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Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

IMPORTANCE Clinical trials assessing the efficacy of IL-6 antagonists in patients hospitalized for COVID-19 have variously reported benefit, no effect, and harm.

OBJECTIVE To estimate the association between administration of IL-6 antagonists compared with usual care or placebo and 28-day all-cause mortality and other outcomes.

DATA SOURCES Trials were identified through systematic searches of electronic databases between October 2020 and January 2021. Searches were not restricted by trial status or language. Additional trials were identified through contact with experts.

STUDY SELECTION Eligible trials randomly assigned patients hospitalized for COVID-19 to a group in whom IL-6 antagonists were administered and to a group in whom neither IL-6 antagonists nor any other immunomodulators except corticosteroids were administered. Among 72 potentially eligible trials, 27 (37.5%) met study selection criteria.

DATA EXTRACTION AND SYNTHESIS In this prospective meta-analysis, risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool. Inconsistency among trial results was assessed using the I^2 statistic. The primary analysis was an inverse variance–weighted fixed-effects meta-analysis of odds ratios (ORs) for 28-day all-cause mortality.

MAIN OUTCOMES AND MEASURES The primary outcome measure was all-cause mortality at 28 days after randomization. There were 9 secondary outcomes including progression to invasive mechanical ventilation or death and risk of secondary infection by 28 days.

RESULTS A total of 10 930 patients (median age, 61 years [range of medians, 52-68 years]; 3560 [33%] were women) participating in 27 trials were included. By 28 days, there were 1407 deaths among 6449 patients randomized to IL-6 antagonists and 1158 deaths among 4481 patients randomized to usual care or placebo (summary OR, 0.86 [95% CI, 0.79-0.95]; $P = .003$ based on a fixed-effects meta-analysis). This corresponds to an absolute mortality risk of 22% for IL-6 antagonists compared with an assumed mortality risk of 25% for usual care or placebo. The corresponding summary ORs were 0.83 (95% CI, 0.74-0.92; $P < .001$) for tocilizumab and 1.08 (95% CI, 0.86-1.36; $P = .52$) for sarilumab. The summary ORs for the association with mortality compared with usual care or placebo in those receiving corticosteroids were 0.77 (95% CI, 0.68-0.87) for tocilizumab and 0.92 (95% CI, 0.61-1.38) for sarilumab. The ORs for the association with progression to invasive mechanical ventilation or death, compared with usual care or placebo, were 0.77 (95% CI, 0.70-0.85) for all IL-6 antagonists, 0.74 (95% CI, 0.66-0.82) for tocilizumab, and 1.00 (95% CI, 0.74-1.34) for sarilumab. Secondary infections by 28 days occurred in 21.9% of patients treated with IL-6 antagonists vs 17.6% of patients treated with usual care or placebo (OR accounting for trial sample sizes, 0.99; 95% CI, 0.85-1.16).

CONCLUSIONS AND RELEVANCE In this prospective meta-analysis of clinical trials of patients hospitalized for COVID-19, administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

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Supplemental content

Group Information: The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group authors and collaborators are listed at the end of this article.

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Excessive systemic inflammation and raised IL-6 levels resulting from dysregulated host immune responses[1-3] are associated with adverse clinical outcomes in patients hospitalized with COVID-19.[4] This led to the design of several randomized clinical trials assessing the efficacy of IL-6 antagonists in patients with COVID-19. The IL-6 antagonists commonly investigated were monoclonal antibodies that bind either to membrane-bound and soluble IL-6 receptors (eg, tocilizumab and sarilumab) or directly to IL-6 (eg, siltuximab).[5]

To address the need for reliable efficacy data to guide clinical management, the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group developed a prospective meta-analysis protocol to perform a prospective meta-analysis of IL-6 antagonists in patients hospitalized for COVID-19. This approach was recently used[6] to evaluate the use of corticosteroids in patients with COVID-19.[7] During this initiative, trials variously reported potential clinical benefit,[8-10] no benefit,[11-13] and potential harm[14] with IL-6 antagonists in patients hospitalized for COVID-19.

The primary objective of this prospective meta-analysis of randomized trials[6] was to estimate the association between administration of IL-6 antagonists, compared with usual care or placebo, and mortality at 28 days after randomization in patients hospitalized for COVID-19. The secondary objectives were to estimate associations within subgroups relating to disease severity (eg, level of respiratory support), treatments at randomization (eg, receipt of corticosteroids), patient characteristics (eg, age), and risk of bias[15] overall and separately for tocilizumab and sarilumab.

Key Points

Question Is administration of IL-6 antagonists associated with 28-day all-cause mortality in patients hospitalized for COVID-19?

Findings This prospective meta-analysis of 27 randomized trials included 10 930 patients, of whom 2565 died by 28 days. The 28-day all-cause mortality was lower among patients who received IL-6 antagonists compared with those who received usual care or placebo (summary odds ratio, 0.86). The summary odds ratios for the association of IL-6 antagonist treatment with 28-day all-cause mortality were 0.78 with concomitant administration of corticosteroids vs 1.09 without administration of corticosteroids.

Meaning Administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in patients hospitalized for COVID-19.

Methods

Identification and Eligibility of Trials

Trials were identified through systematic searches of ClinicalTrials.gov, the EU Clinical Trials Register, and the WHO International Clinical Trials Registry Platform from October 7, 2020, to January 11, 2021. The search terms used were *random** AND *COVID* in the title or abstract, along with terms for common IL-6 antagonists individually (*tocilizumab*, *sarilumab*, *clazakizumab*, *siltuximab*, *olokizumab*) and the term *interleukin 6*. Individual searches were then combined. Searches were not restricted by trial status (ongoing or completed), publication status, or language. Additional trials were identified through contact with experts from the REACT Working Group. Queries regarding eligibility for inclusion were resolved by consensus. Eligible trials randomly assigned patients hospitalized for COVID-19 to IL-6 antagonists vs usual care or placebo. Trials in which anti-IL-6 therapies were combined with other immunomodulatory agents or with active comparators other than systemic corticosteroids were excluded.

Development of Prospective Meta-analysis Protocol

The WHO chief scientist invited investigators of eligible trials to participate in this prospective meta-analysis. Representative investigators and sponsors of potentially eligible trials were asked to participate in weekly development calls for the prospective meta-analysis protocol starting on November 23, 2020. The prospective meta-analysis protocol was registered on the PROSPERO database on January 14, 2021, and regularly updated. The PICO (patient problem or population, intervention, comparison or control, and outcome) framework, definitions of outcomes, and subgroups of interest were agreed upon prior to collection of outcome data.[6] The final version of the prospective meta-analysis protocol was registered before analyses started on March 29, 2021.

Trial-level aggregate data sharing agreements were established. All trials had secured institutional review board approval, but approval was not required for secondary analyses. Informed consent for participation in each trial was obtained, consistent with local institutional review board requirements. Trial investigators were asked to complete baseline and outcome data collection forms that were subsequently verified by trial teams. Finalized data sets from contributing trials were received by May 11, 2021.

Outcomes and Comparisons

The primary outcome measure was all-cause mortality at 28 days after randomization. Two comparisons were specified a priori. The primary comparison investigated the class effect of IL-6 antagonists vs usual care or placebo and tocilizumab and sarilumab were examined separately. The second comparison was of IL-6 antagonists vs corticosteroids.

The secondary outcomes included: (1) invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), or death by 28 days in patients not receiving IMV at randomization (this is the most important secondary outcome for which data on all subgroups were collected); (2) cardiovascular system support (defined as receipt of vasopressors) or death by 28 days in patients not receiving cardiovascular system support at randomization; (3) secondary infections by 28 days (this is the most important safety outcome); (4) in-hospital mortality; (5) kidney replacement therapy (KRT) or death by 28 days in patients not receiving KRT at randomization (excluding patients with underlying dialysis dependence or ≥stage III chronic kidney disease); (6) discharged alive from the hospital by 28 days; (7) mortality by 90 days; (8) duration of IMV up to 28 days (in those receiving IMV at randomization, with duration coded as 28

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days for patients who died); and (9) secondary infections by 90 days. Data on serious adverse events or serious adverse reactions (as defined in each trial) were collected; however, no meta-analysis was planned because diverse definitions were used by different trials.

Subgroup Analyses

Trial investigators supplied summary data for all outcomes according to intervention group, overall, and in subgroups based on: (1) degree of respiratory support at randomization (patient not receiving supplemental oxygen therapy, patient receiving supplemental oxygen therapy [defined as oxygen flow rate ≤15 L/min by face mask or nasal cannula], patient receiving noninvasive ventilation [defined as oxygen flow rate >15 L/min, high-flow nasal cannula, continuous positive airway pressure], or patient receiving IMV or ECMO) and (2) receipt of systemic corticosteroids at randomization. In addition, the following subgroups were used for the outcomes of 28-day all-cause mortality and progression to IMV or death: (1) patients receiving acute organ support therapy at randomization (vasopressors or KRT) among those receiving noninvasive ventilation, IMV, or ECMO; (2) age (<70 years or ≥70 years); (3) sex (female or male); (4) race/ethnicity (collected by investigators in each individual trial); and (5) C-reactive protein level at baseline (categorized as <75, 75-<150, ≥150 µg/mL). The assigned dose of IL-6 antagonists was classified as low (4 mg/kg of tocilizumab; 200 mg of sarilumab) or high (>4 mg/kg of tocilizumab or multiple doses; >400 mg of sarilumab or multiple doses).

Risk of Bias Assessment

For each trial, the risk of bias (low risk, some concerns, or high risk) was assessed using version 2 of the Cochrane Risk of Bias Assessment Tool.[15] Risk of bias assessments were based on the trial protocols and flowcharts following the Consolidated Standards of Reporting Trials together with information supplied by the investigators for each trial in a standard format. Risk of bias assessments were done independently by 3 of the investigators (J.P.T.H., F.S., J.S.) with disagreements resolved through discussion. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence.

Data Analyses

The primary analysis was an inverse variance-weighted fixed-effects meta-analysis of odds ratios (ORs). For the duration of IMV therapy, investigators supplied the mean difference and associated 95% CIs in days comparing the treatment and control groups. For the 90-day outcomes, the trial investigators were asked to estimate hazard ratios and 95% CIs (or log hazard ratios and associated standard errors) using Cox regression. Inconsistency in associations among the trials was quantified using the I^2 statistic. *P* values for heterogeneity were derived using the Cochran Q statistic. Precise *P* values were reported; however, the prospective meta-analysis protocol specified that a threshold for statistical significance would not be used. As a sensitivity analysis for the primary outcome of 28-day all-cause mortality, overall associations also were estimated using random-effects meta-analyses with a restricted maximum likelihood estimate of heterogeneity[16] and Hartung-Knapp adjustment[17,18] to account for uncertainty in the estimation of between-study variance. To obtain illustrative absolute risk estimates for patients not receiving treatment with IL-6 antagonists, a mortality risk of 25% and a progression risk of 33% to IMV or death were assumed (the approximate risks among all eligible patients allocated to usual care or placebo). Meta-analytic ORs were then applied to obtain the corresponding risk with IL-6 antagonists. Because outcome data were generally complete or nearly complete across trials, we restricted the analyses to trial participants with outcomes recorded.

Differences in associations between the subgroups were quantified by calculating ratios of ORs (or analogous statistics for other outcome types) to compare the effects in the subgroups along with corresponding *P* values for interaction. If the ratio of ORs was equal to 1, the estimated associations in the 2 subgroups were the same. The further the ratio of ORs was from 1, the greater was the difference between the estimated associations in the 2 subgroups. Comparisons between subgroups defined by trial characteristics were made using random-effects meta-regression and appropriately accounted for common controls[19] in trials with 3 treatment groups. Comparisons between subgroups defined by patient characteristics were done by estimating trial-specific ratios of ORs comparing associations between subgroups and then combining these in meta-analyses.[20] The ORs in patients not receiving corticosteroids were compared with patients receiving corticosteroids at randomization within the respiratory support subgroups. Subgroup-specific estimates adjusted to correspond with the ratios of ORs that were derived from the within-trial approach were also estimated.

In the sensitivity analyses, associations were estimated that (1) excluded the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial; (2) restricted the analyses to trial results at low risk of bias; (3) restricted the analyses to trials published in peer-reviewed journals; (4) restricted the analyses to placebo-controlled trials; and (5) restricted the analyses to open-label trials. The first and third of these were post hoc sensitivity analyses. All analyses were conducted using Stata version 16 (StataCorp) and new Stata commands to conduct and graph the results of the meta-analyses.[21,22]

Results

A total of 72 potentially eligible trials were identified. After screening these trials, 38 ineligible trials, 3 duplicated records, and 2 trials directly comparing IL-6 antagonists with corticosteroids (NCT04329650 [n = 158 patients] and NCT04345445 [n = 59 patients]) were excluded. Of 29 eligible trials that randomized patients to receive IL-6 antagonists vs usual care or placebo, 1 trial (n = 50 patients) was unable to supply data in a timely manner and 1 trial (n = 295 patients) was still following up patients for the primary outcome.

Among the 27 trials included in the meta-analyses, 9 were published[8-14,23,24] and the remaining 18 were unpublished or

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were reported as preprints (NCT04412772, NCT04331808 [there were 2 separate trials conducted under a common protocol], NCT04330638, NCT04479358, NCT04577534, NCT04435717, NCT04377750, NCT04409262, EU-CTR 2020-001748-24, EU-CTR 2020-001375-32, EU-CTR 2020-001442-19, NCT04324073 [there were 2 separate trials conducted under a common protocol], NCT04315298, NCT04357808, EU-CTR 2020-001531-27, and EU-CTR 2020-002037-15; **Table 1** and eTables 1-3 in Supplement 1). Outcome data were supplied for 10 930 patients, representing 95.4% of all patients randomized in eligible trials (eFigure 1 in Supplement 1). Patients were recruited from 28 countries from February 26, 2020.

The IL-6 antagonists assessed were tocilizumab (19 trials allocating 4299 patients to tocilizumab and 3749 patients to usual care or placebo), sarilumab (9 trials allocating 2073 patients to sarilumab and 753 patients to usual care or placebo), and siltuximab (1 trial allocating 77 patients to siltuximab and 72 patients to usual care or placebo). The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia[8] (REMAP-CAP) and COV-AID (NCT04330638) trials randomized patients to more than 1 IL-6 antagonist. Due to limited data (including outcome events), associations for siltuximab within predefined subgroups were not estimated. Similarly, due to limited data, associations were not estimated in the predefined low-dose strata (2 trials for tocilizumab [27 patients] and in 2 trials for sarilumab [307 patients]), in the no oxygen respiratory support subgroup (27 patients and 4 deaths in 3 trials), and for trials reporting secondary infections at 90 days. Because of the diversity of classification of race/ethnicity among different trials, the subgroup analyses according to race/ethnicity are not reported. Because not all trials estimated hazard ratios for 90-day mortality, the event numbers were also analyzed to estimate the ORs.

The median age across the trials was 61 years (range of medians, 52-68 years) and 3560 patients (33%) were women. Concurrent treatments at randomization varied substantially among the trials. Most patients received respiratory support at randomization. A greater proportion of patients in the sarilumab trials received IMV (31% [873/3136 patients]) compared with patients in the tocilizumab trials (15% [1211/8134 patients]) and a smaller proportion received corticosteroids (35% [890/3136 patients] vs 66% [5317/8134 patients], respectively; Table 1). The primary outcome was missing for 183 patients (1.6%). Three trials recorded no deaths by 28 days (COVID-19: Salvage Tocilizumab as a Rescue Measure [COVID-STORM {NCT04577534}; n = 39]; Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 [COVITOZ-01 {NCT04435717}; n = 26]; and Clinical Trial of the Use of Tocilizumab for Treatment of SARS-CoV-2 Infection [COVID-19; TOCOVID] {NCT04332094} [n = 270]).

Risk of bias was assessed to be low in 22 of the trials contributing to the meta-analysis of 28-day all-cause mortality, comprising 78% of the weight in the analysis. Six trials were judged to have some concerns, mainly due to small numbers of patients being excluded from the data set because they did not receive their assigned intervention. In 1 trial judged as high risk, comprising 0.65% of the weight, the usual procedures were not in place to ensure that the allocation sequence was concealed; however, there was no reason to suspect that the concealed allocation was not implemented as intended. Risk of bias assessments were similar for progression to IMV or death. For secondary infections, results from open-label trials were judged to have some concerns over bias in determining whether such infections had occurred due to the subjective nature of the decision (eFigure 2 and eTable 4 in Supplement 1).

Association Between IL-6 Antagonists and 28-Day All-Cause Mortality

By 28 days after randomization, there were 1407 deaths among 6449 patients randomized to IL-6 antagonists and 1158 deaths among 4481 patients randomized to usual care or placebo. Using a fixed-effects meta-analysis, the summary OR was 0.86 (95% CI, 0.79-0.95; P = .003). This corresponds to an absolute mortality risk of 22% for IL-6 antagonists compared with an assumed mortality risk of 25% for usual care or placebo. The summary OR was 0.89 (95% CI, 0.76-1.05; P = .16) in a sensitivity analysis using random-effects meta-analysis (eFigure 3 in Supplement 1). The certainty in this result was assessed to be high in the GRADE assessment.

In 19 trials that randomized 4299 patients to tocilizumab (960 deaths) and 3749 patients to usual care or placebo (1023 deaths), the summary OR was 0.83 (95% CI, 0.74-0.92; P < .001). This corresponds to an absolute mortality risk of 22% for tocilizumab compared with an assumed mortality risk of 25% for usual care or placebo. In 9 trials that randomized 2073 patients to sarilumab (473 deaths) and 753 patients to usual care or placebo (139 deaths), the summary OR was 1.08 (95% CI, 0.86-1.36; P = .52). This corresponds to an absolute mortality risk of 26% for sarilumab compared with an assumed mortality risk of 25% for usual care or placebo. There was little inconsistency between the trial results (I^2 = 18% overall, I^2 = 3% for tocilizumab, and I^2 = 0% for sarilumab). The inverse association with 28-day all-cause mortality appeared more marked for tocilizumab than for sarilumab (ratio of ORs, 0.76 [95% CI, 0.59-0.98], P = .04 for interaction; **Figure 1** and **Table 2**).

Data on receipt of corticosteroids at randomization were available in 22 trials (9953 patients and 2495 deaths). The summary ORs for 28-day all-cause mortality comparing IL-6 antagonists with usual care or placebo were 1.09 (95% CI, 0.91-1.30) for 3637 patients (830 deaths) not receiving corticosteroids and 0.78 (95% CI, 0.69-0.88) for 6316 patients (1665 deaths) receiving corticosteroids (**Figure 2**). The corresponding absolute mortality risk in patients receiving corticosteroids was 21% for IL-6 antagonists compared with an assumed mortality risk of 25% for usual care or placebo. Based on within-trial estimates combined across 17 trials that included patients receiving and not receiving corticosteroids, the inverse association between IL-6 antagonists and mortality was more marked in patients receiving corticosteroids (ratio of ORs, 0.72 [95% CI, 0.56-0.92]; P = .008 for interaction). The summary OR for the association with mortality for tocilizumab (15 trials, 7490 patients, and 1951 deaths) was 1.06 (95% CI, 0.85-1.33) in patients not receiving corticosteroids at randomization and was 0.77 (95% CI, 0.68-0.87) in patients receiving corticosteroids at randomization. The summary

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Table 1. Selected Characteristics of Included Trials

Trial[a]	Trial registration No.	Treatment group[b]	No. of patients	Age, median (IQR), y	Concomitant therapy at randomization, No. (%)								
					Oxygen flow rate ≤15 L/min[c]	Noninvasive ventilation	Invasive mechanical ventilation	Vasoactive medication[d]	KRT	Remdesivir	Corticosteroids[e]	Convalescent plasma	Anticoagulant drugs[f]
Sarilumab													
CORIMUNO-SARI (1)	NCT04324073	Anti-IL-6	68	61.7 (53.0-71.1)	68 (100)	0	0	0	0	0	3 (4)	0	41 (60)
		Usual care	76	62.8 (56.0-71.7)	76 (100)	0	0	0	0	0	4 (5)	0	38 (50)
CORIMUNO-SARI (ICU)	NCT04324073	Anti-IL-6	48	61.9 (53.8-66.2)	0	16 (33)	32 (67)	0	0	0	0	0	26 (54)
		Usual care	33	61.2 (55.3-68.5)	0	9 (27)	24 (73)	0	0	0	2 (2)	0	17 (52)
Regeneron P2	NCT04315298	Anti-IL-6 (400 mg)	180	56.5 (45.0-68.0)	42 (23)	45 (25)	93 (52)	53 (29)	14 (8)	0	28 (16)	0	0
		Anti-IL-6 (200 mg)	187	60 (47.0-67.0)	40 (21)	41 (22)	104 (56)	58 (31)	11 (6)	0	34 (18)	0	0
		Placebo + usual care	90	60 (52.0-69.0)	28 (31)	23 (26)	39 (43)	28 (31)	3 (3)	0	14 (16)	0	0
Regeneron P3	NCT04315298	Anti-IL-6 (400 mg)	567	63.0 (53.0-72.0)	138 (24)	206 (36)	220 (39)	99 (17)	25 (4)	0	194 (34)	0	0
		Anti-IL-6 (200 mg)	477	60.0 (50.0-69.0)	137 (29)	144 (30)	193 (40)	94 (20)	28 (6)	0	151 (32)	0	0
		Placebo + usual care	286	61.0 (50.0-71.0)	78 (27)	103 (36)	104 (36)	47 (16)	8 (3)	0	99 (35)	0	0
REMAP-CAP	NCT02735707	Anti-IL-6	48	64.5 (53-72.5)	0	40 (83)	8 (17)	4 (8)	0	15 (31)	44 (92)	0	0
		Usual care[g]	65	65 (53-71)	0	57 (88)	8 (12)	1 (2)	0	29 (46)	52 (83)	0	0
Sanofi	NCT04327388	Anti-IL-6 (400 mg)	173	58.0 (48.0-67.0)	137 (79)	11 (6)	23 (13)	6 (4)	0	0	42 (24)	0	0
		Anti-IL-6 (200 mg)	159	58.0 (51.0-67.0)	123 (77)	14 (11)	16 (10)	5 (3)	2 (1)	0	25 (16)	0	0
		Placebo + usual care	84	60 (53.0-69.5)	70 (83)	5 (6)	9 (11)	1 (1)	0	0	16 (19)	0	0
SARCOVID	NCT04357808	Anti-IL-6	20	61.5 (50.5-72)	12 (60)	4 (20)	0	0	0	0	17 (85)	0	19 (95)
		Control	10	62 (58-71)	10 (100)	0	0	0	0	0	8 (80)	0	10 (100)
SARICOR	NCT04357860	Anti-IL-6 (400 mg)	39	57 (49-67)	39 (100)	0	0	0	0	7 (18)	36 (92)	0	39 (100)
		Anti-IL-6 (200 mg)	37	66 (54-73)	37 (100)	0	0	0	0	3 (8)	32 (86)	0	37 (100)
		Usual care	39	57 (51-71)	39 (100)	0	0	0	0	4 (10)	39 (100)	0	39 (100)
SARTRE	EU-CTR 2020-002037-15	Anti-IL-6	70	58.8 (52-65)	70 (100)	0	0	0	0	1 (1)	70 (100)	0	0
		Usual care	70	58.0 (52-64)	70 (100)	0	0	0	0	1 (1)	70 (100)	0	0
Total			**2826**	57-66[h]	**1214** (43)	**718** (25)	**873** (31)	**396** (14.0)	**91** (3)	**60** (2)	**980** (35)	0	**266** (9)
Siltuximab													
COV-AID (B)	NCT04330638	Anti-IL-6	77	65.3 (54.3-71.4)	41 (53)	29 (38)	5 (7)	2 (3)	0	2 (3)	46 (60)	0	68 (88)
		Usual care[i]	72	63.3 (56.1-72.8)	39 (54)	23 (32)	9 (13)	4 (6)	0	3 (4)	42 (58)	0	60 (83)
Total			**149**	64	**80** (54)	**52** (35)	**14** (9)	**6** (4)	0	**5** (3)	**88** (59)	0	**128** (86)

(continued)

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Table 1. Selected Characteristics of Included Trials (continued)

Trial[a]	Trial registration No.	Treatment group[b]	No. of patients	Age, median (IQR), y	Concomitant therapy at randomization, No. (%)								
					Oxygen flow rate ≤15 L/min[c]	Noninvasive ventilation	Invasive mechanical ventilation	Vasoactive medication[d]	KRT	Remdesivir	Corticosteroids[e]	Convalescent plasma	Anticoagulant drugs[f]
Tocilizumab													
ARCHITECTS	NCT04412772	Anti-IL-6	10	61.0 (46-67)	0	0	10 (100)	5 (50)	2 (20)	8 (80)	9 (90)	10 (100)	7 (70)
		Placebo + usual care	11	62.0 (54-71)	1 (9)	0	10 (91)	7 (64)	1 (9)	11 (100)	11 (100)	11 (100)	3 (37)
BACC Bay	NCT04356937	Anti-IL-6	161	61.6 (46.4-69.7)	133 (83)	5 (3)	0	2 (1)	0	34 (21)	3 (2)	0	0
		Placebo + usual care	82	56.5 (44.7-67.8)	61 (74)	5 (6)	1 (1)	1 (1)	0	15 (18)	1 (1)	0	0
CORIMUNO-TOCI (1)	NCT04331808	Anti-IL-6	63	64.0 (57.1-74.3)	63 (100)	0	0	0	0	0	10 (16)	0	35 (56)
		Usual care	67	63.3 (57.1-72.3)	67 (100)	0	0	0	0	0	12 (18)	0	33 (49)
CORIMUNO-TOCI (ICU)	NCT04331808	Anti-IL-6	49	63.2 (59.4-70.9)	0	13 (27)	36 (73)	0	0	0	8 (16)	0	17 (35)
		Usual care	43	65.4 (57.6-70.5)	0	12 (28)	31 (72)	0	0	0	4 (9)	0	14 (33)
COVACTA	NCT04320615	Anti-IL-6	294	63.0 (52.0-71.0)	78 (27)	94 (32)	113 (38)	77 (26)	0	19 (6)	36 (12)	3 (1)	0
		Placebo + usual care	144	61.5 (53.8-70.0)	44 (31)	39 (27)	55 (38)	38 (26)	0	4 (3)	33 (23)	1 (1)	0
COV-AID (A)	NCT04330638	Anti-IL-6	81	62.4 (53.3-74.8)	39 (48)	32 (40)	8 (10)	5 (6)	1 (1)	6 (7)	48 (59)	0	73 (90)
		Usual care[i]	72	63.3 (56.1-72.8)	39 (54)	23 (32)	9 (13)	4 (6)	0	3 (4)	42 (58)	0	60 (83)
COVIDOSE-2 (substudy A)	NCT04479358	Anti-IL-6 (120 mg)	10	65.0 (53-69)	6 (60)	0	0	0	1 (10)	8 (80)	3 (30)	0	1 (10)
		Anti-IL-6 (40 mg)	10	65.0 (54-68)	5 (50)	1 (10)	0	0	0	7 (70)	3 (30)	0	4 (40)
		Usual care	8	65.0 (55-68)	4 (50)	1 (13)	0	0	0	5 (63)	2 (25)	0	2 (25)
COVIDSTORM	NCT04577534	Anti-IL-6	26	64.5 (15)	15 (58)	6 (23)	0	0	0	0	17 (65)	0	5 (19)
		Usual care	13	68.0 (17)	7 (54)	4 (31)	0	1 (8)	0	0	13 (100)	0	2 (15)
COVINTOC	EU-CTR 2020/05/025369	Anti-IL-6	91	56.0 (47-63)	48 (53)	28 (31)	5 (6)	12 (13)	0	14 (15)	24 (26)	0	87 (96)
		Usual care	89	54.0 (43-63)	56 (63)	20 (23)	4 (5)	12 (13)	0	13 (15)	8 (9)	0	86 (97)
COVITOZ-01	NCT04435717	Anti-IL-6 (2 doses)	7	56.0 (42-67)	5 (57)	0	0	0	0	2 (29)	4 (57)	0	5 (71)
		Anti-IL-6 (1 dose)	10	58.0 (53-64)	6 (60)	0	0	0	0	3 (30)	6 (60)	0	9 (90)
		Usual care	9	58.0 (47-62)	6 (67)	0	0	0	0	4 (44)	7 (78)	0	7 (78)
EMPACTA	NCT04372186	Anti-IL-6	249	57.0 (46-66)	161 (64)	64 (26)	0	2 (1)	3 (1)	114 (46)	174 (70)	5 (2)	228 (91)
		Placebo + usual care	128	56.0 (45-65)	81 (64)	36 (28)	0	4 (3)	3 (2)	62 (49)	87 (69)	1 (1)	120 (95)
HMO-0224-20	NCT04377750	Anti-IL-6	37	61.8	0	16 (43)	21 (57)	27 (73)	4 (11)	9 (24)	31 (84)	0	37 (100)
		Placebo + usual care	17	65.8	0	5 (29)	12 (71)	12 (71)	5 (29)	3 (18)	15 (88)	0	17 (100)
IMMCOVA	EU-CTR 2020-001748-24	Anti-IL-6	22	64.0 (56-70)	10 (46)	12 (55)	0	1 (5)	0	3 (14)	21 (96)	0	22 (100)
		Usual care	27	62.0 (53-68)	9 (33)	18 (67)	0	5 (19)	0	4 (15)	26 (96)	0	27 (100)

(continued)

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Table 1. Selected Characteristics of Included Trials (continued)

Trial[a]	Trial registration No.	Treatment group[b]	No. of patients	Age, median (IQR), y	Concomitant therapy at randomization, No. (%)								
					Oxygen flow rate ≤15 L/min[c]	Noninvasive ventilation	Invasive mechanical ventilation	Vasoactive medication[d]	KRT	Remdesivir	Corticosteroids[e]	Convalescent plasma	Anticoagulant drugs[f]
PRETOVID	EU-CTR 020-001375-32	Anti-IL-6	174	67 (60-74)	125 (72)	38 (22)	2 (1)	8 (5)	0	36 (21)	151 (87)	0	0
		Usual care	180	66 (56-75)	128 (71)	43 (24)	1 (<1)	11 (6)	0	29 (16)	162 (90)	0	0
RECOVERY	NCT04381936	Anti-IL-6	2022	63.5 (54.2-73.6)	931 (46)	819 (41)	268 (13)	0	28 (1)	544 (27)	1664 (82)	425 (21)	1178 (58)
		Usual care	2094	64.3 (55.0-73.9)	928 (44)	867 (41)	294 (14)	0	29 (1)	573 (27)	1721 (82)	485 (23)	1244 (59)
REMAP-CAP	NCT02735707	Anti-IL-6	353	61.0 (54-71)	1 (<1)	248 (70)	104 (30)	63 (18)	0	72 (20)	214 (61)	0	0
		Usual care[g]	358	61.0 (53-70)	2 (1)	237 (66)	119 (33)	79 (22)	2 (1)	72 (21)	217 (63)	0	0
REMDACTA	NCT04409262	Anti-IL-6	430	61.0	29 (7)	336 (78)	65 (15)	0	0	83 (24)	367 (85)	0	0
		Placebo + usual care	210	59.0	13 (6)	175 (83)	22 (11)	0	0	40 (19)	184 (88)	0	0
TOCIBRAS	NCT04403685	Anti-IL-6	65	54.6 (44.2-70.2)	39 (60)	15 (23)	11 (17)	9 (14)	0	0	45 (69)	0	53 (82)
		Usual care	64	57.9 (46.9-69.4)	28 (44)	26 (41)	10 (16)	7 (11)	0	0	47 (73)	0	54 (84)
TOCOVID	NCT04332094	Anti-IL-6	136	52.0 (44.0-60.5)	74 (54)	0	0	0	0	0	46 (34)	0	123 (90)
		Usual care	134	54.0 (42.0-60.0)	81 (60)	0	0	0	0	1 (1)	45 (34)	0	127 (95)
Total			**8050**[j]	52-68[h]	**3223** (40)	**3238** (40)	**1211** (15)	**382** (5)	**79** (1)	**1693** (21)	**5317** (66)	**941** (12)	**3860** (46)
Anti-IL-6 vs corticosteroids[k]													
STORM	NCT04345445	Tocilizumab	29	53.3 (14.84)	65 (81)	0	0	0	0	25 (31)	5 (6)	8 (10)	0
		Corticosteroids	30	53.1 (20.97)	62 (79)	0	0	0	0	26 (33)	4 (5)	11 (14)	0
SILCOR	NCT04329650	Siltuximab	80	61.33 (23.52)	17 (59)	1 (3)	0	0	0	0	0	0	0
		Corticosteroids	78	62.70 (21.2)	24 (80)	4 (13)	0	0	1 (3)	0	1 (3)	0	0

Abbreviations: IQR, interquartile range; KRT, kidney replacement therapy.

[a] Additional trial characteristics appear in eTable 1 and eTable 2 in Supplement 1.

[b] Control indicates use of placebo in blinded trials and usual care alone in open-label trials.

[c] By face mask or nasal cannula.

[d] Norepinephrine or epinephrine.

[e] Dexamethasone, methylprednisolone, prednisolone, or hydrocortisone.

[f] Heparin or low-molecular-weight heparin.

[g] There were 21 patients in the usual care group for both treatment comparisons.

[h] Expressed as range of medians.

[i] Common control group across the COV-AID trial.

[j] Baseline data but not outcome data supplied for 1 patient in the COVIDOSE substudy A and for 1 patient in the COVINTOC trial.

[k] These trials were not included in the meta-analysis.

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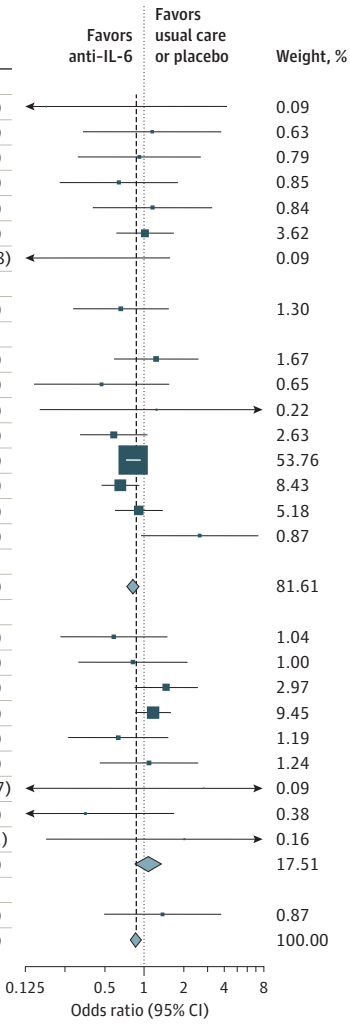
Figure 1. Association Between IL-6 Antagonists vs Usual Care or Placebo and Primary Outcome of 28-Day All-Cause Mortality

Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	2/11	0/10	0.18 (0.01-4.27)	0.09
BACC-Bay	4/82	9/161	1.15 (0.34-3.87)	0.63
CORIMUNO-TOCI-1	8/67	7/63	0.92 (0.31-2.71)	0.79
CORIMUNO-TOCI-ICU	10/43	8/49	0.64 (0.23-1.82)	0.85
COV-AID[a]	7/72	9/81	1.16 (0.41-3.29)	0.84
COVACTA	28/144	58/294	1.02 (0.62-1.68)	3.62
COVIDOSE2-SS-A	2/8	0/19	0.07 (<0.01-1.58)	0.09
COVIDSTORM	0/13	0/26	NA[b]	
COVINTOC	15/88	11/91	0.67 (0.29-1.55)	1.30
COVITOZ	0/9	0/17	NA[b]	
EMPACTA	11/128	26/249	1.24 (0.59-2.60)	1.67
HMO-020-0224	8/17	11/37	0.48 (0.15-1.56)	0.65
ImmCoVA	2/27	2/22	1.25 (0.16-9.67)	0.22
PreToVid[c]	34/180	21/174	0.59 (0.33-1.06)	2.63
RECOVERY	729/2094	621/2022	0.83 (0.73-0.95)	53.76
REMAP-CAP[d]	116/358	85/353	0.66 (0.48-0.92)	8.43
REMDACTA	41/210	78/430	0.91 (0.60-1.39)	5.18
TOCIBRAS	6/64	14/65	2.65 (0.95-7.42)	0.87
TOCOVID	0/134	0/136	NA[b]	
Subgroup I^2 = 3.3%	1023/3749	960/4299	0.83 (0.74-0.92)	81.61
Sarilumab				
CORIMUNO-SARI-1	14/76	8/68	0.59 (0.23-1.51)	1.04
CORIMUNO-SARI-ICU	11/33	14/48	0.82 (0.32-2.14)	1.00
REGENERON-P2	19/90	104/367	1.48 (0.85-2.57)	2.97
REGENERON-P3	64/286	264/1044	1.17 (0.86-1.60)	9.45
REMAP-CAP[d]	19/65	10/48	0.64 (0.26-1.53)	1.19
SANOFI	7/84	30/332	1.09 (0.46-2.58)	1.24
SARCOVID	0/10	2/20	2.84 (0.12-64.87)	0.09
SARICOR	4/39	3/76	0.36 (0.08-1.69)	0.38
SARTRE	1/70	2/70	2.03-0.18-22.91)	0.16
Subgroup I^2 = 0%	139/753	437/2073	1.08 (0.86-1.36)	17.51
Siltuximab				
COV-AID[a]	7/72	10/77	1.39 (0.50-3.86)	0.87
Overall I^2 = 18.2%	1158/4481	1407/6449	0.86 (0.79-0.95)	100.00



The area of the data marker for each trial is proportional to its weight in the fixed-effects meta-analysis.

[a] Common control group across both treatment comparisons of the COV-AID trial.

[b] NA indicates not available; there were insufficient data to estimate odds ratio.

[c] The data for the PreToVid trial are based on events up until 30 days after randomization.

[d] There were 21 patients in the control group for both treatment comparisons. The analyses have been adjusted to correct for this.

ratio of ORs (based on within-trial comparisons) was 0.69 (95% CI, 0.52-0.91; P = .008 for interaction). The corresponding summary ORs for sarilumab (8 trials, 2406 patients, and 538 deaths) were 1.18 (95% CI, 0.88-1.58) and 0.92 (95% CI, 0.61-1.38), respectively. The summary ratio of ORs (based on within-trial comparisons) was 0.77 (95% CI, 0.44-1.33; P = .34 for interaction). The corresponding absolute mortality risks in patients receiving corticosteroids were 20% for tocilizumab and 23% for sarilumab compared with an assumed mortality risk of 25% for usual care or placebo. In additional analyses, associations were compared in patients not receiving and receiving corticosteroids at randomization within the respiratory support subgroups. The tendency for more marked inverse associations among patients receiving corticosteroids appeared broadly consistent across respiratory support subgroups; however, the associations were not estimated precisely.

Detailed results, forest plots, and comparisons between subgroups for 28-day all-cause mortality appear in Supplements 1 and 2. Data on respiratory support at randomization were available in 21 trials (9835 patients and 2493 deaths). The summary ORs for 28-day all-cause mortality comparing IL-6 antagonists with usual care or placebo were 0.81 (95% CI, 0.67-0.98) in 3954 patients (560 deaths) receiving supplemental oxygen at randomization, 0.83 (95% CI, 0.72-0.96) in 3864 patients (1132 deaths) receiving noninvasive ventilation or high-flow nasal cannula at randomization, and 0.95 (95% CI, 0.78-1.16) in 2017 patients (801 deaths) receiving IMV or ECMO at randomization (P = .71 for the differences between associations across these subgroups; Table 2). The corresponding summary ORs for tocilizumab were 0.82 (95% CI, 0.67-1.00), 0.80 (95% CI, 0.68-0.93), and 0.92 (95% CI, 0.72-1.17), respectively (P = .43 for differences between subgroups) and the corresponding summary ORs for sarilumab were 0.74 (95% CI, 0.42-1.30), 1.20 (95% CI, 0.78-1.84), and 1.05 (95% CI, 0.74-1.50), respectively (P = .65 for differences between subgroups).

The associations between IL-6 antagonists and 28-day all-cause mortality within other subgroups defined by patient characteristics at randomization appeared consistent across all

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Table 2. Subgroup Analysis of 3 Outcomes by Treatment Group and Respiratory Support, Organ Support, Age, Sex, and C-Reactive Protein Level

	All anti-IL-6 agents				Tocilizumab				Sarilumab			
	No. of events/total patients				No. of events/total patients				No. of events/total patients			
Subgroup	Anti-IL-6	Control	I^2, %	OR (95% CI)	Anti-IL-6	Control	I^2, %	OR (95% CI)	Anti-IL-6	Control	I^2, %	OR (95% CI)
28-d mortality												
Respiratory support at randomization												
Oxygen flow rate ≤15 L/min	277/2246	283/1708	0	0.81 (0.67-0.98)	232/1622	256/1407	0	0.82 (0.67-1.00)	41/583	27/301	0	0.74 (0.42-1.30)
Noninvasive ventilation	588/2209	544/1655	8	0.83 (0.72-0.96)	463/1684	505/1479	0	0.80 (0.68-0.93)	119/496	40/191	0	1.20 (0.78-1.84)
IMV or ECMO	496/1289	305/728	0	0.95 (0.78-1.16)	250/634	244/559	6	0.92 (0.72-1.17)	246/650	64/174	20	1.05 (0.74-1.50)
Acute organ support at randomization												
No cardiovascular system support	123/616	135/501	14	0.68 (0.51-0.91)	106/536	120/457	10	0.70 (0.51-0.94)	11/48	18/64	0	0.66 (0.26-1.64)
Cardiovascular system support	70/196	59/153	17	0.89 (0.56-1.42)	69/190	59/153	14	0.93 (0.58-1.47)	1/4	1/1	0	0.14 (0.00-5.95)
Age group, y												
<70	674/4209	522/2931	0	0.89 (0.78-1.02)	446/2864	456/2457	0	0.86 (0.74-0.99)	225/1291	67/490	9	1.10 (0.80-1.52)
≥70	703/1727	629/1310	17	0.82 (0.70-0.95)	514/1254	567/1136	8	0.76 (0.64-0.89)	182/450	65/179	0	1.17 (0.80-1.71)
Sex												
Female	413/1933	311/1335	0	0.96(0.80-1.15)	294/1365	270/1134	0	0.96 (0.79-1.17)	117/553	43/209	0	0.95 (0.62-1.46)
Male	964/4003	840/2906	1	0.83 (0.74-0.93)	666/2753	753/2459	0	0.78 (0.69-0.88)	290/1188	89/460	0	1.17 (0.88-1.55)
C-reactive protein level, μg/mL[a]												
<75	83/710	57/429	0	0.84 (0.56-1.26)	36/344	36/260	0	0.80 (0.46-1.39)	46/354	21/171	0	0.89 (0.49-1.62)
75-<150	451/1957	467/1635	3	0.79 (0.67-0.92)	357/1484	435/1456	9	0.76 (0.65-0.90)	90/438	33/184	0	1.01 (0.62-1.64)
≥150	678/2366	490/1625	0	0.96 (0.83-1.11)	427/1507	429/1365	0	0.91 (0.77-1.07)	246/831	64/271	4	1.16 (0.83-1.62)
Progression to IMV, EMCO, or death by 28 d												
Respiratory support at randomization												
Oxygen flow rate ≤15 L/min	362/2266	396/1778	0	0.75 (0.64-0.89)	299/1724	359/1505	0	0.72 (0.60-0.86)	55/501	37/273	0	0.96 (0.60-1.53)
Noninvasive ventilation	856/2129	805/1636	14	0.77 (0.68-0.89)	694/1690	750/1483	0	0.74 (0.64-0.85)	145/410	60/168	0	1.06 (0.71-1.57)
Acute organ support at randomization												
No cardiovascular system support	207/524	202/424	26	0.72 (0.55-0.95)	173/451	183/382	2	0.70 (0.53-0.93)	NA[b]	NA[b]	NA[b]	NA[b]
Cardiovascular system support	12/16	8/15	0	1.58 (0.30-8.30)	12/16	8/15	0	1.58 (0.30-8.30)	NA[b]	NA[b]	NA[b]	NA[b]

(continued)

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Table 2. Subgroup Analysis of 3 Outcomes by Treatment Group and Respiratory Support, Organ Support, Age, Sex, and C-Reactive Protein Level (continued)

	All anti-IL-6 agents				Tocilizumab				Sarilumab			
	No. of events/total patients				No. of events/total patients				No. of events/total patients			
Subgroup	Anti-IL-6	Control	I^2, %	OR (95% CI)	Anti-IL-6	Control	I^2, %	OR (95% CI)	Anti-IL-6	Control	I^2, %	OR (95% CI)
Age group, y												
<70	649/3160	622/2387	0	0.78 (0.68-0.89)	523/2457	566/2079	0	0.76 (0.66-0.87)	110/654	60/320	0	0.87 (0.60-1.27)
≥70	577/1402	586/1137	0	0.75 (0.64-0.89)	477/1112	548/1017	0	0.70 (0.59-0.84)	91/267	39/123	0	1.20 (0.74-1.97)
Sex												
Female	362/1526	334/1149	14	0.81 (0.68-0.98)	300/1223	306/1014	14	0.80 (0.66-0.97)	57/289	31/141	2	0.83 (0.48-1.44)
Male	864/3036	874/2375	7	0.75 (0.67-0.85)	700/2346	808/2082	0	0.71 (0.63-0.81)	144/632	68/302	0	1.08 (0.76-1.55)
C-reactive protein level, µg/mL[a]												
<75	87/687	77/443	0	0.74 (0.51-1.09)	52/426	55/307	0	0.69 (0.43-1.12)	33/250	23/138	0	0.83 (0.43-1.59)
75-<150	453/1632	504/1450	0	0.76 (0.65-0.89)	389/1335	481/1325	0	0.73 (0.62-0.87)	54/265	23/129	0	1.14 (0.63-2.07)
≥150	519/1595	492/1248	0	0.78 (0.67-0.92)	407/1235	453/1109	0	0.74 (0.62-0.88)	100/333	43/147	34	1.03 (0.65-1.63)
Secondary infections to 28 d[c]												
Respiratory support at baseline												
Oxygen flow rate ≤15 L/min	100/1244	60/789	1	1.06 (0.75-1.52)	63/620	45/488	35	1.04 (0.68-1.60)	34/583	15/301	0	1.06 (0.56-2.02)
Noninvasive ventilation	260/1052	122/487	0	0.96 (0.74-1.24)	155/567	94/352	0	0.92 (0.67-1.26)	99/456	28/135	0	1.01 (0.63-1.63)
IMV or ECMO	380/913	139/318	22	0.86 (0.65-1.15)	134/266	76/151	23	0.76 (0.49-1.20)	244/642	63/167	53	0.94 (0.65-1.34)

Abbreviations: ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; OR, odds ratio.

[a] Normal level is less than 5 µg/mL.

[b] Insufficient data to investigate the comparison of subgroups within trials.

[c] Full results within extended subgroups were not collected for outcomes other than all-cause mortality and progression to IMV, ECMO, or death at 28 days.

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Figure 2. Subgroup Analysis of 3 Outcomes by Treatment Group and Corticosteroid Use

Outcome and treatment	I^2, %	No. of events/total patients		Odds ratio (95% CI)	Ratio of odds ratios (95% CI)	I^2, %	P value
		Control	Anti-IL-6				
28-d mortality							
All anti-IL-6							
No corticosteroid use	0	293/1280	537/2357	1.09 (0.91-1.30)	0.72 (0.56-0.92)	0	.008
Corticosteroid use	0	838/2848	827/3468	0.78 (0.69-0.88)			
Tocilizumab							
No corticosteroid use	0	211/898	254/1192	1.06 (0.85-1.33)	0.69 (0.52-0.91)	0	.008
Corticosteroid use	0	793/2585	693/2815	0.77 (0.68-0.87)			
Sarilumab							
No corticosteroid use	0	83/384	283/1134	1.18 (0.88-1.58)	0.77 (0.44-1.33)	0	.34
Corticosteroid use	0	48/281	124/607	0.92 (0.61-1.38)			
Progression to IMV, ECMO, or death at 28 d							
All anti-IL-6							
No corticosteroid use	0	308/1004	399/1541	0.96 (0.79-1.17)	0.78 (0.59-1.02)	0	.07
Corticosteroid use	0	893/2496	822/2986	0.71 (0.63-0.80)			
Tocilizumab							
No corticosteroid use	0	250/791	266/1016	0.95 (0.76-1.20)	0.70 (0.52-0.94)	0	.02
Corticosteroid use	0	859/2283	729/2518	0.69 (0.61-0. 78)			
Sarilumab							
No corticosteroid use	0	59/214	126/498	0.98 (0.67-1.44)	1.41 (0.65-3.07)	0	.38
Corticosteroid use	0	38/227	75/423	1.08 (0.67-1.75)			
28-d secondary infections[a]							
All anti-IL-6							
No corticosteroid use	3	165/758	434/1820	0.92 (0.74-1.15)	0.96 (0.63-1.46)	0	.85
Corticosteroid use	1	160/798	310/1378	1.04 (0.82-1.31)			
Tocilizumab							
No corticosteroid use	0	86/385	146/659	0.79 (0.57-1.10)	0.94 (0.51-1.71)	11	.83
Corticosteroid use	16	132/573	210/772	1.04 (0.80-1.36)			
Sarilumab							
No corticosteroid use	8	79/373	285/1130	1.03 (0. 77-1.38)	0.94 (0.52-1.72)	6	.85
Corticosteroid use	0	28/225	92/560	0.94 (0.58-1.52)			

For the outcome of progression to invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO), or death at 28 days, only patients not receiving IMV or ECMO at randomization were included in the analyses. All trials supplied data until 28 days after randomization, except for the PreToVid trial for which data are based on events up until 30 days after randomization. The ratios of odds ratios (ROR) compare the associations of anti–IL-6 agents with outcomes between patients receiving and not receiving corticosteroids within each trial. The displayed summary ROR for each comparison is based on a meta-analysis of trial-specific RORs. Only the trials that recruited patients receiving and not receiving corticosteroids at randomization contribute to these meta-analyses. The estimated RORs are not necessarily consistent with the ratios of the subgroup ORs (left panel), which were calculated from meta-analyses within subgroups defined by receipt or no receipt of corticosteroids at randomization.

[a] The odds ratios are based on raw percentages while the ratios of odds ratios account for pooling trials of different sizes.

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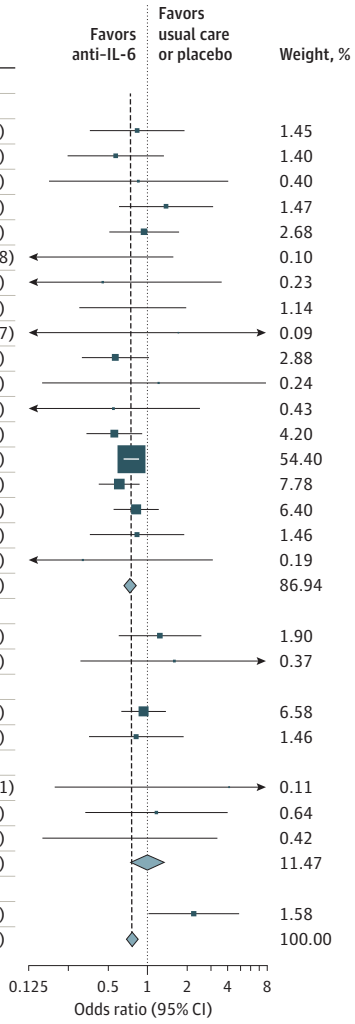
Figure 3. Association Between IL-6 Antagonists vs Usual Care or Placebo and Secondary Outcome of Progression to Invasive Mechanical Ventilation, Extracorporeal Membrane Oxygenation, or Death

Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	1/1	0/0	NA[a]	
BACC-Bay	10/81	17/161	0.84 (0.37-1.92)	1.45
CORIMUNO-TOCI-1	18/67	11/63	0.58 (0.25-1.34)	1.40
CORIMUNO-TOCI-ICU	6/12	6/13	0.86 (0.18-4.13)	0.40
COV-AID[b]	12/63	18/73	1.39 (0.61-3.17)	1.47
COVACTA	20/89	39/181	0.95 (0.51-1.75)	2.68
COVIDOSE2-SS-A	2/8	0/19	0.07 (<0.01-1.58)	0.10
COVIDSTORM	2/13	2/26	0.46 (0.06-3.69)	0.23
COVINTOC	11/84	9/86	0.78 (0.30-1.98)	1.14
COVITOZ	0/9	1/17	1.73 (0.06-46.77)	0.09
EMPACTA	24/128	29/249	0.57 (0.32-1.03)	2.88
HMO-020-0224	3/5	11/17	1.22 (0.16-9.47)	0.24
ImmCoVA	6/27	3/22	0.55 (0.12-2.52)	0.43
PreToVid[c]	56/179	35/172	0.56 (0.34-0.91)	4.20
RECOVERY	754/1800	619/1754	0.76 (0.66-0.87)	54.40
REMAP-CAP[d]	127/239	102/249	0.61 (0.43-0.88)	7.78
REMDACTA	54/188	91/365	0.82 (0.56-1.22)	6.40
TOCIBRAS	17/54	15/54	0.84 (0.37-1.91)	1.46
TOCOVID	3/134	1/136	0.32 (0.03-3.15)	0.19
Subgroup I^2 = 0%	1126/3181	1009/3657	0.74 (0.66-0.82)	86.94
Sarilumab				
CORIMUNO-SARI-1	20/76	21/68	1.25 (0.61-2.58)	1.90
CORIMUNO-SARI-ICU	4/9	9/16	1.61 (0.31-8.32)	0.37
REGENERON-P2			NA[a]	
REGENERON-P3	43/182	142/631	0.94 (0.64-1.39)	6.58
REMAP-CAP[d]	24/57	15/40	0.83 (0.36-1.89)	1.46
SANOFI			NA[a]	
SARCOVID	0/10	3/20	4.20 (0.20-89.61)	0.11
SARICOR	4/39	9/76	1.18 (0.34-4.09)	0.64
SARTRE	4/70	3/70	0.74 (0.16-3.43)	0.42
Subgroup I^2 = 0%	99/443	202/921	1.00 (0.75-1.35)	11.47
Siltuximab				
COV-AID[b]	12/63	25/72	2.26 (1.02-5.00)	1.58
Overall I^2 = 0%	1220/3609	1236/4650	0.77 (0.70-0.85)	100.00



The area of the data marker for each trial is proportional to its weight in the fixed-effects meta-analysis. Progression to requiring invasive mechanical ventilation or extracorporeal membrane oxygenation or death among patients not receiving invasive mechanical ventilation at randomization.

[a] NA indicates not available; there were insufficient data to estimate odds ratio or the trial did not supply data for this outcome.

[b] Common control group across both treatment comparisons of the COV-AID trial.

[c] The data for the PreToVid trial are based on events up until 30 days after randomization.

[d] There were 21 patients in the control group for both treatment comparisons. The analyses have been adjusted to correct for this.

these subgroups (all *P* values for comparisons between subgroups were greater than .11; Table 2 and Supplement 2).

Association Between IL-6 Antagonists and Progression to IMV or Death

Among patients not requiring IMV at randomization (24 trials), 1236 of 4650 randomized to IL-6 antagonists and 1220 of 3609 randomized to usual care or placebo progressed to requiring IMV or ECMO or died within 28 days. Most of the data (87%) were from trials assessing tocilizumab. The summary ORs compared with usual care or placebo were 0.77 (95% CI, 0.70-0.85; *P* < .001) for all IL-6 antagonists, 0.74 (95% CI, 0.66-0.82) for tocilizumab, and 1.00 (95% CI, 0.74-1.35) for sarilumab (**Figure 3**). The corresponding absolute risks of progression to IMV or death were 28% for all IL-6 antagonists, 27% for tocilizumab, and 33% for sarilumab compared with an assumed risk of 33% for usual care or placebo. There was little inconsistency between the trial results (I^2 = 0% for each meta-analysis). The certainty in the overall result was assessed to be high in the GRADE assessment. The ratio of ORs comparing the associations for tocilizumab and sarilumab was 0.74 (95% CI, 0.54-1.01; *P* = .06 for interaction).

The summary ORs for progression to IMV or death were 0.96 (95% CI, 0.79-1.17) in 2545 patients (707 progressed) not receiving corticosteroids and 0.71 (95% CI, 0.63-0.80) in 5482 patients (1715 progressed) receiving corticosteroids (Figure 2).

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The corresponding absolute risk for progression to IMV or death in patients receiving corticosteroids was 26% for IL-6 antagonists compared with an assumed risk of 33% for usual care or placebo. The ratio of ORs comparing the associations in those receiving and not receiving corticosteroids was 0.78 (95% CI, 0.59-1.02; P = .07 for interaction based on within-trial estimates combined across trials). The corresponding summary ORs for tocilizumab (17 trials, 6608 patients, and 2104 progressed) were 0.95 (95% CI, 0.76-1.20) and 0.69 (95% CI, 0.61-0.78), respectively, and the corresponding ratio of ORs was 0.70 (95% CI, 0.52-0.94; P = .02 for interaction). The corresponding summary ORs for sarilumab (7 trials, 1362 patients, and 298 progressed) were 0.98 (95% CI, 0.67-1.44) and 1.08 (95% CI, 0.67-1.75), respectively, and the corresponding ratio of ORs was 1.41 (95% CI, 0.65-3.07; P = .38 for interaction). The corresponding absolute risks for progression to IMV or death in patients receiving corticosteroids were 25% for tocilizumab and 35% for sarilumab compared with an assumed risk of 33% for progression to IMV or death for usual care or placebo.

The summary ORs for progression to IMV or death comparing IL-6 antagonists with usual care or placebo were 0.75 (95% CI, 0.64-0.89) in 4044 patients (758 progressed) receiving supplemental oxygen at randomization and 0.77 (95% CI, 0.68-0.89) in 3765 patients (1661 progressed) receiving noninvasive ventilation or high-flow nasal cannula (P = .67 for differences between these associations; Table 2). The corresponding summary ORs for tocilizumab were 0.72 (95% CI, 0.60-0.86) and 0.74 (95% CI, 0.64-0.85), respectively (P = .92 for differences between subgroups) and the corresponding summary ORs for sarilumab were 0.96 (95% CI, 0.60-1.53) and 1.06 (95% CI, 0.71-1.57), respectively (P = .31 for differences between subgroups). The corresponding absolute risks for progression to IMV or death were 27% for all IL-6 antagonists, 27% for tocilizumab, and 33% for sarilumab compared with an assumed risk for progression to IMV or death of 33% for usual care or placebo.

The associations between IL-6 antagonists and progression to IMV or death within other subgroups defined by patient characteristics at randomization appeared consistent across all other subgroups (all P values for comparisons between subgroups were greater than .28; Table 2 and Supplement 3).

Association Between IL-6 Antagonists and Infections by 28 Days

Among the 22 trials that reported 28-day infection outcomes, 750 events occurred among 3428 patients randomized to IL-6 antagonists and 330 events occurred among 1787 patients randomized to usual care or placebo. The fixed-effect summary OR was 0.99 (95% CI, 0.85-1.16) and there was little inconsistency between the trial results (I^2 = 0%, P = .49 for heterogeneity; Figure 3). The certainty in this result was assessed to be moderate in the GRADE assessment due to minor concerns over risk of bias (because of subjectivity in the outcome assessment) and minor concerns over imprecision (because of the result being compatible with a slightly lower or higher risk among those receiving IL-6 antagonists). The ORs were 0.95 (95% CI, 0.77-1.16) for tocilizumab and 1.03 (95% CI, 0.80-1.32) for sarilumab (**Figure 4** and Table 2). The summary ORs within subgroups were close to 1. Data on 28-day secondary infections appear in Supplement 4.

Association Between IL-6 Antagonists and Other Secondary Outcomes

Data on in-hospital mortality were available from 19 trials. The summary ORs for in-hospital mortality comparing IL-6 antagonists with usual care or placebo were 0.80 (95% CI, 0.71-0.89) in 7261 patients (1848 deaths), with little inconsistency between trials (I^2 = 0%) (**Table 3**). Most of the data (90.7%) were from 14 trials (6587 patients and 1741 deaths) assessing tocilizumab and the summary OR was 0.80 (95% CI, 0.71-0.90).

Among patients not requiring cardiovascular system support at randomization (15 trials), 344 of 1587 patients randomized to IL-6 antagonists and 343 of 1199 patients randomized to usual care or placebo progressed to requiring cardiovascular system support or death within 28 days. Most of the data (2553/2786 patients; 91.1%) were from 13 trials assessing tocilizumab. The summary ORs were 0.71 (95% CI, 0.59-0.86) for IL-6 antagonists and 0.70 (95% CI, 0.57-0.85) for tocilizumab. Among patients not requiring KRT at randomization (13 trials), 935 of 3653 patients randomized to IL-6 antagonists and 1069 of 3351 patients randomized to usual care progressed to requiring KRT or died within 28 days. The summary OR was 0.79 (95% CI, 0.71-0.88); most of the data (6884/7004 patients; 98.2%) were from 12 trials assessing tocilizumab.

Among 10 904 patients recruited to participate in 26 trials, 6609 were discharged alive by 28 days. The summary OR comparing IL-6 antagonists with usual care or placebo was 1.22 (95% CI, 1.12-1.33), favoring IL-6 antagonists. The corresponding ORs were 1.30 (95% CI, 1.18-1.43) for tocilizumab and 0.95 (95% CI, 0.79-1.15) for sarilumab.

Data were available for all-cause mortality at 90 days in 13 trials and at 60 days in 4 trials (1104 deaths among 4651 patients). Two trials reported no events. The summary OR comparing IL-6 antagonists with usual care or placebo was 0.89 (95% CI, 0.76-1.04). The corresponding ORs were 0.85 (95% CI, 0.69-1.05) for tocilizumab and 0.92 (95% CI, 0.74-1.16) for sarilumab. Additional survival analyses for all-cause mortality at 90 days are reported in eTable 5 in Supplement 1.

Among 1171 patients who were receiving IMV at randomization and were recruited to 9 trials, the weighted mean difference comparing IL-6 antagonists with usual care or placebo in the duration of IMV was −0.84 (95% CI, −1.82 to 0.13), favoring IL-6 antagonists. Most of the data were from 8 trials assessing tocilizumab (1101/1171 patients; 94.0%).

Table 3 and Supplements 5-10 provide detailed analyses comparing IL-6 antagonists with usual care or placebo overall and in predefined subgroups for all of the secondary outcomes. Although the associations appeared broadly consistent across subgroups, many were not estimated precisely.

Serious Adverse Events or Reactions

Data describing serious adverse events were supplied by 23 trials. Risks of serious adverse events were broadly similar for patients randomized to IL-6 antagonists and to usual care or placebo across all trials. Data on secondary infections at 90 days after randomization were limited (11 trials and 310 events)

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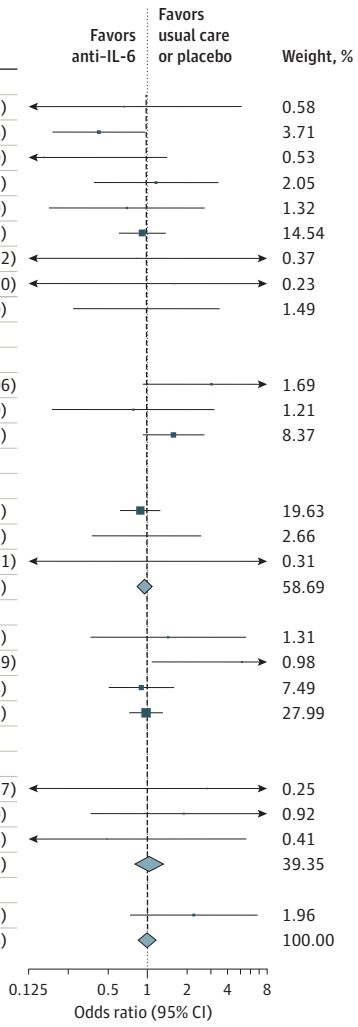
Figure 4. Association Between IL-6 Antagonists vs Usual Care or Placebo and Secondary Infections

Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	3/11	2/10	0.67 (0.09-5.13)	0.58
BACC-Bay	14/82	13/161	0.43 (0.19-0.96)	3.71
CORIMUNO-TOCI-1	6/67	1/63	0.16 (0.02-1.40)	0.53
CORIMUNO-TOCI-ICU	7/43	9/49	1.16 (0.39-3.43)	2.05
COV-AID[a]	5/72	4/81	0.70 (0.18-2.70)	1.32
COVACTA	58/143	113/295	0.91 (0.61-1.37)	14.54
COVIDOSE2-SS-A	1/8	2/19	0.82 (0.06-10.62)	0.37
COVIDSTORM	0/13	1/26	1.59 (0.06-41.70)	0.23
COVINTOC	5/89	5/91	0.98 (0.27-3.50)	1.49
COVITOZ			NA[b]	
EMPACTA			NA[b]	
HMO-020-0224	8/17	27/37	3.04 (0.92-10.06)	1.69
ImmCoVA	6/27	4/22	0.78 (0.19-3.20)	1.21
PreToVid[c]	28/180	39/174	1.57 (0.92-2.69)	8.37
RECOVERY			NA[b]	
REMAP-CAP			NA[b]	
REMDACTA	71/213	131/429	0.88 (0.62-1.25)	19.63
TOCIBRAS	10/64	10/65	0.98 (0.38-2.55)	2.66
TOCOVID	1/34	1/136	0.99 (0.06-15.91)	0.31
Subgroup I^2 = 1.2%	223/1163	362/1658	0.95 (0.77-1.16)	58.69
Sarilumab				
CORIMUNO-SARI-1	4/76	5/68	1.43 (0.37-5.55)	1.31
CORIMUNO-SARI-ICU	2/33	12/48	5.17 (1.07-24.89)	0.98
REGENERON-P2	19/90	71/367	0.90 (0.51-1.58)	7.49
REGENERON-P3	78/286	279/1044	0.97 (0.72-1.31)	27.99
REMAP-CAP			NA[b]	
SANOFI			NA[b]	
SARCOVID	0/10	2/20	2.84 (0.12-64.87)	0.25
SARICOR	2/39	7/76	1.88 (0.37-9.50)	0.92
SARTRE	2/70	1/70	0.49 (0.04-5.56)	0.41
Subgroup I^2 = 0%	107/604	377/1693	1.03 (0.80-1.32)	39.35
Siltuximab				
COV-AID[a]	5/72	11/77	2.23 (0.74-6.78)	1.96
Overall I^2 = 0%	330/1787	750/3428	0.99 (0.85-1.16)	100.00



The area of the data marker for each trial is proportional to its weight in the fixed-effects meta-analysis.

[a] Common control group across both treatment comparisons of the COV-AID trial.

[b] NA indicates not available; the trial did not supply data for this outcome.

[c] The data for the PreToVid trial are based on events up until 30 days after randomization.

(eTable 6 in Supplement 1), but the risk of secondary infections by 28 days was similar in patients treated with IL-6 antagonists (750/3428; 21.9%) and in those treated with usual care or placebo (330/1787; 17.6%) (OR accounting for trial sample sizes, 0.99 [95% CI, 0.85-1.16]).

Additional Analyses

The results of the prespecified and post hoc sensitivity analyses for the outcomes of 28-day all-cause mortality; progression to IMV, ECMO, or death by 28 days; and secondary infections by 28 days appear in eTable 7 in Supplement 1. After excluding the large RECOVERY trial, the ORs comparing tocilizumab with usual care or placebo were 0.82 (95% CI, 0.68-0.98) for 28-day all-cause mortality and 0.71 (95% CI, 0.59-0.84) for progression to IMV or death within 28 days (consistent with the primary analyses). The ORs for the trials at low risk of bias were similar to the overall ORs. The ORs restricted to trials published in peer-reviewed journals were consistent with the overall ORs for tocilizumab but were imprecisely estimated for sarilumab because of exclusion of the largest trial. The ORs were similar for open-label and placebo-controlled trials; however, the association of sarilumab compared with usual care for secondary infections appeared more marked in open-label trials (1.97 [95% CI, 0.89-4.34]) than in placebo-controlled trials (0.96 [95% CI, 0.74-1.24]). Supplement 1 includes summary details for all of the sensitivity analyses. Supplements 2-10 include details of prespecified sensitivity analyses by risk of bias and blinding status. Further additional analyses for all outcomes within patients receiving and not receiving corticosteroids at randomization appear in Supplement 11. The baseline and outcome data collection forms appear in Supplement 12. The prospective meta-analysis protocol appears in Supplement 13.

Discussion

In this prospective meta-analysis based on 10 930 patients hospitalized for COVID-19 from 27 randomized clinical trials, administration of IL-6 antagonists was associated with lower all-cause mortality 28 days after randomization. Administration

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Table 3. Additional Outcomes With Analysis by Respiratory Support and Corticosteroid Use

	All anti-IL-6 agents				Tocilizumab				Sarilumab			
	No. of events/total patients				No. of events/total patients				No. of events/total patients			
Outcome and patient group	Anti-IL-6	Control	I^2, %	OR (95% CI)	Anti-IL-6	Control	I^2, %	OR (95% CI)	Anti-IL-6	Control	I^2, %	OR (95% CI)
In-hospital mortality												
All patients	858/3727	990/3534	0	0.80 (0.71 to 0.89)	800/3323	941/3264	0	0.80 (0.71 to 0.90)	44/327	53/291	0	0.70 (0.44 to 1.12)
Respiratory support at randomization												
Oxygen flow rate ≤15 L/min	218/1636	262/1471	0	0.75 (0.62 to 0.92)	196/1369	241/1276	0	0.75 (0.61 to 0.93)	18/226	21/195	0	0.72 (0.36 to 1.44)
Noninvasive ventilation	409/1283	463/1280	2	0.83 (0.71 to 0.99)	387/1196	449/1232	0	0.83 (0.70 to 0.99)	14/58	15/63	0	0.98 (0.40 to 2.40)
IMV or ECMO	214/500	245/508	0	0.81 (0.63 to 1.04)	200/456	232/482	0	0.84 (0.65 to 1.10)	12/39	16/31	0	0.42 (0.16 to 1.15)
Corticosteroid use at randomization												
No	229/1005	226/870	20	0.94 (0.75 to 1.18)	199/844	193/751	22	1.02 (0.80 to 1.29)	28/130	34/121	0	0.67 (0.37 to 1.22)
Yes	613/2464	743/2414	0	0.75 (0.66 to 0.85)	585/2221	728/2264	0	0.74 (0.65 to 0.85)	16/197	18/168	0	0.81 (0.38 to 1.71)
Progression to cardiovascular system support or death[a]												
All patients	344/1587	343/1199	0	0.71 (0.59 to 0.86)	314/1447	316/1106	0	0.70 (0.57 to 0.85)	30/140	39/113	0	0.80 (0.42 to 1.52)
Respiratory support at randomization												
Oxygen flow rate ≤15 L/min	72/738	64/499	0	0.74 (0.51 to 1.07)	64/650	60/450	0	0.71 (0.48 to 1.05)	8/88	4/49	0	1.03 (0.31 to 3.44)
Noninvasive ventilation	192/519	209/438	8	0.65 (0.49 to 0.84)	173/475	189/397	9	0.63 (0.48 to 0.84)	19/44	30/56	0	0.64 (0.28 to 1.45)
IMV or ECMO	64/100	53/82	0	1.13 (0.57 to 2.26)	61/96	51/80	0	1.18 (0.59 to 2.39)	3/4	4/6	0	1.50 (0.09 to 25.39)
Corticosteroid use at randomization												
No	143/652	123/423	0	0.80 (0.57 to 1.11)	138/636	118/407	0	0.76 (0.54 to 1.07)	5/16	6/18	0	1.81 (0.31 to 10.44)
Yes	185/841	205/687	0	0.67 (0.52 to 0.86)	160/717	184/611	0	0.66 (0.50 to 0.86)	24/124	32/93	0	0.71 (0.35 to 1.43)
Progression to kidney replacement therapy or death[b]												
All patients	935/3653	1069/3351	14	0.79 (0.71 to 0.88)	920/3586	1051/3298	14	0.79 (0.71 to 0.88)	15/67	22/74	0	0.80 (0.36 to 1.76)
Respiratory support at randomization												
Oxygen flow rate ≤15 L/min	234/1489	263/1288	25	0.79 (0.65 to 0.97)	234/1477	263/1278	25	0.79 (0.65 to 0.97)	NA[c]	NA[c]	NA[c]	NA[c]
Noninvasive ventilation	439/1329	523/1298	29	0.76 (0.64 to 0.89)	428/1286	507/1258	23	0.77 (0.65 to 0.91)	NA[c]	NA[c]	NA[c]	NA[c]
IMV or ECMO	247/492	263/470	0	0.88 (0.68 to 1.15)	243/484	262/468	0	0.88 (0.68 to 1.15)	NA[c]	NA[c]	NA[c]	NA[c]
Corticosteroid use at randomization												
No	261/959	239/732	0	0.98 (0.78 to 1.22)	258/952	235/721	0	0.97 (0.78 to 1.22)	3/7	5/13	0	1.55 (0.22 to 10.83)
Yes	661/2425	890/2363	2	0.74 (0.66 to 0.84)	649/2365	796/2322	8	0.75 (0.66 to 0.85)	12/60	16/59	0	0.79 (0.33 to 1.89)

(continued)

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Table 3. Additional Outcomes With Analysis by Respiratory Support and Corticosteroid Use (continued)

Outcome and patient group	All anti-IL-6 agents				Tocilizumab				Sarilumab			
	No. of events/total patients		I^2, %	OR (95% CI)	No. of events/total patients		I^2, %	OR (95% CI)	No. of events/total patients		I^2, %	OR (95% CI)
	Anti-IL-6	Control			Anti-IL-6	Control			Anti-IL-6	Control		
Proportion discharged alive from the hospital at 28 d												
All patients	4017/6432	2592/4472	16	1.22 (1.12 to 1.33)	2736/4282	2127/3740	0	1.30 (1.18 to 1.43)	1227/2073	478/753	0	0.95 (0.78 to 1.15)
Respiratory support at randomization												
Oxygen flow rate ≤15 L/min	1923/2337	1371/1800	0	1.32 (1.12 to 1.55)	1390/1713	1113/1499	0	1.40 (1.18 to 1.66)	498/583	258/301	0	0.93 (0.60 to 1.43)
Noninvasive ventilation	1257/2215	820/1659	27	1.27 (1.11 to 1.45)	964/1690	726/1483	26	1.30 (1.13 to 1.51)	278/496	104/191	0	1.10 (0.77 to 1.56)
IMV or ECMO	351/1289	168/728	0	1.18 (0.94 to 1.48)	172/634	125/559	0	1.24 (0.94 to 1.63)	117/650	45/174	0	1.06 (0.72 to 1.57)
Corticosteroid use at randomization												
No	1438/2458	780/1368	21	1.10 (0.95 to 1.27)	832/1293	576/986	10	1.17 (0.97 to 1.42)	580/1134	205/384	31	0.96 (0.75 to 1.22)
Yes	2240/3534	1665/2911	0	1.31 (1.18 to 1.46)	1828/2881	1474/2646	0	1.36 (1.21 to 1.52)	384/607	202/283	0	0.97 (0.68 to 1.38)
90-d mortality (binary outcome)												
All patients	721/3039	383/1612	4	0.89 (0.76 to 1.04)	265/1367	231/1073	10	0.85 (0.69 to 1.05)	442/1595	156/560	0	0.92 (0.74 to 1.16)
Respiratory support												
Oxygen flow rate ≤15 L/min	88/874	43/461	0	1.17 (0.78 to 1.74)	38/388	23/277	0	1.20 (0.67 to 2.12)	45/445	20/184	35	1.05 (0.59 to 1.87)
Noninvasive ventilation	252/1003	154/553	22	0.81 (0.63 to 1.04)	110/478	102/377	32	0.77 (0.56 to 1.06)	135/496	53/191	0	0.90 (0.61 to 1.33)
IMV or ECMO	382/954	175/410	0	0.88 (0.69 to 1.13)	114/299	103/241	0	0.85 (0.59 to 1.22)	266/650	75/174	27	0.91 (0.65 to 1.29)
Corticosteroid use at randomization												
No	430/1744	188/783	0	0.97 (0.78 to 1.19)	118/582	93/413	2	0.86 (0.62 to 1.20)	310/1131	96/372	0	1.07 (0.81 to 1.41)
Yes	294/1138	185/665	0	0.84 (0.66 to 1.06)	144/620	135/505	0	0.84 (0.63 to 1.13)	138/472	53/178	0	0.81 (0.55 to 1.21)
Duration of IMV[d]												
All patients	610	561	0	−0.84 (−1.82 to 0.13)[e]	565	535	0	−0.76 (−1.76 to 0.24)[e]	40	32	0	−2.07 (−10.24 to 11.57)[e]
Corticosteroid use at randomization												
No	304	218	0	−1.12 (−2.61 to 0.38)[e]	266	195	0	−0.95 (−2.54 to 0.64)[e]	NA[c]	NA[c]	NA[c]	NA[c]
Yes	298	332	0	−0.26 (−1.57 to 1.04)[e]	291	330	0	−0.23 (−1.55 to 1.08)[e]	NA[c]	NA[c]	NA[c]	NA[c]

Abbreviations: ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; NA, not available; OR, odds ratio.

[a] Among patients who were not receiving cardiovascular system support at randomization.

[b] Among patients who were not receiving kidney replacement therapy at randomization.

[c] Insufficient data to investigate the comparison of subgroups within trials.

[d] Among patients who required IMV at randomization.

[e] Data are expressed as weighted mean difference (95% CI).

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of IL-6 antagonists also was associated with lower progression to IMV or death, cardiovascular support or death, and KRT or death in patients not receiving support for the corresponding organ at randomization and with a greater probability of being discharged alive by 28 days. Administration of IL-6 antagonists was not associated with an increased risk of 28-day infection compared with usual care or placebo. There was no clear association between administration of IL-6 antagonists and all-cause mortality at 90 days or in the duration of IMV among patients who required IMV at randomization; however, the data were limited.

Among the a priori–defined subgroups, the association of IL-6 antagonists with improved outcomes appeared more marked among patients who were receiving corticosteroids at randomization compared with those who were not. The association of IL-6 antagonists with lower 28-day all-cause mortality was more marked among patients who did not require IMV at randomization, consistent with the inverse association of progression to IMV or death among these patients. However, these differences between subgroups may have arisen due to sampling variation. Associations appeared broadly consistent across patient subgroups according to levels of cardiovascular support, C-reactive protein level, age, and sex.

In general, associations with improved outcomes were more marked for tocilizumab than for sarilumab, although comparisons between tocilizumab and sarilumab were indirect (made between trials). However, the trials of sarilumab were generally done earlier in the pandemic than those of tocilizumab and before corticosteroids became the standard of care.[7] The majority of patients in trials of sarilumab were not receiving corticosteroids at randomization, whereas the majority of patients in trials of tocilizumab were receiving corticosteroids at randomization. When comparisons were made within groups defined by receipt of corticosteroids at randomization, the differences between associations for these 2 IL-6 antagonists were less marked. Nearly 3 times as many patients were randomized to trials comparing tocilizumab with usual care or placebo compared with trials comparing sarilumab with usual care or placebo. For this reason, associations were estimated more precisely for tocilizumab than for sarilumab. Both drugs were IL-6 receptor antagonists, but there may be differences between tocilizumab and sarilumab in receptor binding or lung concentrations.[25] Concurrent administration of IL-6 antagonists[5] and corticosteroids,[26] which both have anti-inflammatory effects, may provide greater improvement than either type of drug given individually.[8,9]

This prospective meta-analysis included an estimated 97% of patients randomized to IL-6 receptor antagonists vs usual care worldwide. Because data were shared based on standardized definitions of outcomes and subgroups agreed upon in advance, these aggregate data meta-analyses had many of the advantages of individual-patient data meta-analyses while avoiding the need to establish formal data sharing agreements. The methods used in this meta-analysis limit bias in the selection and appraisal of trials with prespecified subgroup analyses based on clinically relevant questions. For tocilizumab, the results from other trials were similar to those from the large RECOVERY trial, supporting generalizability of the findings across settings.

Limitations

This study has several limitations. First, some of the included trials are ongoing and have not been published in peer-reviewed journals. It is possible that lack of participation or participation by some of the ongoing trials may be based on knowledge of their interim results. This limitation was addressed in the sensitivity analyses and the results were consistent with the primary analyses.

Second, there were limited data for some comparisons and questions of interest such as IL-6 antagonists vs corticosteroids and the effect of siltuximab. Third, potential differences in treatment effect by differences in the baseline risk of death (eg, that arose either from trial-specific eligibility criteria, geographic differences, or improving trends in the outcomes of patients with COVID-19 during the pandemic) could not be accounted for.

Fourth, the definitions and reporting of serious adverse events were not consistent across the trials and therefore a meta-analysis for this secondary end point was not conducted. Fifth, larger trials were mainly conducted in high-income settings; 65.9% of the tocilizumab data were provided by participants in the RECOVERY trial[9] and 71.0% of the sarilumab data were provided by participants in the Regeneron trial (NCT04315298).

Conclusions

In this prospective meta-analysis of clinical trials of patients hospitalized for COVID-19, administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

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