EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

TOCILIZUMAB FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V 9.0	**20/04/2021**	Ninth version
V 9.1	**07/05/2021**	Literature searches, Literature screening, Data extraction
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Major changes from previous version

Chapter, page no.	Major changes from version 9.0
Summary	Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab Table 4-8 Ongoing trials of single agent tocilizumab

Disclaimer

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
CRP	C-Reactive Protein
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
TCZ	Tocilizumab
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signalling. Tocilizumab is indicated (EMEA-approved) for the treatment of • rheumatoid arthritis in adults • giant cell arteritis in adults • active systemic juvenile idiopathic arthritis in patients aged ≥2 years • juvenile idiopathic polyarthritis in patients aged ≥2 years chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.

Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis.

The sources and search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signaling.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).
One researcher of NIPN extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25). For prospective single arm studies the Newcastle-Ottawa Scale (NOS) is used to assess the methodological rigor and applicability.

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of NIPN is searching and extracting the data for the eligible studies.. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Tocilizumab is a humanised IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signaling. IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells. Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin [4].

3.2 Regulatory Status

The Market Authorisation Holder of tocilizumab is Roche Pharma. Tocilizumab is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. Tocilizumab is indicated (EMA-approved) for the treatment of:

- rheumatoid arthritis in adults
- giant cell arteritis in adults
- active systemic juvenile idiopathic arthritis in patients aged ≥2 years
- juvenile idiopathic polyarthritis in patients aged ≥2 years
- chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients aged ≥2 years [5].

Tocilizumab is not authorised in Covid-19 patients (EMA, FDA).

3.3 Level of Evidence

Sixty-three hospitalized adult patients with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Patients received either TCZ IV (8 mg/kg) or SC (324 mg); (the optional second dose within 24 hours 52 of 63 patients), and all of the patients received off-label antiretroviral protease inhibitors. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO2/FiO2 ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison [6].

The phase III COVACTA (NCT04320615) study of tocilizumab did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge in patients treated with tocilizumab. The COVACTA study did not identify any new safety signals for tocilizumab.

The phase III REMDACTA (NCT04409262) has ended, and participants are no longer being treated. REMDACTA did not meet its primary (time from randomization to hospital discharge or "ready for discharge" up to day 28) and key secondary endpoints, which included likelihood of death, likelihood of progression to mechanical ventilation or death, and clinical status.The phase III EMPACTA

(NCT04372186) study has interim results available, and participants are receiving an intervention or are being examined, but potential participants are not currently being recruited or enrolled. The EMPACTA study showed that patients with COVID-19 associated pneumonia who received tocilizumab plus standard of care were less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]). The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the tocilizumab arm versus 19.3% in the placebo arm. The EMPACTA study did not identify any new safety signals for tocilizumab [28].

A phase III trial involving 243 patients who require hospital but not mechanical ventilation evaluates the effects of tocilizumab compared to placebo. Tocilizumab was not effective for preventing intubation or death, the hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64) (HR 0.83;95% confidence interval [CI], 0.38 to 1.81; P=0.64) [11]. The TOBICRAS phase III randomized clinical trial was terminated early, after 129 patients had been enrolled, because of an increased number of deaths at 15 days in the tocilizumab group [12].

The RECOVERY trial (NCT04381936) is an ongoing randomised trial investigating whether potential treatments for COVID-19 reduce the risk of death. Participants with progressive COVID-19 may undergo an optional subsequent randomisation between tocilizumab and no additional treatment. A total of 2022 patients were randomly allocated to receive tocilizumab by intravenous infusion and were compared with 2094 patients randomly allocated to usual care alone. 82% of patients were taking a systemic steroid such as dexamethasone. Treatment with tocilizumab significantly reduced deaths: 596 (29%) of the patients in the tocilizumab group died within 28 days compared with 694 (33%) patients in the usual care group (rate ratio 0·86; [95% confidence interval [CI] 0·77 to 0·96]; p=0·007), an absolute difference of 4%. The study also showed that tocilizumab shortens the time until patients are successfully discharged from hospital and reduces the need for a mechanical ventilator (https://www.recoverytrial.net/files/recovery-press-release-tocilizumab_final.pdf).

The ESCAPE Phase II, non-randomized, open label clinical trial (NCT04339712) has ended, results have not been peer-reviewed yet. The aim of this study was to conduct one trial of personalized immunotherapy in patients with SARS-CoV-2 (COVID-19) associated with organ dysfunction and with laboratory findings of macrophage activation syndrome (MAS) or immune dysregulation (CID). Patients with MAS and CID with increased aminotransferases were assigned to intravenous anakinra; those with CID and normal aminotransferases to tocilizumab. The primary outcome was at least 25% decrease of sequential organ failure assessment (SOFA) score and/or 50% increase of respiratory ratio by day 8; 28-day mortality, change of SOFA score by day 28; serum biomarkers and cytokine production by mononuclear cells were secondary endpoints. The primary study endpoint was met in 58.3% of anakinra-treated patients and in 33.3% of tocilizumab-treated patients (odds ratio 3.11; 95% CIs 1.29-7.73; P: 0.011). No differences were found in mortality and in SOFA score changes. Anakinra increased capacity of mononuclear cells to produce IL-6. Survivors by day 28 who received anakinra were distributed to scales of the WHO clinical progression of lower severity. Greater incidence of secondary infections was found with tocilizumab treatment.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are insufficient data from clinical trials on the use of tocilizumab in patients with COVID-19. The data currently available are presented in Table 4-1, Table 4-2, Table 4-3, Table 4-4 and Table 4-5. The currently available evidence on all-cause mortality, frequency of adverse events, duration of hospitalization, disease severity and hospital discharges is not conclusive, as there is no statistically significant association between these outcomes and the treatment with tocilizumab. For mortality, any adverse events and hospitalization, studies show a trend towards favouring standard of care over tocilizumab, whereas for severe adverse events and the progression of disease, study results tend to favour tocilizumab.

4.2 Safety evidence from observational studies

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab. In two prospective cohort studies with high risk of bias, safety evidence has been reported. In a retrospective analysis of data from 21 patients, no adverse reaction were observed during the treatment [7]. During the 10-day follow-up Toniati et al. 2020 recorded three cases of severe adverse events: two patients developed septic shock and died, one had gastrointestinal perforation requiring urgent surgery and was alive at day 10 [8].

4.3 Ongoing studies

Several RCTs and interventional nRCTs related to tocilizumab alone or in combination therapy are currently ongoing.

4.4 Scientific conclusion about status of evidence generation

High quality evidence from ongoing RCTs are expected to assess effectiveness and safety of tocilizumab in COVID-19 patients.

Future controlled trials in patients with severe illness are needed to confirm or exclude the possibility of treatment benefit with tocilizumab.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard of care	Risk with tocilizumab				
All-cause mortality [9]; [10]; [11]; [12]; [13]; [14]; [15]; [16]; [17]	289 per 1000	260 per 1000 (231 to 289)	RR 0.90 (0.80 to 1.04)	6503 (9 RCTs)	moderate	Compared to SoC tocilizumab probably reduces the risk of mortality
Number of patients with any adverse event [9]; [12]; [13]; [14]; [17]; [18]	505 per 1000	565 per 1,000 (449 to 702)	RR 1.12 (0.89 to 1.39)	1333 (6 RCTs)	very low	Compared to standard treatment could increase the number of patients with adverse events
Number of patients with severe adverse events [9]; [10]; [11]; [12]; [13]; [14]; [15]; [17]; [18]	146 per 1000	134 per 1,000 (113 to 161)	RR 0.92 (0.77 to 1.10)	2454 (9 RCTs)	moderate	Compared to SoC tocilizumab probably reduces the risk of severe adverse events
Length of stay in hospital [9]; [13]; [15]	Rosas 2020: HR 1.35 [95% CI (1.02; 1.79) Salama 2020: HR 1.16 [95% CI (0.91; 1.48)] REMAP study: HR 1.41 [95% CI (1.18; 1.68)] Cumulatively length of hospitalization differs between the two groups in favour of Tocilizumab (HR: 1.32 (95% CI 1.16, 1.49) p <0.0001)			(3 RCTs)	moderate	Compared to SoC there is no effect on the number of days of hospitalization
Length of stay in hospital (mean days) [12]	SMD 0.42 lower (0.77 lower to 0.07 lower)			129 (1 RCT)	low	Compared to SoC there is no effect on the number of days of hospitalization
Progression of disease severity [10]; [11]; [14]; [16]; [17]	160 per 1,000	127 per 1,000 (109 to 144)	RR 0.79 (0.68 to 0.90)	4501 (6 RCTs)	moderate	Compared to SoC tocilizumab probably reduces the risk of progression of disease severity
Number of patients discharged [10]; [11]; [16]	500 per 1,000	530 per 1,000 (475 to 589)	RR 1.06 (0.95 to 1.18)	4481 (3 RCTs)	very low	Compared to SoC there is no effect on the number of patients discharged
Duration of hospitalization in intensive care [15]	HR 1.42 [IC95% (1.18; 1.71) in favor of tocilizumab			(1 RCT)1	moderate	Compared to SoC tocilizumab probably reduces the number of days of hospitalization in intensive care

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard of care	Risk with tocilizumab				
Mortality patients of moderate severity [16]	217 per 1000	186 per 1000 (156 to 225)	RR 0.86 (0.72 to 1.04)	1868 (1 RCT)	moderate	Compared to SoC tocilizumab probably reduces the risk of mortality
Mortality severe patients [9]; [10]; [15]; [16]	353 per 1000	310 per 1000 (278 to 342)	RR 0.88 (0.79 to 0.97)	3008 (4 RCTs)	moderate	Compared to SoC tocilizumab probably reduces the risk of mortality
Mortality critical patients [16]	483 per 1000	469 per 1000 (391 to 555)	RR 0.97 (0.81 to 1.15)	562 (1 RCT)	moderate	Compared to SoC tocilizumab probably reduces the risk of mortality
Number of patients with respiratory failure and respiratory distress syndrome [17]	45 per 1000	55 per 1000 (15 to 198)	RR 1.21 (0.34 to4.36)	179 (1 RCT)	low	Compared to standard treatment could increase the number of patients with ARDS

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio

Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with favipiravir	Risk with tocilizumab				
Number of patients with any adverse event [19]	284 per 1000	400 per 1000	RR 0.71 (0.15 to 3.50)	12 (1 RCT)	very low	
Number of patients with serious adverse events [19]	No serious adverse event reported				very low	
Number of patients with significant improvement in lung disease on CT [19]	The study reports that there was a significant difference in favour of favipiravir (P = 0.034), HR 3.16 [95% CI 0.62-16.10]				very low	

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio

Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of favipiravir + tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with favipiravir	Risk with favipiravir+tocilizumab				
Number of patients with any adverse event [19]	286 per 1000	643 per 1000	RR 2.25 (0.65 to 7.73)	21 (1 RCT)	very low	
Number of patients with serious adverse events [19]	No serious adverse event reported				very low	
Number of patients with significant improvement in lung disease on CT [19]	The study reports that the cumulative rate of lung lesion remission on day 14 was significantly higher in the combined group than in the favipiravir group (HR 2.66 95% CI [1.08-6.53], P = 0.019).				very low	

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio

Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of favipiravir + tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with tocilizumab	Risk with favipiravir+tocilizumab				
Number of patients with any adverse event [19]	400 per 1000	644 per 1000	RR 1.61 (0.51 to 5.04)	19 (1 RCT)	moderate	
Number of patients with serious adverse events [19]	No serious adverse event reported				very low	
Number of patients with significant	There was no significant difference in the cumulative remission rate of lung lesions on day 14 between the combination group and the tocilizumab group HR 1.28 [95% CI 0.39-4.23] P = 0.575				very low	

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with tocilizumab	Risk with favipiravir+tocilizumab				
improvement in lung disease on CT [19]						

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio

Table 4-5 Summary of findings (SoF) table for published RCT related to effectiveness and safety of tocilizumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with sarilumab	Risk with tocilizumab				
All-cause mortality [15]	208 per 1000	277 per 1000 (156 to 494)	RR 1.33 (0.75 to 2.37)	401 (1 RCT)	moderate	Compared to sarilumab tocilizumab probably increase the risk of mortality
Number of patients with serious adverse events [15]	0 per 1.000	0 per 1000 (0 to 0)	RR 2.63 (0.16 to 44.48)	401 (1 RCT)	low	Compared to sarilumab tocilizumab probably increase the risk of serious adverse events

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal antibody Tocilizumab	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality											
9 [1,2,3,4,5,6,7,8,9]	randomised trials	serious [a]	not serious	not serious	not serious	none	821/3365 (24.4%)	908/3138 (28.9%)	**RR 0.90** (0.80 to 1.0)	**29 fewer per 1.000** (from 58 fewer to 0 more)	⊕⊕⊕◯ MODERATE
Number of patients with any adverse event											
6 [1,4,5,7,9,10]	randomised trials	serious [b]	very serious [c]	not serious	not serious	none	465/806 (57.7%)	266/527 (50.5%)	**RR 1.12** (0.89 to 1.39)	**61 more per 1.000** (from 56 fewer to 197 more)	⊕◯◯◯ VERY LOW
Number of patients with severe adverse events											
9 [1,2,3,4,5,6,7,9,10]	randomised trials	serious [d]	not serious	not serious	not serious	none	228/1380 (16.5%)	157/1074 (14.6%)	**RR 0.92** (0.77 to 1.10)	**12 fewer per 1.000** (from 34 fewer to 15 more)	⊕⊕⊕◯ MODERATE
Length of stay in hospital											
3 [1,4,6]	randomised trials	serious [e]	not serious	not serious	not serious	none	Rosas 2020: HR 1.35 [95% CI (1.02; 1.79) Salama 2020: HR 1.16 [95% CI (0.91; 1.48)] REMAP study: HR 1.41 [95% CI (1.18; 1.68)] Cumulatively length of hospitalization differs between the two groups in favour of Tocilizumab (HR: 1.32 (95% CI 1.16, 1.49) p <0.0001)				⊕⊕⊕◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal antibody Tocilizumab	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
Length of stay in hospital (mean days)											
1 [7]	randomised trials	serious [f]	not serious	not serious	serious [g]	none	65	64		SMD **0.42 lower** (0.77 lower to 0.07 lower)	⨁⨁◯◯ LOW
Progression of COVID-19 disease											
6 [1,2,3,5,8,9]	randomised trials	serious [h]	not serious	not serious	not serious	none	302/2312 (13.1%)	351/2189 (16.0%)	**RR 0.79** (0.68 to 0.90)	**34 fewer per 1.000** (from 51 fewer to 16 fewer)	⨁⨁⨁◯ MODERATE
Number of patients discharged											
3 [2,3,8]	randomised trials	serious [i]	very serious [j]	not serious	not serious	none	1292/2243 (57.6%)	1118/2238 (50.0%)	**RR 1.06** (0.95 to 1.18)	**30 more per 1.000** (from 25 fewer to 90 more)	⨁◯◯◯ VERY LOW
Duration of hospitalization in intensive care											
1 [6]	randomised trials	serious [j]	not serious	not serious	not serious	none	HR 1.42 [IC95% (1.18; 1.71) in favor of tocilizumab				⨁⨁⨁◯ MODERATE
Mortality patients of moderate severity											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal antibody Tocilizumab	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
1 [8]	randomised trials	serious [k]	not serious	not serious	not serious	none	175/935 (18.7%)	202/933 (21.7%)	**RR 0.86** (0.72to 1.04)	**30 fewer per 1.000** (from 61 fewer to 9 more)	⊕⊕⊕◯ MODERATE
Mortality severe patients											
4 [1,2,6,8]	randomised trials	serious [l]	not serious	not serious	not serious	none	454/1530 (29.7%)	521/1478 (35.3%)	**RR 0.88** (0.79 to 0.97)	**42 fewer per 1.000** (from 74 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE
Mortality critical patients											
1 [8]	randomised trials	serious [k]	not serious	not serious	not serious	none	125/268 (46.6%)	142/294 (48.3%)	**RR 0.97** (0.81 to 1.15)	**14 fewer per 1.000** (from 92 fewer to 72 more)	⊕⊕⊕◯ MODERATE
Number of patients with respiratory failure and respiratory distress syndrome											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Monoclonal antibody Tocilizumab	Standard treatment	Relative (95% CI)	Absolute (95% CI)	
1 [9]	randomised trials	serious [m]	not serious	not serious	serious [g]	none	5/91 (5.5%)	4/88 (4.5%)	**RR 1.21** (0.34 to 4.36)	**10 more per 1.000** (from 30fewer to 153 more)	⨁⨁◯◯ LOW

Explanations

a. Downgraded of one level for performance bias at high risk in 5 studies and at unclear risk in 3 studies, unclear risk of selection bias in 3 studies, unclear risk of detection bias in 3 studies and high risk of attrition bias in one study
b. Downgraded of one level for performance bias at high risk in 3 studies and at unclear risk in 2 studies, unclear selection bias in 3 studies, unclear detection bias in 3 studies and unclear attrition and reporting bias in one study
c. Downgraded of two levels for high heterogeneity: i^2=69%
d. Downgraded of one level for performance bias at high risk in 5 studies and at unclear risk in 3 studies, unclear selection bias in 4 studies, unclear detection bias in 3 studies and attrition bias at high risk in 1 study and unclear in t another study, unclear risk of reporting bias in one study
e. Downgraded of one level for performance bias at high risk in one study and unclear in another, unclear risk of selection bias in 2 studies, unclear risk of detection bias in one study
f. Downgraded of one level for performance bias at high risk and at unclear risk of detection bias
g. Downgraded of one level for small sample size (<200)
h. Downgraded of one level for performance bias at high risk in 3 studies and unclear in 2 studies, unclear risk of selection bias in 2 studies, unclear risk of detection bias in 2 studies and high risk of attrition bias in one study
i. Downgraded of one level for performance bias at high risk in 2 studies and unclear in another
j. Downgraded of two levels for high heterogeneity: i^2=77%
k. Downgraded of one level for performance bias at high risk
l. Downgraded of one level for performance bias at high risk in 3 studies, unclear risk of selection bias in one study and unclear risk of detection bias in one study
m. Downgraded of one level for high risk of attrition bias and unclear risk of detection bias

Source: [15]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir	Tocilizumab	Relative (95% CI)	Absolute (95% CI)	
Number of patients with any adverse event											
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/7 (28.6%)	2/5 (40.0%)	**RR 0.71** (0.15 to 3.50)	**116 fewer per 1.000** (from 340 fewer to 1.000 more)	⨁◯◯◯ VERY LOW
Number of patients with serious adverse events											
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	No serious adverse event reported				⨁◯◯◯ VERY LOW
Number of patients with significant improvement in lung disease on CT											
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	The study reports that there was a significant difference in favour of favipiravir (P = 0.034), HR 3.16 [95% CI 0.62-16.10]				⨁◯◯◯ VERY LOW

Explanations
a. Downgraded of two levels for high risk of performance bias and unclear risk of selection bias
b. Downgraded of two levels for very small sample size
Source: [17]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir+Tocilizumab	Favipiravir	Relative (95% CI)	Absolute (95% CI)		
Number of patients with any adverse event												
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9/14 (64.3%)	2/7 (28.6%)	**RR 2.25** (0.65 to 7.73)	**357 more per 1.000** (from 100 fewer to 1.000 more)	⨁◯◯◯ VERY LOW	
Number of patients with serious adverse events												
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	No serious adverse event reported				⨁◯◯◯ VERY LOW	
Number of patients with significant improvement in lung disease on CT												
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	The study reports that the cumulative rate of lung lesion remission on day 14 was significantly higher in the combined group than in the favipiravir group (HR 2.66 95% CI [1.08-6.53], P = 0.019).				⨁◯◯◯ VERY LOW	

Explanations

a. Downgraded of two levels for high risk of performance bias and unclear risk of selection bias
b. Downgraded of two levels for very small sample size

Source: [17]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir+Tocilizumab	Tocilizumab	Relative (95% CI)	Absolute (95% CI)	
Number of patients with any adverse event											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Favipiravir+Tocilizumab	Tocilizumab	Relative (95% CI)	Absolute (95% CI)	
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9/14 (64.3%)	2/5 (40.0%)	**RR 1.61** (0.51 to 5.04)	**244 more per 1.000** (from 196 fewer to 1.000 more)	⨁◯◯◯ VERY LOW
Number of patients with serious adverse events											
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	No serious adverse event reported				⨁◯◯◯ VERY LOW
Number of patients with significant improvement in lung disease on CT											
1 [1]	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	There was no significant difference in the cumulative remission rate of lung lesions on day 14 between the combination group and the tocilizumab group HR 1.28 [95% CI 0.39-4.23] P = 0.575				⨁◯◯◯ VERY LOW

Explanations
a. Downgraded of two levels for high risk of performance bias and unclear risk of selection bias
b. Downgraded of two levels for very small sample size
Source [16]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Sarilumab	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality											
1 [1]	randomised trials	serious [a]	not serious	not serious	not serious	none	98/353 (27.8%)	10/48 (20.8%)	**RR 1.3**3 (0.75 to 2.37)	**69 more per 1.000** (from 52 fewer to 285 more)	⨁⨁⨁◯ MODERATE
Number of patients with serious adverse events											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Sarilumab	Relative (95% CI)	Absolute (95% CI)	
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	9/353 (2.5%)	0/48 (0.0%)	**RR 2.63** (0.16 to 44.48)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW

Explanations

a. Downgraded of one level for high risk of performance bias
b. Downgraded of one level for wide CI

Source: [15]

Table 4-6 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Rosas et al 2020 [9] COVACTA NCT04320615	Salvarani et al 2020 [10] NCT04346355	Stone et al 2020 [11] NCT04356937	Salama et al 2020 [13] EMPACTA NCT04372186	Hermine et al 2020 [14] NCT04331808
Study design, study phase	randomized, double-blind, placebo-controlled, phase 3	open-label, randomized clinical trial, phase 2	randomized, double-blind, placebo-controlled phase 3 trial	randomized, double-blind, placebo-controlled phase 3 trial	cohort-embedded, investigator-initiated, open-label, bayesian randomized phase 2 clinical trial
Centres (single centre or multicentre), country, setting	global, multicenter	multicenter, Italy	multicenter, United States	global, multicenter	multicenter, France
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	452 patients **TCZ**: age mean (SD) 60.9 (14.6) 69.7% male **placebo**: age mean (SD) 60.6 (13.7); 70.1% male; severe	126 patients median (range) age of 60.0 (53.0-72.0) years 61.1% male	243 patients; median age 59.8 years (range, 21.7 to 85.4); 58% male	389 patients TCZ: 60.2% male; mean (± SD) age 56.0 ±14.3 years placebo:57% male; mean (± SD) age 55.6 ±14.9 years	131 patients median (IQR) age was 64 (57.1-74.3) years 68% male moderate, severe
Inclusion criteria	18 years or older with severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test	18 years and older, with COVID-19 pneumonia confirmed by positive polymerase chain reaction test; acute respiratory distress syndrome	19 to 85 years of age with COVID-19 pneumonia confirmed by positive polymerase chain reaction test; requiring hospital but not mechanical ventilation	18 years and older, with COVID-19 pneumonia confirmed by positive polymerase chain reaction test	18 years and older, with COVID-19 pneumonia confirmed by positive polymerase chain reaction test
Exclusion criteria	progression to death is imminent and inevitable within the next 24 hours; active tuberculosis or bacterial, fungal, or viral infection	ICU admission, known hypersensitivity to tocilizumab, and any condition preventing future admission to ICU, such as advanced age with multiple comorbidities, as well as the patient's expressed will to avoid future intubation	Uncontrolled bacterial, fungal, or non-COVID viral infection, active TB	progression to death is imminent and inevitable within the next 24 hours; active tuberculosis or bacterial, fungal, or viral infection	acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high blood pressure, diabetes, chronic kidney diseases, hematological diseases, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected
Intervention (generic drug name and	tocilizumab infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose	TCZ: 8 mg/kg up to a maximum of 800 mg),	TCZ: 8 mg per kilogram of body weight administered	TCZ 8 mg/kg, maximum 800 mg	TCZ 8 mg/kg, maximum 800 mg +standard care per local practice

Author, year, reference number/Study name/Study ID	Rosas et al 2020 [9] COVACTA NCT04320615	Salvarani et al 2020 [10] NCT04346355	Stone et al 2020 [11] NCT04356937	Salama et al 2020 [13] EMPACTA NCT04372186	Hermine et al 2020 [14] NCT04331808
dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	800 mg; up to 1 additional dose may be given if clinical symptoms worsen or show no improvement	followed by a second dose after 12 hours	intravenously, not to exceed 800 mg		
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	placebo	supportive care following the treatment protocols of each center	placebo	placebo+standard care per local practice	placebo+standard care per local practice
Primary Outcome(s)	clinical status on a 7-category ordinal scale at day 28	clinical worsening within 14 days since randomization	intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo	cumulative proportion of patients requiring mechanical ventilation	>5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival without need of ventilation at day 14
Patient-relevant secondary outcome(s)	clinical status at day 14 on the 7-category ordinal scale, mortality at day 28, ventilator-free days to day 28, time to	evaluation of the efficacy of early vs late administration of tocilizumab in admission to ICU with mechanical	clinical worsening, discontinuation of supplemental oxygen,	time to hospital discharge or ready for discharge; time to a ≥2 category improvement in	clinical status assessed with the WHO-CPS scores at day 7 and day 14, overall survival, time to discharge, time to

Author, year, reference number/Study name/Study ID	Rosas et al 2020 [9] COVACTA NCT04320615	Salvarani et al 2020 [10] NCT04346355	Stone et al 2020 [11] NCT04356937	Salama et al 2020 [13] EMPACTA NCT04372186	Hermine et al 2020 [14] NCT04331808
	improvement from baseline in ≥2 categories on the 7-category ordinal scale, and time to hospital discharge	ventilation, mortality, and tocilizumab toxic effects		clinical status; time to clinical failure; mortality rate	oxygen supply independency, biological factors such as C-reactive protein level, and adverse events.
Follow-up (days, months)	60 days	30 days	28 days	60 days	90 days
Sponsor/ lead institution	Hoffmann-La Roche	Azienda Unità Sanitaria Locale Reggio Emilia	Massachusetts General Hospital	Genentech, Inc.	Assistance Publique - Hôpitaux de Paris

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-7 Study characteristics of included RCTs, continued

Author, year, reference number/Study name/Study ID	Gordon et al 2021 [15] REMAP-CAP	Veiga et al. 2021 [12] TOCIBRAS	Horby et al. 2021 [16] RECOVERY	Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India	Wang et al 2020 [18] ChiCTR2000029765	Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894
Study design, study phase	phase IV randomized, open label; multifactorial, adaptive platform trial	prospective, randomized, superiority, open-label, controlled trial	Phase 2 and 3 randomized, open label; factorial assignment	open-label, multicentre, randomised, controlled, phase 3 trial	randomized controlled phase 4 trial	single-arm, open-label, phase 2
Centres (single centre or multicentre), country, setting	international	multicenter, Brazil	multicenter UK	multicenter India	multicenter, China	multicentre China
Patient population (number of included patients/ Mean age and	353 (toc vs, sarilumab) patients critically ill COVID-19.	129 patients mean age 57 (SD 14) years; 68% men	4116 patients mean age 63.6 years (SD 13.7) 66% male	180 patients median age (IQR) 56 (47–63), SoC:54 (43–63) Male 84%; SoC: 86%	65 patients	26 patients; median 73.5 years (34–89) 53.8 % (14/26) male Common, severe or critical

Author, year, reference number/Study name/Study ID	Gordon et al 2021 [15] REMAP-CAP	Veiga et al. 2021 [12] TOCIBRAS	Horby et al. 2021 [16] RECOVERY	Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India	Wang et al 2020 [18] ChiCTR2000029765	Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894
sex/ Disease severity*)	mean age 61,5 (SD: 12,5) years; 73,9% male					
Inclusion criteria	Critically ill, >18 years, with Covid-19, admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support	severe or critically ill need for oxygen supplementation less than 24 hours before the randomization positive inflammatory tests	clinical evidence of progressive COVID-19	moderate to severe COVID-19	18 to 85 years; diagnosed with the common type of NCP (including severe risk factors) and severe cases of new coronavirus pneumonia	Laboratory-confirmed cases according to Chinese guidelines of COVID-19; Male or female more than 18 years old; Increased interleukin-6;Sign the informed consent
Exclusion criteria	presumption that death was imminent with lack of commitment to full support, and prior participation in REMAP-CAP within 90 days.	need for mechanical ventilation for 24 hours or more before the randomizatio active uncontrolled infection liver disease, cirrhosis or elevated AST or ALT above 5 times the upper level limit renal disease with estimate glomerular filtration below 30 mL/min/1.72 m^2	contra-indication to tocilizumab	contra-indication to tocilizumab	pregnant or lactating women; 3. ALT / AST> 5 ULN, neutrophils <0.5, platelets less than 50; diagnosis of rheumatic immune-related diseases; active pulmonary tuberculosis, with definite bacterial and fungal infections.	Allergic to favipiravir or tocilizumab; Pregnant or lactating woman; ALT or AST > 5 times of upper limit of normal; Patients with active hepatitis, tuberculosis, and definite bacterial or fungal infections; Other conditions judged by the investigators.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate,	tocilizumab single intravenous administration 8mg/Kg	TCZ 8 mg/kg, maximum 800 mg +standard care	TCZ 8 mg/kg, maximum 800 mg	a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg+ additional dose (optional)	TCZ 400 mg +standard care per local practice	tocilizumab+favipiravir Favipiravir: On the 1st day, 1600mg twice a day; from the 2nd to the 7th day, 600mg twice a day. Oral administration, the maximum number of days taken is not more than 7 days. Tocilizumab: The first IV dose is 4 ~ 8mg/kg and the recommended dose

Author, year, reference number/Study name/Study ID	Gordon et al 2021 [15] REMAP-CAP	Veiga et al. 2021 [12] TOCIBRAS	Horby et al. 2021 [16] RECOVERY	Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India	Wang et al 2020 [18] ChiCTR2000029765	Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894
Severe, Critical COVID-19)						is 400mg. For fever patients, an additional application (the same dose as before) is given if there is still fever within 24 hours after the first dose and the interval between two medications ≥ 12 hours. (mild n=0; common/moderate n=8; severe n=5; critical n=1) tocilizumab (mild n=0; common/moderate n=2; severe n=5; critical n=0)
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	sarilumab single iv administration 400mg	standard care	usual care	standard care	placebo+standard care per local practice	favipiravir (mild n=0; common/moderate n=2; severe n=3; critical n=0)
Primary Outcome(s)	an ordinal scale combining in-hospital mortality and days free of organ support to day 21	clinical status measured at 15 days using a seven level ordinal scale	all-cause mortality	proportion of patients with progression of COVID-19 from moderate to severe or from severe to death up to day 14	cure rate	cumulative lung lesion remission rate

Author, year, reference number/Study name/Study ID	Gordon et al 2021 [15] REMAP-CAP	Veiga et al. 2021 [12] TOCIBRAS	Horby et al. 2021 [16] RECOVERY	Soin et al. 2021 [17] COVINTOC CTRI/2020/05/025369 Clinical Trials Registry India	Wang et al 2020 [18] ChiCTR2000029765	Zhao et al. 2020 [19] NCT04310228 ChiCTR2000030894
Patient-relevant secondary outcome(s)	all-cause mortality; hospital mortality Health-related Quality of life assessment, EQ5D-5L and WHODAS 2.0	all-cause mortality hospital mortality improvement of SOFA scale ventilator free days	duration of hospital stay composite endpoint of death or need for mechanical ventilation or ECMO	improvement of cytokine release syndrome ventilator-free days, organ failure-free days, ICU-free days, time to clinical improvement according to COVID-19 grade, time to hospital discharge, mortality	mortality; ventilator utilization; hospitalization day	improvement of clinical symptoms the changes of blood routine test and IL-6; changes of oxygen therapy
Follow-up (days, months)	90 days	29 days	28 days and up to 6 months	28 days		3 months
Sponsor/ lead institution	MJM Bonten, UMC Utrecht	Beneficência Portuguesa de São Paulo	University of Oxford	Medanta Institute of Education and Research, Roche India, Cipla India, and Action COVID-19 India	The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital)	Peking University First Hospital

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-8 Summary of safety from observational studies (AE and SAE) of tocilizumab

Author, year	Xu et al 2020 [7]	Luo et al 2020 [21]	Toniati et al 2020 [8]	Somers et al 2020 [23]	Rossi et al 2020 [24]	Petrak et al [25]	Mikulska et al. [26]	Malekzadeh et al. [27]	Perrone et al. [28]	Di Niso et al 2020 [29]	Sciascia et al 2020 [6]	Price et al 2020 [31]	Antony et al 2020 [32]
Country	China	China	Italy	USA	France	USA	Italy	Iran	Italy	Italy	Italy	USA	USA
Sponsor/ lead institution	Department of Science and Technology of Anhui Province and Health Commission of Anhui Province China National Center for Biotechnology Development 175	Zhongfaxincheng campus of Tongji Hospital	n.a.	National Institutes of Health Centers for Disease Control and Prevention American Society for Transplantation and Cellular Therapy New Investigator Award	Centre Hospitalier Intercommunal Robert Ballanger Groupe Hospitalier Pitie-Salpetriere	n.a.	n.a.	AryoGen Co., Iran	National Cancer Institute, Naples	n.a.	ASL Città di Torino	The Yale School of Medicine Institutional Review Board (2000027792)	
Intervention/ Product (drug name)	tocilizumab lopinavit/ritonavir; INF-α; ribavirin;	tocilizumab/ tocilizumab +methylprednizolone	tocilizumab + standard pharmacological protocol	tocilizumab + standard pharmacological protocol	tocilizumab	tocilizumab + steroid or vasopressors or hydroxychloroquine and azithromycin	tocilizumab and/or methylprednisolone+SOC	tocilizumab	tocilizumab	tocilizumab + SoC	tocilizumab	tocilizumab	tocilizumab

Dosage	4-8 mg/kg max 800 mg	n.a.	8 mg/kg max 800 mg	8 mg/kg max 800 mg	400 mg	4 mg/kg max 800 mg	8 mg/kg max 800 mg, methylprednisolone 1mg/kg for 5 days intravenously, then 0.5mg/kg for 5 days	sc 324 mg tocilizumab <100 kg; ≥100 kg 486 mg + SOC	2 doses of TCZ 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours	sc 324 mg tocilizumab + SOC	sc 324 mg, iv 8 mg/kg max 800 mg tocilizumab	iv 8 mg/kg tocilizumab	TCZ 4 mg/kg/day q12hr
Comparator	n.a.	n.a.	n.a.	standard pharmacological protocol	standard pharmacological protocol	n.a.	standard pharmacological protocol	n.a.	n.a.	n.a.	no	no	n.a.
Study design	observational	observational	observational	observational, controlled study	observational	observational	observational	observational	observational	observational	observational	observational	observational
Setting	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital	hospital
Number of pts	21	15	100	154	246	145	196	126	301	70	63	239	80
Inclusion criteria	patients with severe and criticalCOVID-19	patients infected with COVID-19	infected with COVID-19; absence of contraindication to tocilizumab	patients were admitted to Michigan Medicine from March 9-April 20, 2020 for severe COVID-19 pneumonia ,required invasive mechanical ventilation	patients hospitalized with COVID-19	patients hospitalized with COVID-19	COVID-19 pneumonia	severe or critical COVID-19	patients hospitalized with COVID-19	COVID-19 pneumonia	patients infected with COVID-19	patients infected with COVID-19	patients infected with COVID-19 oxygen (O2) supplement of >3L, pneumonia severity index score ≤130

Exclusion criteria	active pulmonary tuberculosis combined with clear bacterial infection and fungal infection	n.a.	contraindication to TCZ, suspected or confirmed bacterial infection, an active diverticulitis or GIT perforation, neutropenia ,thrombocytopenia	<16 years intubated for conditions unrelated to COVID-19, enrolled into a RCT for sarilumab	lack of consent palliative care patients patients in ICU patients transferred from ICU	missing data	intubated treated with remdesivir pregnancy	hypersensitivity to TCZ, history of infection HBV, HCV, HIV, hepatic disorders, bone marrow suppression, active peptic ulcer, diverticulitis, or any other GI disorders that increase the risk of GI perforation, pregnancy, breast-feeding, any concurrent active infection other than COVID-19, and severe renal impairment	contraindicated TCZ, ALT/AST > 5 times the upper limit of the normality, neutrophils count < 500 /mmc, platelets < 50.000/mmc, bowel diverticulitis or perforation	suspected or confirmed concomitant bacterial or fungal systemic infection, active diverticulitis or GIT perforation, neutropenia, platelets count < 50 × 109/L, creatinine clearance < 30 ml/min, serum levels of ALT/AST > 5 times the upper limit of the normal range, or pregnancy.	n.a.	n.a.	mechanically ventilated patients, end-stage comorbid conditions, such as cardiomyopathy, cardiac arrhythmia, cancer, septic shock, end-stage renal disease
Age of patients (yrs)	56.8±16.5 (25–88)	73 (62-80)	62 (IQR 57–71])	58±14.9	67.6 ±15.3	58.1	67.9 years (range, 30–100)	median 55 (20–85) years	≤ 60: 122 (40.5%) 61-70: 107 (35.5%) 71 + : 72 (23.9%)	median 60 (IQR 52, 75)	n.a.	n.a.	median 63 (51-72)

Disease severity	severe	moderate/severe	severe	severe	severe	severe	severe	severe or critical	severe	severe	severe	severe/ non severe	severe
Follow-up (months)	Hospitalization days (range) 15.1±5.8 (10–31)	1 week after tocilizumab therapy	10-day follow-up	Median follow-up 47 days (28-67).	28-day maximum follow-up	15.3 days length of hospital stay	median follow-up of 53 days (range 4–70, interquartile range 33–57)	median 8 days (5–12)	up to 30 days	35 days	14 days	≥21 days	6 days
Loss to follow-up, n (%)	0	0	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
RoB	high	high	high	high	high	high	high	high	high	high	high	high	high
Safety – Outcomes*													
Overall AEs, n (%)	n.a	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Serious AE (SAE), n (%)	0%	n.a.	3%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Most frequent AEs n (%)	n.a.	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Most frequent SAEs, n (%)	n.a.	n.a.	3%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
AEs of special interest, n (%)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Death as SAE, n (%)	n.a.	n.a.	2%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Withdrawals due AEs, n (%)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

*** by arms, if available, (Robins-I):**
https://training.cochrane.org/handbook/current/chapter-25

Abbreviations: CI=Confidence interval; RR=Risk ratio

Table 4-9 Ongoing trials of single agent tocilizumab

Trial Identifier/registry ID(s)/contact	ChiCTR2000029765	NCT04317092 TOCIVID-19	NCT04306705 TACOS	NCT04315480	NCT04372186 EMPACTA	NCT02735707 REMAP-CAP	NCT04381936 RECOVERY	NCT04871854
Study design, study phase	Phase 4 A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). RCT parallel	Phase 2 Multicenter single-arm, open-label, phase 2 study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia non randomized	A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19 retrospective	Phase 2 Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 (COVID-19) Infection With Severe Multifocal Interstitial Pneumonia non randomized, single arm	Phase III A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia RCT parallel	Phase IV randomized, open label; international, multifactorial, adaptive platform trial	Phase 2 and 3 randomized, open label; factorial assignment	Phase 2 randomized, open label;
Recruitment status	Recruiting	Active, not recruiting	Recruiting	Active, not recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	198 severe	301 n.a.	target sample size: 120 n.a.	38 severe	379.n.a.	353 (toc vs, sarilumab) patients critically ill COVID-19.	2022 severe participants with progressive COVID-19	60 severe, breast cancer patients and non cancer patients
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital	Hospital	Hospital	hospital	hospital	hospital
Intervention drug name and dosage	tocilizumab, n.a	tocilizumab 2 doses of TCZ 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours	Tocilizumab or CRRT (continuous renal replacement therapy) or SoC	tocilizumab single intravenous administration 8mg/Kg	tocilizumab 8 mg/kg IV (max 800 mg) + SOC	tocilizumab single intravenous administration 8mg/Kg	tocilizumab 8 mg/kg IV (max 800 mg).	tocilizumab n.a.
Comparator (drug name and dosage)	conventional therapy	n.a.	n.a.	n.a.	placebo+ SOC	sarilumab single iv administration 400mg	no additional treatment	n.a.

Trial Identifier/registry ID(s)/contact	ChiCTR2000029765	NCT04317092 TOCIVID-19	NCT04306705 TACOS	NCT04315480	NCT04372186 EMPACTA	NCT02735707 REMAP-CAP	NCT04381936 RECOVERY	NCT04871854
Primary Outcomes	cure rate mortality;ventilator utilization;hospitalization day	Lethality rate two weeks / one month after registration	Proportion of Participants With Normalization of Fever and Oxygen Saturation Through Day 14	arrest in deterioration of pulmonary function; improving in pulmonary function; need of oro-tracheal intubation; death	Cumulative Proportion of Participants Requiring Mechanical Ventilation by Day 28	respiratory and cardiovascular organ support-free days up to day 21	all-cause mortality	Overall survival (OS) and progression free survival after treatment of tocilizumab
Sponsor/ lead institution, country (also country of recruitment if different)	The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital) China	National Cancer Institute, Naples Italy	Tongji Hospital China	Università Politecnica delle Marche Italy	Genentech, Inc. USA, Brazil, Kenya, Mexico, Peru, South Africa	MJM Bonten, UMC Utrecht	University of Oxford	Beni-Suef University

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-10 Ongoing trials of combination therapies tocilizumab

Trial Identifier	NCT04332094	NCT04424056	NCT04310228	NCT04600141	NCT04330638 COV-AID	NCT04678739	NCT04779047
Study design, study phase	Phase 2, Pilot, Randomized, Multicenter, Open-label RCT parallel, open label	Phase 3 open label randomized therapeutic trial RCT parallel, open label	Not Applicable Phase, Multicenter, RCT parallel, open label	Phase III, Parallel Assignment RCT parallel, open label	Phase III; randomized, open label	Phase III; randomized, open label	Phase 4 randomized, open label
Recruitment status	Recruiting	Not yet recruiting	Recruiting	Not yet recruiting	Active, not recruiting	Recruiting	Recruiting
Number of Patients, Disease severity	276 patients Severity 3-4 according to the WHO 7-point ordinal scale	216 patients COVID19 infection pneumonia at stage 2b or advanced stage 3	150 patients n.a.	severe COVID-19 infection	342, critical ill	150 patients severe COVID-19.	150 patients n.a.
Setting (hospital, ambulatory,..)	hospital	hospital	hospital	hospital	hospital	hospital	hospital
Intervention drug name and dosage	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	favipiravir + tocilizumab	Tocilizumab iv 8mg/kg/dose + Therapeutic dosage heparin	tocilizumab (iv 8mg/kg/dose) tocilizumab+anakinra (100 mg for 28 days) anakinra anakinra+siltuximab (iv 11 mg/kg) siltuximab	A loading dose of Remdesivir I/V 5mg/kg (less than 40kg) or 200mg (>40kg) on day 1, then 2.5mg/kg (less than 40kg) or 100mg (>40kg) daily following randomization. Tocilizumab I/V 8mg/Kg up to 800mg highest 12 hours apart	remdesivir iv 200 mg at day 1 then 100 mg once daily for 5 days and tocilizumab 800 mg once
Comparator (drug name and dosage)	hydroxychloroquine, azithromycin	standard of care	favipiravir, tocilizumab	Heparin - Therapeutic dosage (Group 1) and Heparin - Prophylactic	usual care	Treatment as given without Remdesivir and Tocilizumab	hydroxychloroquine 400 mg twice daily at day 1 then 200 mg twice daily for 5 days and tocilizumab 800 mg once

Trial Identifier	NCT04332094	NCT04424056	NCT04310228	NCT04600141	NCT04330638 COV-AID	NCT04678739	NCT04779047
				dosage (Group 2)			
Primary Outcomes	in-hospital mortality	ventilation free days at D28	Clinical cure rate	Proportion of patients with clinical improvement in 30 days	Time to clinical improvement	Time to clinical improvement Duration of ICU Stay; Mortality Rate; Time to Recovery, Hospital stay	percentage of clinical cure
Sponsor/ lead institution, country (also country of recruitment if different)	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau Spain	Assistance Publique Hopitaux De Marseille France	Peking University First Hospital China	University of Sao Paulo Brazil	University Hospital, Ghent Belgium	M Abdur Rahim Medical College and Hospital	October 6 University

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	03/05/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	03/05/2021
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	03/05/2021

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [33];[34]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in table 6.2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated a long with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

As a supplement we used Microsoft Academics Graph (MAG) to identify further relevant research. We used articles previously included in the EUnetHTA rolling collaborative review until last search and ran the Bring up-to-date function in EPPI Reviewer. Bring up-to-date uses the neural networks of MAG to identify publications similar to input articles, added to the MAG database.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
Embase 1974 to 2021 Ovid MEDLINE(R) ALL 1946 to 2021		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE] 2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019	From 06/04/2021 until 03/05/2021	1032

		or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 or MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dt. use medall [time limits in MEDLINE] 7 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR		

		2021043* OR 202105*).dc. use oemezd [time limits in Embase] 8 (1 and (3 or 5) and 6) use medall 9 (2 and (4 or 5) and 7) use oemezd		

6.3 Search strategy to identify ongoing studies

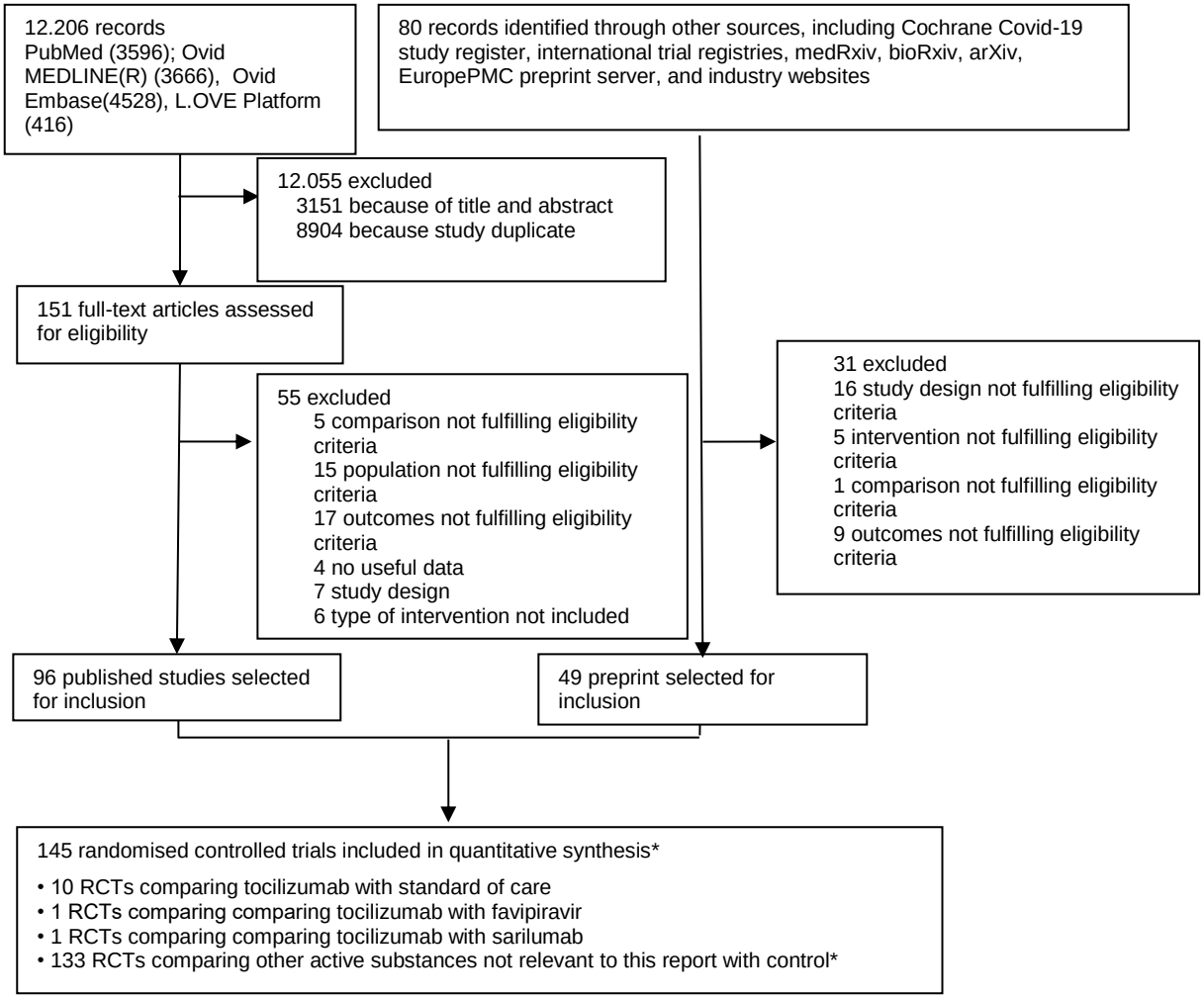
NIPN is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and tocilizumab are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

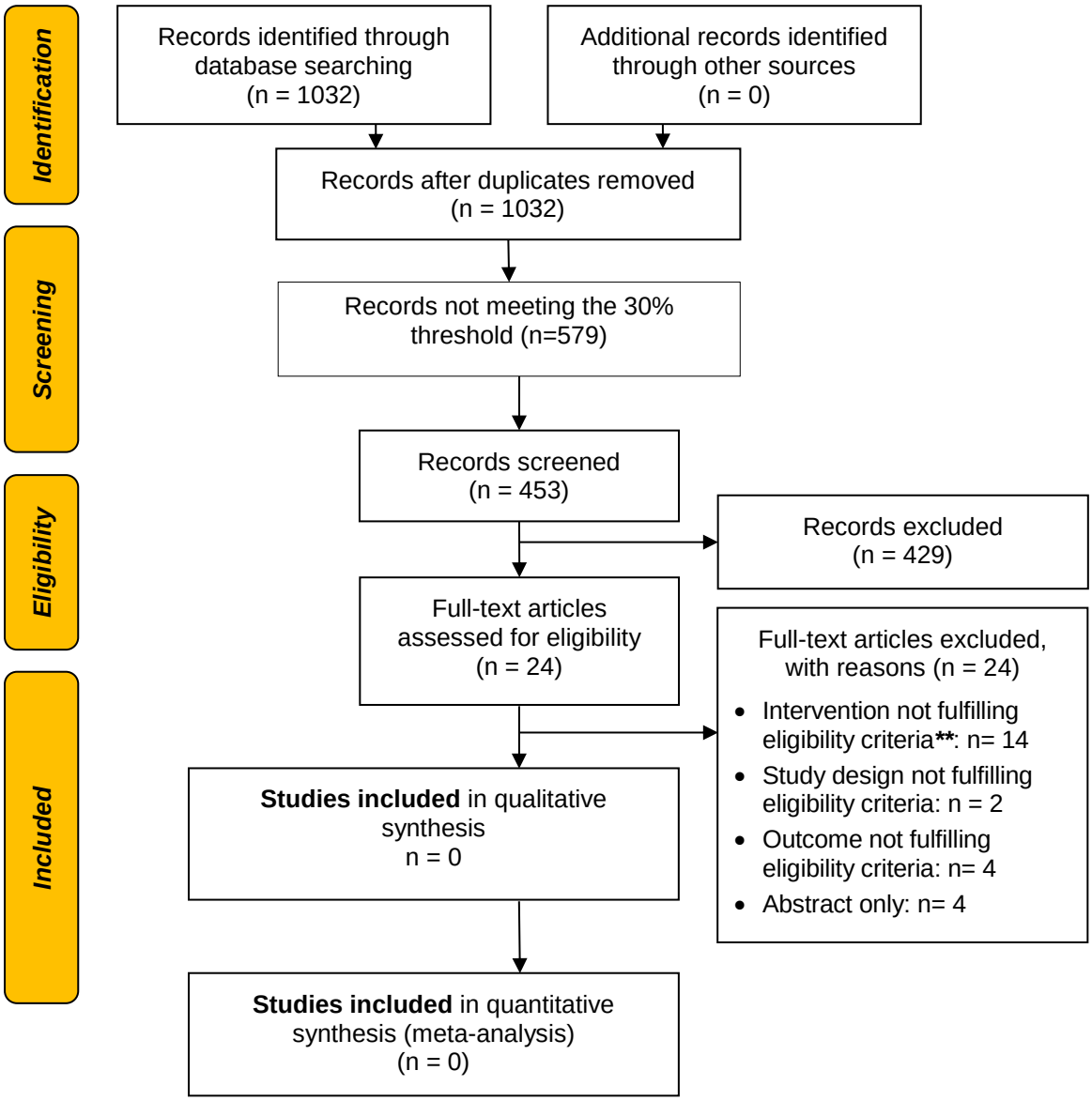
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid19 Terms used at "other terms": • tocilizumab • Actemra	07/05/2021	56 2 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and tocilizumab 2. covid-19 and Actemra 3. SARS-CoV-2 and tocilizumab 4. SARS-CoV-2 and Actemra	07/05/2021	3 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and tocilizumab 2. covid-19 and Actemra 3. SARS-CoV-2 and tocilizumab 4. SARS-CoV-2 and Actemra	07/05/2021	35 0 new

***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.4 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs
RCT = randomised controlled trial;
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews