both protocols (supplementary table S5 (TOCI-2) and supplementary table S6 (SARI-2)). Additionally, we performed additional *post hoc* subgroup analyses according to WHO-CPS score and time from ICU admission to randomisation (⩽1 *versus* >1 day) and CRP levels (<150 or >150 mg·mL^{-1}) (supplementary tables S5 and S6).

TABLE 1 Characteristics at randomisation

	TOCI-2 trial		SARI-2 trial	
	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	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·m^{-2})	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·m^{-2}	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	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^{-1})	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)
S_{pO2} (%)	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)
P_{aO2}/F_{IO2} ratio	128 (100–175) (n=45)	138 (101–187) (n=35)	132 (106–204) (n=41)	102 (86–155) (n=31)
Time from symptoms onset to randomisation (days)	11 (9–15) (n=47)	11 (9–14) (n=42)	11 (9–15)	11 (8–21) (n=31)
Time from ICU admission to randomisation (days)[#]	1 (1–2) (n=42)	2 (0–4) (n=38)	3 (1–4) (n=38)	3 (1–4) (n=28)
Coexisting conditions				
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 1–3) 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	6/44 (14)	5/41 (12)	1/44 (2)	5/29 (17)
Laboratory values				
CRP (mg·L^{-1})	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^{-1})	2280 (1475–3912) (n=44)	2041 (1000–3420) (n=34)	1426 (1065–2528) (n=36)	1683 (1169–3245) (n=21)
Neutrophil count (×10^9 L^{-1})	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 (×10^9 L^{-1})	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)
Lymphocyte/neutrophil 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)
Haemoglobin (g·dL^{-1})	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^{-1})	273 (203–352)	255 (191–341) (n=41)	243 (181–277) (n=47)	253 (182–311)
Creatinine (µmol·L^{-1})	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)

Data are presented as median (interquartile range) or n/N (%). BMI: body mass index; WHO-CPS: World Health Organization Clinical Progression Scale; S_{pO_2}: peripheral oxygen saturation; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; ICU: intensive care unit; CRP: C-reactive protein; [#]: only computed for patients in the ICU at randomisation.

Secondary outcomes

The evolution of WHO-CPS scores during 14-day follow-up are given supplementary figure S3 and supplementary table S7. Although some trends were observed, no significant difference was observed in both the TOCI-2 and SARI-2 protocols in day 28 ventilator-free days (supplementary table S8), oxygen supply independency (59% *versus* 49% and 44% *versus* 36%) (supplementary table S9) cumulative incidence of discharge (59% *versus* 49% and 44% *versus* 36%) (supplementary table S10) or time to ICU discharge (72% *versus* 60% or 60% *versus* 71%) (supplementary table S11).

Overall, with a median (range) follow-up of 95 (59–217) and 91 (36–210) days, at day 90, 12 (24%) and 14 (29%) patients had died in the TCZ and SARI groups *versus* 13 (30%) and 13 (39%) in their respective UC control groups (adjusted HR 0.67 (95% CI 0.30–1.49) and 0.74 (95% CI 0.35–1.58)) (figure 2c and d, and supplementary table S12). Causes of deaths were similar in all groups, mainly due to acute respiratory distress syndrome, and are summarised in table 3.

The *post hoc* pooled analyses of both anti-IL-6R antibodies and UC are shown for the day 14 primary outcome (supplementary figure S5a) and day 90 overall survival (supplementary figure S5b).

TABLE 2 Primary and secondary outcomes

Outcome	TOCI-2 trial			SARI-2 trial		
	Tocilizumab (n=49)	Usual care (n=43)	Treatment effect	Sarilumab (n=48)	Usual care (n=33)	Treatment effect
Primary outcomes						
No improvement in WHO-CPS score at day 4 (n (%))	35 (71)	30 (70)	1.7% (−13.6–17.1%)[¶]	34 (71)	26 (79)	−7.3% (−22.5–8.7%)[¶]
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[#] >48 h at day 14 (%)	47 (32–60)	42 (27–56)	HR 1.19 (0.71–2.04)[+]	38 (24–51)	33 (18–50)	HR 1.05 (0.55–2.07)[+]
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	90 (82–99)	79 (68–92)	HR 0.37 (0.12–1.15)	75 (64–88)	73 (59–90)	HR 0.95 (0.40–2.25)
Estimate at day 28	84 (74–95)	77 (65–90)	HR 0.56 (0.22–1.46)	71 (59–85)	67 (52–85)	HR 0.89 (0.40–1.96)
Estimate at day 90	76 (64–89)	70 (57–85)	HR 0.67 (0.30–1.49)	71 (59–85)	61 (46–80)	HR 0.74 (0.35–1.58)
WHO-CPS score (0–10)						
Median (IQR) at day 4	7 (7–8)	8 (7–8)	OR 0.85 (0.39–1.82)[§]	7 (7–8)	8 (7–8)	OR 0.88 (0.38–2.02)[§]
Median (IQR) at day 7	7 (5–8)	8 (7–8)	OR 0.69 (0.32–1.47)[§]	8 (7–8)	8 (7–8)	OR 1.07 (0.47–2.40)[§]
Median (IQR) at day 14	7 (5–8)	7 (5–9)	OR 0.68 (0.32–1.43)[§]	7 (5–10)	7 (5–10)	OR 1.13 (0.50–2.57)[§]
Day 2 to day 14 longitudinal analysis			OR 0.76 (0.27–2.13)[f]			OR 0.72 (0.21–2.41)[f]
Day 28 ventilator-free days (mean±SD)	12.8±10.7	10.3±11.1	MD −2.5 (−6.9–1.7)	10.3±11.1	8.7±11.0	MD −1.5 (−6.1–3.9)
Patients with WHO-CPS ⩾7 (mean±SD)	9.8±9.5	7.2±9.4	MD −2.5 (−6.6–2.7)	7.5±9.5	4.6±7.6	MD −2.9 (−7.4–1.7)
Oxygen supply independency (%)						
Estimate at day 28	59 (44–72)	49 (33–63)	HR 1.44 (0.82–2.52)	44 (29–57)	36 (20–53)	HR 1.20 (0.59–2.44)
Estimate at day 90	69 (53–80)	64 (47–77)	HR 1.28 (0.80–2.03)	71 (52–83)	56 (35–72)	HR 1.29 (0.74–2.25)
Discharge (%)						
Estimate at day 28	55 (40–68)	42 (27–56)	HR 1.45 (0.80–2.63)	35 (22–49)	30 (16–46)	HR 1.21 (0.55–2.66)
Estimate at day 90	70 (54–82)	60 (44–74)	HR 1.35 (0.84–2.17)	65 (48–77)	52 (33–68)	HR 1.30 (0.71–2.37)
ICU discharge (%)[++]						
Estimate at day 28	72 (55–84)	60 (42–74)	HR 1.28 (0.73–2.24)	60 (43–74)	71 (50–85)	HR 0.78 (0.42–1.44)
Estimate at day 90	84 (66–93)	83 (63–93)	HR 1.15 (0.73–1.81)	79 (61–89)	82 (57–93)	HR 0.84 (0.49–1.47)

Data are presented with 95% confidence intervals, unless otherwise stated; all treatment effects are estimates adjusted on age and centre. WHO-CPS: World Health Organization Clinical Progression Scale; NIV: noninvasive ventilation; IQR: interquartile range: ICU: intensive care unit; HR: hazard ratio; OR: odds ratio; MD: mean difference. [#]: NIV or high-flow oxygen; [¶]: median posterior absolute risk difference with 90% credible intervals; [+]: median posterior HR adjusted for age and centre; [§]: median posterior OR adjusted for age and centre; [f]: median posterior OR in a proportional odds model, adjusted for baseline WHO-CPS score, age and centre; [++]: only for patients in the ICU at randomisation (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).

Biological response

Mean CRP levels decreased rapidly in the TCZ and SARI arms, and lymphocyte count was increased (supplementary figure S4) mainly in the TCZ arm but not in the SARI arm.

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 randomisation and day 90, respectively (table 3). Serious adverse events occurred in 20 (32%) and 29 (43%), respectively (p=0.21) (supplementary table S13). The number of bacterial and fungal serious infections was higher in the TCZ and SARI groups than in the UC groups (27 *versus* 13 or 19 *versus* 4).

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 HFO, NIV or MV, for decreasing the

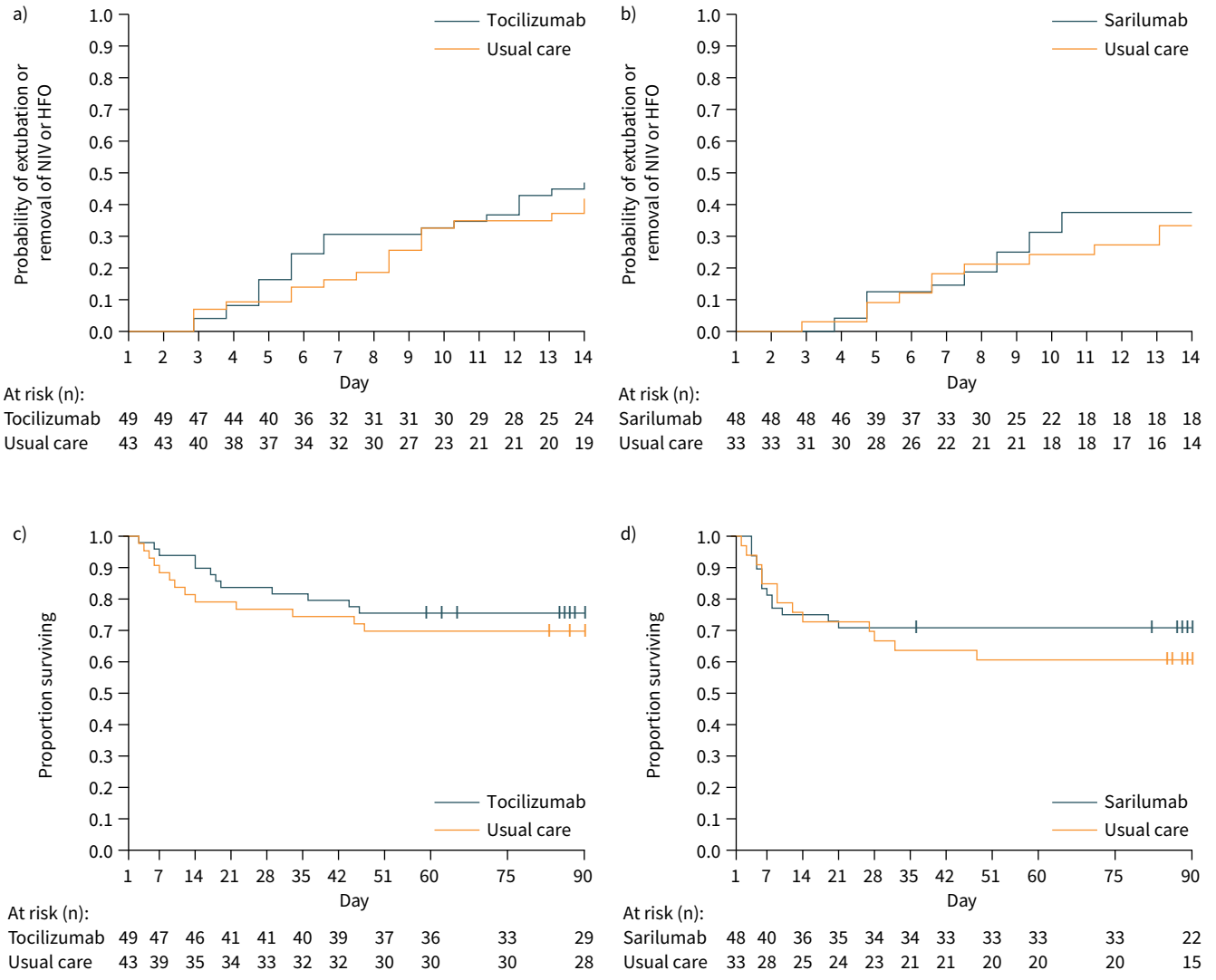


FIGURE 2 Occurrence of events during follow-up. Kaplan–Meier cumulative estimates of probability of the primary outcome (removal of device (mechanical ventilation, high-flow oxygen (HFO) or noninvasive ventilation (NIV) support)) and death up to day 14 for a) TOCI-2 (treatment with tocilizumab) and b) SARI-2 (treatment with sarilumab); and overall survival for c) TOCI-2 (tocilizumab arm compared with usual care arm) and d) SARI-2 (sarilumab arm compared with usual care arm).

proportion of patients alive with removal of intubation, NIV or HFO (for >48 h) at day 14. However, a slight numerical (but not statistically significant) increase of survival up to day 90 was found with both anti-IL-6R antibodies (76% and 71% *versus* 70% and 61% with UC; HR 0.67 (95% CI 0.30–1.49) and 0.74 (95% CI 0.35–1.58), respectively (pooled analysis HR 0.71, 95% CI 0.61–1.23)). TCZ and SARI did not induce any significant increase in serious adverse events but there was a numerical increase of serious infections.

In patients in the ICU requiring HFO, NIV or MV (WHO-CPS score ⩾6), the only standard of care was DXM [6], which in the RECOVERY trial has been shown to increase day 28 overall survival, particularly in patients treated shortly after admission to the ICU. The time of IL-6R antagonism introduction seems to be important, as also suggested by a large emulated multicentre trial involving 433 patients which found that in spite of an increased risk of secondary infections, the risk of in-hospital mortality was lower in patients treated with TCZ in the first 2 days of ICU admission compared with patients whose treatment did

TABLE 3 Adverse events (AEs), serious AEs (SAEs) and causes of death

	TOCI-2 trial		SARI-2 trial	
	Tocilizumab (n=49)	Usual care (n=43)	Sarilumab (n=48)	Usual care (n=33)
AEs				
Patients with at least one AE	33 (67)[#]	30 (70)	32 (68)[f]	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
SAEs				
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 ischaemic events	3	2	1	1
Haemorrhagic events	5	2	2	2
Renal failure	4	4	4	4
Hepatic toxicity	12	5	5	3
Anaemia	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)
Cause 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
Haemorrhagic stroke	1	2	1	0
Pulmonary embolism	2	0	1	0
Heart failure	0	0	1	0

Data are presented as n or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome. [#]: p=0.83 *versus* usual care (Fisher's exact test); [¶]: p=0.55 *versus* usual care (Poisson model); [+]: p=1.00 *versus* usual care (Fisher's exact test); [§]: p=0.28 *versus* usual care (Poisson model); [f]: p=1.00 *versus* usual care (Fisher's exact test); [##]: p=0.27 *versus* usual care (Poisson model); [¶¶]: p=0.64 *versus* usual care (Fisher's exact test); [++]: p=0.44 *versus* usual care (Poisson model).

not include early use of TCZ [17]. TCZ and SARI, two anti-IL-6Rs registered for the treatment of rheumatoid arthritis and cytokine 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 noncritically ill patients requiring oxygen (WHO-CPS score 5), several studies suggest that TCZ reduces mortality at day 28 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 the 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 OR 1.64, 95% CI 1.25–2.14) or SARI (median OR 1.76, 95% CI 1.17–2.91) arms, which was associated with better overall survival, and this beneficial effect was observed for all secondary analyses that included WHO-CPS improvement at day 14 and time to discharge [20]. In the RECOVERY trial, TCZ improved overall survival in patients requiring oxygen support. However, although a trend in favour of TCZ was observed for patients on MV, it did not reach significance (HR 0.93, 95% CI 0.74–1.18) [21]. Interestingly in these two studies, most of the patients received corticosteroids, particularly DXM (>80%), and the effects of TCZ and SARI seem to provide additional benefit to DXM. Additionally, the higher effect observed in the REMAP-CAP study might likely be due to the fact that patients were enrolled and treated within 24 h after starting MV. More recently, in the prospective meta-analysis of the WHO (that included REMAP-CAP and

RECOVERY), on 10 390 hospitalised patients for pneumonia, randomised in 27 trials, confirming the results of the REMAP-CAP and RECOVERY studies, IL-6 antagonist treatment decreased mortality at day 28 (OR 0.86, 95% CI 0.79–0.95; p=0.003) and these results were even better in the group of patients receiving corticosteroids (OR 0.77 (95% CI 0.68–0.87) for TCZ and 0.92 (95% CI 0.61–1.38) for SARI) [18]. Furthermore, in a subgroup analysis, among 1171 patients (recruited in nine trials) who were receiving MV at randomisation, the weighted mean difference comparing IL-6 antagonists with UC or placebo in the duration of MV was −0.84 (95% CI −1.82 to 0.13), favouring IL-6 antagonists (95% of patients receiving TCZ in this analysis). Taken together, the benefit from DXM and possibly of anti-IL-6R 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 the hyperinflammatory response or balancing the damage repairment, or both.

In the TOCI-2 and SARI-2 protocols, DXM was very barely used, and a majority of patients (84 out of 146 (56%)) were included and treated after day 1 of ICU admission, which might be too late, with pulmonary lesions being already established.

Even if the primary end-point was not reached, it is interesting and somewhat surprising to observe a nonsignificant trend in day 90 better overall survival with both anti-IL-6R antibodies. This might be due to a slight decrease of ventilator-free days until day 28 with TCZ and SARI *versus* UC (mean difference −2.5 (95% CI −6.9–1.7) and −1.5 (95% CI −6.1–3.9) days, respectively). Interestingly, the difference in overall survival up to 90 days in our two trials between UC and UC+anti-IL-6R antibodies is not far from that observed in the REMAP-CAP study. Indeed, in REMAP-CAP, the HRs of survival up to day 90 corresponded to 0.63 (95% CrI 0.49–0.81) for TCZ and 0.55 (95% CrI 0.30–0.82) for SARI, which were not far from the HRs of death up to day 90 in our study: 0.67 (95% CI 0.30–1.49) for TCZ and 0.74 (95% CI 0.35–1.58) for SARI.

Regarding safety, the main difference between these two trials in ICU patients and the previous trials of anti-IL-6R antibodies in patients on oxygen in medical wards is a numerical increase of serious infections in the SARI and TCZ arms (n=46) *versus* UC (n=17). This increased risk of serious infections (which was only statistically significant with TCZ) with anti-IL-6R antibodies is easily explained by the higher fragility of these patients in the 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-IL-6R antibodies in critically ill patients [18] with COVID-19 may be a compromise between reducing deleterious pulmonary hyperinflammation 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 pandemic. However, it is unlikely that unblinding could lead to measurement bias in this group of critically ill patients since the decision for extubation was based on objective parameters related to arterial oxygen tension/inspiratory oxygen fraction (P_{aO_2}/F_{IO_2}) ratio. Another limitation is that UC could differ among centres and over time. However, the short period of accrual and the stratification of randomisation may have limited the impact of such a lack of standardisation. Because of the design of the CORIMUNO-19 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]. Our study was also not designed to compare the respective effects of TCZ and SARI that showed similar effects here.

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 with COVID-19. However, the recent WHO meta-analysis results [18] are consistent with our results on mortality at day 90, suggesting that anti-IL-6R antibodies plus DXM could be an option in patients with critical COVID-19.

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This study was registered at ClinicalTrials.gov with identifier numbers NCT04331808 and NCT04324073. Authors will share data upon approval by the Steering Committee of the CORIMUNO-19 platform. Individual de-identified participant data, study protocols and the statistical analysis plan (SAP) will be shared for any purpose upon approval. Data will be available after publication for 15 years.

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Conflict of interest: P-L. Tharaux has received honoraria for participation on advisory boards for Travere therapeutics. All other author disclose no potential conflicts of interest related to this work.

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