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 1.1	**09/2020**	Literature searches, Literature screening, Data extraction
V 1.2	**09/2020**	Data extraction and analysis complete
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V 2.0	**15/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
p. 17	• completed Table 4-4 [Ongoing trials of combination therapies tocilizumab]

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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/services/covid-19/) 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:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- 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.

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.

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 using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

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	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

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 is searching and extracting the data for the eligible studies.

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 signalling. 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. 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. Patient 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.

Currently no completed, withdrawn, suspended or terminated RCTs on the safety and efficacy of tocilizumab in COVID-19 patients were found in ClinicalTrials.gov and EudraCT registers.

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.

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 study with high risk of bias have been reported safety evidence. 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 at 30 days	32 per 1000	33 per 1000 (5 to 229)	RR1.05 (0.15 to 7.22)	123 (1 RCT) 1	low	Compared to SoC there is no effect on 30-day all cause mortality

Source: [9]
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	Tocilizumab	Trattamento standard	Relative (95% CI)	Absolute (95% CI)	
Mortality, any cause, at 30 days											
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	2/60 (3.3%)	2/63 (3.2%)	**RR 1.05** (0.15 to 7.22)	**2 more per 1.000** (from 27 fewer to 197 more)	⨁⨁◯◯ LOW

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. Downgraded of one level for high risk of detection bias and unclear risk of selection bias

b. Downgraded of one level for small sample size

References: [10]

Table 4-2 Summary of safety from observational studies (AE and SAE) of tocilizumab

Author, year	Xu et al 2020 [7]	Luo et al 2020 [11]	Toniati et al 2020 [8]	Somers et al 2020 [12]	Rossi et al 2020 [13]
Country	China	China	Italy	USA	France
Sponsor	n.a.	n.a.	n.a.	n.a.	Centre Hospitalier Intercommunal Robert Ballanger Groupe Hospitalier Pitie-Salpetriere
Intervention/Product (drug name)	tocilizumab lopinavit/ritonavir; INF-α; ribavirin;	tocilizumab/ tocilizumab+methylprednizolone	tocilizumab+ standard pharmacological protocol	tocilizumab+ standard pharmacological protocol	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
Comparator	n.a.	n.a.	n.a.	standard pharmacological protocol	standard pharmacological protocol
Study design	observational	observational	observational	observational, controlled study	observational
Setting	hospital	hospital	hospital	hospital	hospital
Number of pts	21	15	100	154	246
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
Age of patients (yrs)	56.8±16.5 (25–88)	73 (62-80)	62 (IQR 57–71])	58±14.9	67.6 ±15.3
Disease severity	severe	moderate/severe	severe	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

Author, year	Xu et al 2020 [7]	Luo et al 2020 [11]	Toniati et al 2020 [8]	Somers et al 2020 [12]	Rossi et al 2020 [13]
Loss to follow-up, n (%)	0	0	0	0	n.a.
RoB	high	high	high	high	high
Overall AEs, n (%)	n.a	n.a.	100%	n.a.	n.a.
Serious AE (SAE), n (%)	0%	n.a.	3%	n.a.	n.a.
Most frequent AEs n (%)	n.a.	n.a.	100%	n.a.	n.a.
Most frequent SAEs, n (%)	n.a.	n.a.	3%	n.a.	n.a.
AEs of special interest, n (%)	n.a.	n.a.	n.a.	n.a.	n.a.
Death as SAE, n (%)	n.a.	n.a.	2%	n.a.	n.a.
Withdrawals due AEs, n (%)	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 4-3 Ongoing trials of single agent tocilizumab

Active substance	**tocilizumab**	**tocilizumab**	**tocilizumab**	**tocilizumab**	**tocilizumab**
Sponsor	The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital)	Roche	National Cancer Institute, Naples	Tongji Hospital Collaborators: Hubei Xinhua Hospital Wuhan No.1 Hospital Wuhan central hospital	Università Politecnica delle Marche Collaborator: Azienda Ospedaliera Ospedali Riuniti Marche Nord
Trial Identifier	ChiCTR2000029765	NCT04320615 COVATA	NCT04317092	NCT04306705	NCT04315480
Phase & Intention	Phase 4 A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19).	Phase 3 A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia	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	A Retrospective Study of Evaluating Safety and Efficacy of Tocilizumab Compared to Continuous Renal Replacement Therapy in Controlling CRS Triggered by COVID-19	Phase 2 Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 (COVID-19) Infection With Severe Multifocal Interstitial Pneumonia
Study design	RCT parallel	RCT parallel, double blind	non randomized	retrospective	non randomized, single arm
Status of trial	Recruiting	Completed*	Recruiting	Recruiting	Active, not recruiting
Duration/End of Study	n.a.	April 3, 2020-July 28, 2020	December 19, 2020-December 19, 2022	Estimated completion: June 2020	Estimated completion: May 2020
Study details	n.a.	n.a.	n.a.	n.a.	n.a.
Number of Patients	198	330	target sample size: 330	target sample size: 120	38
Disease severity	severe	severe	n.a.	n.a.	severe
Setting	Hospital	Hospital	Hospital	Hospital	Hospital
Location/Centres	China	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, United Kingdom, United States	Italy	China	Italy
Intervention drug name and dosage	tocilizumab, n.a	tocilizumab 8 mg/kg IV (max 800 mg), up to 1 additional dose if clinical symptoms worsen or show no improvement.	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

Active substance	**tocilizumab**	**tocilizumab**	**tocilizumab**	**tocilizumab**	**tocilizumab**
Comparator (drug name and dosage)	conventional therapy	placebo 1 IV infusion of placebo matched to tocilizumab	n.a.	n.a.	n.a.
Duration of observation/ Follow-up	n.a.	up to 60 days	up to 1 month	up to 28 days	14 days
Primary Outcomes	cure rate mortality;Ventilator utilization;Hospitalization day	Clinical Status Assessed Using a 7-Category Ordinal Scale to Day 28 Time to Clinical Improvement (TTCI); Time to Improvement of at Least 2 Categories Relative to Baseline on a 7-Category Ordinal Scale of Clinical Status; Incidence of Mechanical Ventilation; Ventilator-Free Days to Day 28; Organ Failure-Free Days to Day 28; Incidence of Intensive Care Unit (ICU) Stay; Duration of ICU Stay; Time to Clinical Failure, Mortality Rate; Time to Hospital Discharge; Duration of Time on Supplemental Oxygen; Percentage of Participants with Adverse Events; COVID-19 (SARS-CoV-2) Viral Load Over Time; Time to Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) Virus Negativity; Proportion of Participants with Post-Treatment Infection	One-month mortality rate; Interleukin-6 level; Lymphocyte count; CRP (C-reactive protein) level; PaO2 (partial pressure of oxygen) / FiO2 (fraction of inspired oxygen, FiO2) ratio (or P/F ratio); Change of the SOFA (Sequential Organ Failure Assessment); Number of participants with treatment-related side effects as assessed by Common Terminology Criteria for Adverse Event (CTCAE) version 5.0; Radiological response; Duration of hospitalization; Remission of respiratory symptoms	Proportion of Participants With Normalization of Fever and Oxygen Saturation Through Day 14; Duration of hospitalization; Proportion of Participants With Normalization of Fever Through Day 14; Time to first negative in 2019 novel Corona virus RT-PCR test; Change from baseline in white blood cell and differential count ; in hsCRP; in cytokines IL-1β, IL-10, sIL-2R, IL-6, IL-8 and TNF-α; in proportion of CD4+CD3/CD8+CD3 T cells	arrest in deterioration of pulmonary function; improving in pulmonary function; need of oro-tracheal intubation; death

Active substance	tocilizumab	tocilizumab	tocilizumab	tocilizumab	tocilizumab
		Serum Concentration of IL-6; sIL-6R; Feritin; CRP; TCZ			
Results/Publication	n.a.	n.a.	n.a.		

Abbreviations: n.a.=not applicable; * COVATA study did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumoni.

Table 4-4 Ongoing trials of combination therapies tocilizumab

Active substance	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab
Sponsor	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	Assistance Publique Hopitaux De Marseille	Hoffmann-La Roche	Peking University First Hospital
Trial Identifier	NCT04332094	NCT04424056	NCT04409262	NCT04310228
Phase & Intention	Phase 2, Pilot, Randomized, Multicenter, Open-label	Phase 3 open label randomized therapeutic trial	Phase III, Randomized, Double-Blind, Multicenter Study	Not Applicable Phase, Multicenter, Randomized and Controlled Clinical Trial
Study design	RCT parallel, open label	RCT parallel, open label	RCT parallel, double blind	RCT parallel, open label
Status of trial	Recruiting	Not yet recruiting	Recruiting	Recruiting
Duration/End of Study	September 2020	November 1, 2022	September 10, 2020	May 2020
Study details	n.a.	n.a	n.a	n.a
Number of Patients	276	216	450	150
Disease severity	Severity 3-4 according to the WHO 7-point ordinal scale	COVID19 infection pneumonia at stage 2b or advanced stage 3	severe COVID-19 pneumonia	n.a.
Setting	hospital	hospital	hospital	hospital
Location/Centres	Spain	France	Brazil, Russian Federation, United States	China
Intervention drug name and dosage	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab
Comparator (drug name and dosage)	hydroxychloroquine, azithromycin	standard of care	remdesevir	favipiravir, tocilizumab
Duration of observation/ Follow-up	2 weeks	28 days	60 days	3 months

Active substance	tocilizumab, hydroxychloroquine, azithromycin	anakinra +/- ruxolitinib tocilizumab +/- ruxolitinib	remdesivir + tocilizumab	favipiravir + tocilizumab
Primary Outcomes	in-hospital mortality	ventilation free days at D28	Clinical Status as Assessed by the Investigator Using a 7-Category Ordinal Scale of Clinical Status on Day 2	Clinical cure rate
Results/Publication	n.a.	n.a.	n.a.	n.a.

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