EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

ANAKINRA FOR THE TREATMENT OF COVID-19

Project ID: RCR07
Monitoring Report

Version 1.0, August 2020

Template version July 2020

This Rolling Collaborative Review Living Document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V0.1	**July 2020**	Literature searches, Literature screening, Data extraction
V0.2	**10/08/2020**	Data extraction and analysis complete
V0.3	**11/08/2020**	Check of data extraction and analysis
V1.0	**12/08/2020**	First version

Disclaimer

The content of this "Rolling Collaborative Review" (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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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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How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR07) Authoring Team. Anakinra for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 9 pages. Report No.: RCR07. Available from: https //www.eunethta.eu.

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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
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
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
SOP	Standard Operating Procedure
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, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the 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	Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
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.pdf) 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. Table 1 - Summary of findings (SoF) 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 table1 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 2 - 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	Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Observational studies (comparative or single-arm prospective studies and 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 3 - 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

Anakinra (Kineret®) is an immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology). Anakinra neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation [4]. Boehringer Ingelheim RCV GmbH & Co KG, Austria and Pfizer Health AB, Sweden, are listed as manufacturers of the biological active substance, and Swedish Orphan Biovitrum AB, Sweden, as Marketing Authorisation Holder, responsible for batch release.

3.2 Regulatory Status

Anakinra is authorised in the EU for Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Still's Disease [4, 5]. Kineret® received a marketing authorisation valid throughout the European Union on 8 March 2002; Anakinra received the FDA approval in November 2001. It is available as a solution for injection under the skin.

Anakinra is not authorised in Covid-19 patients (EMA, FDA) [5].

3.3 Level of Evidence

As of August 12 2020, no publications related to RCTs evaluating Anakinra treatment in COVID-19 patients were found.

Related to safety evidence from observational studies, one prospective cohort study was found: the Ana-COVID study, with 52 consecutive severe Covid-19 patients who received subcutaneous Anakinra at dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment and supportive care (with a historical comparison group, n=44 patients, who received standard care), published by Huet et al. 2020 [6].

Safety outcomes measured were an increase in liver aminotransferase enzymes (more than three times the upper limit of normal), thromboembolic events (confirmed by a CT pulmonary angiogram for pulmonary embolism and by a venous doppler for deep vein thrombosis of the lower limbs), bacteraemia (confirmed when the patient had a recognised pathogen cultured from one or more blood cultures), and premature discontinuation of treatment. Authors reported an increase in liver aminotransferases occurred in seven (13%) patients in the Anakinra group and four (9%) patients in the historical group. Ten (19%) patients in the Anakinra group and five (11%) in the historical group developed a thromboembolic event during the hospital stay. Among the Anakinra group, seven (13%)

had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis. None of the patients in the Anakinra group had a documented bacterial infection during the hospital stay [6]. Summary of safety can be found in Table 4-1.

Several ongoing RCTs and one interventional nRCT are registered in EudraCT and ClinicalTrials.gov registers, including 40 to 342 COVID-19 patients per study. Five RCTs evaluate Anakinra alone, two RCTs evaluate Anakinra alone and in combination with ruxolitinib, and one RCT evaluates Anakinra alone and in combination with siltuximab or tocilizumab. Details can be found in Table 4-2, Table 4-3 and Table 4-4. No completed, withdrawn, suspended or terminated interventional studies were found in ClinicalTrials.gov and EUdraCT registers.

The US COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend either for or against any other immunomodulatory therapy in patients with severe COVID-19 disease [7].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Currently, no publications related to RCTs of Anakinra treatment in COVID-19 patients were found.

4.2 Safety evidence from observational studies

In one prospective cohort study with high risk of bias, an increase in liver aminotransferases occurred in similar frequency in both groups. More patients in the Anakinra group developed a thromboembolic event (pulmonary embolism, deep vein thrombosis of the lower limbs, and arterial thrombosis). None of the patients had a documented bacterial infection during the hospital stay.

4.3 Ongoing studies

Several RCTs and one interventional nRCT related to Anakinra alone or in combination therapy are currently ongoing.

4.4 Scientific conclusion about status of evidence generation

At the moment, effectiveness and safety of Anakinra treatment from RCTs in COVID-19 patients could not be assessed. The same is true for safety from prospective observational studies because only one prospective cohort study with high risk of bias was found.

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

Table 4-1 Summary of safety from observational studies (AE and SAE) of Anakinra [6]

Author, year	Huet, 2020
Country	France
Sponsor	Groupe Hospitalier Paris Saint-Joseph
Intervention/Product (drug name)	Anakinra
Dosage	100 mg twice a day for 72 h, then 100 mg daily for 7 days
Comparator	Standard treatments and supportive care
Study design	Observational prospective cohort study with historical control
Setting	Hospital
Number of pts	52 in anakinra group and 44 in historical control
Inclusion criteria	Aged 18 years or older and admitted to Groupe Hospitalier Paris Saint-Joseph with severe COVID-19-related bilateral pneumonia on chest x-ray or lung CT scan; either laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and either an oxygen saturation of 93% or less under oxygen 6 L/min or more, or aggravation (saturation ≤93% under oxygen 3 L/min) with a loss of 3% of oxygen saturation in ambient air over the previous 24 h.
Age of patients (yrs)	71.0 in anakinra group vs 71.1 in historical group
Disease severity	Severe COVID-19-related bilateral pneumonia requiring oxygen therapy
Follow-up (months)	Until discharge from hospital or death
Loss to follow-up, n (%)	None
RoB	High
Overall AEs, n (%)	Not published
Serious AE (SAE), n (%)	Increase in liver aminotransferases: Seven (13%) patients in the anakinra group vs four (9%) patients in the historical group Thromboembolic event: Ten (19%) patients in the anakinra group vs five (11%) in the historical group (among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis)
Most frequent AEs n (%)	Not reported
Most frequent SAEs, n (%)	See above
AEs of special interest, n (%)	Not reported
Death as SAE, n (%)	Not reported
Withdrawals due AEs, n (%)	Not reported

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

Table 4-2 Ongoing trials of single agent Anakinra

Active substance	Anakinra	Anakinra	Anakinra
Sponsor/Collaborator	Fundacion Miguel Servet	Karolinska University Hospital	University Hospital, Tours / INSERM CIC-P 1415, University Hospital Center of Tours Swedish Orphan Biovitrum (SOBI)
Trial Identifier	NCT04443881 (ANA-COVID-GEAS)	NCT04412291, EudraCT 2020-001748-24 (ImmCoVA) Study	NCT04364009 EudraCT 2020-001734-36 (ANACONDA)
Phase & Intention	Phase 2/3, investigating the efficacy and safety of intravenous administration of anakinra, an interleukin 1 receptor antagonist (IL-1), added to standard treatment, compared to standard treatment alone, to reduce hyperinflammation and respiratory distress in patients with SARS-CoV-2 infection	Phase 2, to Compare Standard-of-care With Anakinra and Tocilizumab Treatment The Immunomodulation-CoV Assessment (ImmCoVA) Study	Phase 3, to assess the efficacy of Anakinra + optimized Standard of Care (oSOC) as compared to oSOC alone on the condition of patients with COVID-19 infection and worsening respiratory symptoms
Study design	RCT, open label, parallel group, 2-arm, multicenter study	RCT, open label, parallel group assignment	RCT, open label, parallel group assignment
Status of trial	Recruiting	Recruiting	Recruiting
Duration/End of Study	May 2020 - March 2021	June 2020 – February 2021	April 2020 – September 2020
Study details			
Number of Patients	180	120	240
Disease severity	Severe pneumonia COVID-19	Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation	Patients with COVID-19 infection and worsening respiratory symptoms
Setting	Hospital	Hospital	Hospital
Location/Centres	Spain	Sweden	France
Intervention drug name and dosage	Anakinra (100 mg/ 6 hours) i.v infusión during 15 days plus standard of care	Anakinra total dose of 400mg per day (divided in 4 doses of 100 mg iv every 6 hours) for 7 days + Standard of care	Anakinra 400mg from Day 1 to Day 3 (two injections of 100 mg each 12 hours) and 200mg the remaining 7 days plus Optimized Standard of Care (oSOC)
Comparator (drug name and dosage)	Standard of care	Tocilizumab: 8mg/kg for a single infusion iv up to max 800 mg + Standard of care Standard of care alone	Optimized Standard of Care (oSOC)
Duration of observation/ Follow-up	Up to 28 days	Up to 60 days	Up to 28 days

Active substance	Anakinra	Anakinra	Anakinra
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary: Treatment success, defined as number of patients not requiring mechanical ventilation by Day 15; Number of patients not requiring mechanical ventilation; Time to mechanical ventilation; Time to oxygen saturation normalization; Stay in ICU and hospitalization Secondary: Total mortality rate; Mortality 48 hours, 7 days, in ICU and hospital Viral clearance / viral shedding; Frequency and severity of AEs	Primary: Time to recovery [Time Frame: Day 1 through Day 29] Secondary: Mortality [Time Frame: Up to day 29]; Number of Days on mechanical ventilation [Time Frame: Up to day 29]; Number of days of supplemental oxygen use [Time Frame: Up to day 29]; Number of patients requiring initiation of mechanical ventilation [Time Frame: Up to day 29]; Time to improvement in oxygenation for at least 48 hours Time Frame: Up to day 29]; Mean change in the 8-point ordinal scale Time Frame: Up to day 29; Proportion of patients on level e-h on the 8-point ordinal scale at day 15 [Time Frame: Day 15; Time to improvement in one category from admission using the 8-point ordinal scale [Time Frame: Up to day 29; Mean change in Sequential organ failure assessment score (SOFA) [Time Frame: Up to day 29]; Time to resolution of fever for at least 48 hours by clinical severity [Time Frame: Up to day 29; Time to change in National Early Warning Score 2 (NEWS2) scoring system [Time Frame: Up to day 29; Time to score of <2 maintained for 24 hours in NEWS2 scoring system (National Early Warning Score) [Time Frame: Up to day 29]; Mean change in NEWS2 scoring system (National Early Warning Score) [Time Frame: Up to day 29]; Number of days with fever [Time Frame: Up to day 29]; Fever defined as >36.6°C (axilla), >37.2°C (oral) or >37.8°C (rectal or tympanic); Number of days of resting respiratory rate >24 breaths/min [Time Frame: Up to day 29]; Time to saturation ≥94% on room air [Time Frame: Up to day 29]; Incidence of serious adverse events [Time Frame: Up to day 60]; Incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic infection Time Frame: Up to day 29]; Incidence of severe or life-threatening bacterial, invasive fungal, or opportunistic	Primary: Treatment success [Time Frame: After 14 days of treatment] Secondary: Treatment success [Time Frame: After 3 days, 10 days and 28 days of treatment; OMS progression scale (on a 7 point ordinal scale) [Time Frame: After 3 days, 10 days, 14 days and 28 days; of treatment; Overall survival [Time Frame: After 3 days, 10 days, 14 days and 28 days of treatment; Time to ICU admission [Time Frame: Up to 28 days; Time to ventilatory support [Time Frame: Up to 28 days ; Change in National Early Warning Score (NEW)from baseline to Day 3, Day 10, Day 14 and Day 28 [Time Frame: After 3 days, 10 days, 14 days and 28 days ; of treatment]; Change in inflammatory parameter [Time Frame: From baseline to Day 3, Day 10, Day 14 and Day 28 ; Change in inflammatory parameter; Hospital length of stay [Time Frame: Up to 28 days; ICU parameter; Number of participants with treatment-related adverse events as assessed by CTCAE v4.0 [Time Frame: Up to 28 days; Predictors of efficacy of Anakinra [Time Frame: After 14 days of treatment]

Active substance	Anakinra	Anakinra	Anakinra
		infection in patients with grade 4 neutropenia [Time Frame: Up to day 60]; Incidence of hypersensitivity reactions [Time Frame: Up to day 29]; Incidence of infusion reactions [Time Frame: Up to day 29]; Number of ventilator free days in the first 28 days [Time Frame: Baseline to day 29]; Number of patients requiring non-invasive ventilation [Time Frame: Up to day 29]; Number of patients requiring the use of high flow nasal cannula [Time Frame: Up to day 29]; Number of patients requiring Extracorporeal membrane oxygenation (ECMO) [Time Frame: Up to day 29]; Number of patients that have been admitted into an intensive care unit (ICU) [Time Frame: Up to day 29]; Number of days of hospitalization in survivors [Time Frame: Up to day 29]; Number of deaths due to any cause [Time Frame: Up to day 60]	
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Table 4-3 Ongoing trials of single agent Anakinra (continued) and combination therapies

Active substance	Anakinra	Anakinra	**Anakinra alone** (and **Anakinra + Siltuximab** and **Anakinra + Tocilizumab**)
Sponsor/Collaborator	Swedish Orphan Biovitrum	Hellenic Institute for the Study of Sepsis	University Hospital, Ghent / Belgium Health Care Knowledge Centre
Trial Identifier	NCT04324021 EudraCT 2020-001167-93	NCT04339712 EudraCT 2020-001039-29 (ESCAPE)	NCT04330638 (COV-AID)
Phase & Intention	Phase 2/3, to assess the efficacy and safety of Emapalumab or Anakinra, versus standard of care (SoC)	Phase 2, to assess personalized immunotherapy in patients with SARS-CoV-2 (COVID-19) associated with organ dysfunction and with laboratory findings of macrophage activation syndrome or immune dysregulation	Phase 3, to test the safety and effectiveness of individually or simultaneously blocking IL-6 and IL-1 versus standard of care on blood oxygenation and systemic cytokine release syndrome in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic cytokine release syndrome

Active substance	**Anakinra**	**Anakinra**	**Anakinra alone** (and **Anakinra + Siltuximab** and **Anakinra + Tocilizumab**)
Study design	RCT, open label, parallel group assignment	nRCT interventional study	RCT, open label, factorial assignment
Status of trial	Recruiting	Recruiting	Recruiting
Duration/End of Study	April 2020 - September 2020	April 2020 - April 2022	April 2020 - December 2020
Study details			
Number of Patients	54	40	342
Disease severity	Patients With SARS-CoV-2 Infection	Life-threatening organ dysfunction by SARS-CoV-2	COVID-19 Patients with Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome
Setting	Hopsital	Hospital	Hospital
Location/Centres	Italy	Greece	Belgium
Intervention drug name and dosage	Anakinra i.v infusion four times daily for 15 days. 400 mg/day in total, divided into 4 doses given every 6 hours + Standard of care Emapalumab i.v infusion every 3rd day for a total 5 infusions. Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg + Standard of care	Anakinra 200mg three times daily (every eight hours) for 7 days Tocilizumab 8mg/kg body weight once up to a maximum of 800mg	Anakinra as a daily subcutaneous injection of 100 mg for 28 days or until hospital discharge, whichever is first Siltuximab via single IV infusion at a dose of 11 mg/kg Tocilizumab via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection Anakinra + Siltuximab Anakinra + Tocilizumab
Comparator (drug name and dosage)	Standard of care	No comparator	Usual care
Duration of observation/ Follow-up	Up to weeks 10	Up to day 90	Up to 28 days and 10-20 weeks
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary: Treatment success [Time Frame: Up to Day 15] Secondary: Time to mechanical ventilation; Change from baseline in Modified Early Warning system score; Change from baseline in resting peripheral capillary oxygen saturation (SpO2); Change of different laboratory parameters; Overall survival [Time Frame: Weeks 6 and 10; Time to hospital discharge [Time Frame: Weeks 6 and 10	Primary: Change of baseline total sequential organ failure assessment (SOFA) score; Improvement of lung involvement measurements; Increase of pO2/FiO2 ratio Secondary: Comparison of the primary endpoint with historical comparators; Change of SOFA score on day 28; Mortality on day 28; Mortality on day 90; Change of cytokine stimulation between days 0 and 4; Change of gene expression between days 0 and 4; Change of serum/plasma proteins between days 0 and 4; Classification of immune function of screened	Primary: Time to Clinical Improvement [Time Frame: at day 15] Secondary: Time to improvement in oxygenation; Mean change in oxygenation; Number of days with hypoxia; Number of days of supplemental oxygen use; Time to absence fever for more than 48h without antipyretics ; Number of days with fever; Time to halving of CRP levels compared to peak value during trial; Time to halving of ferritin levels compared to peak value during trial; Incidence of AEs (Adverse Events) ; Incidence of SAEs;

Active substance	**Anakinra**	**Anakinra**	**Anakinra alone** (and **Anakinra + Siltuximab** and **Anakinra + Tocilizumab**)
		patients who are not enrolled in study drug since they do not have MAS or immune dysregulation	Duration of hospital stay; Duration of hospital stay in survivors; Mean change of SOFA score; Mean change of SOFA score between day 1 and day 15; Percentage of patients reporting each severity rating on a 6-point ordinal scale in relation to serum IL-1; Percentage of patients reporting each severity rating on a 6-point ordinal scale in relation to serum IL-6; All-cause mortality rate; and 16 more outcome
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Table 4-4 Ongoing trials of single agents Anakinra (continued) and combination therapies

Active substance	**Anakinra**	**Anakinra alone** (and **Anakinra plus Ruxolitinib**	**Anakinra alone** (and **Anakinra plus Ruxolitinib**)
Sponsor/Collaborator	NAVARRABIOMED - FUNDACIÓN MIGUEL SERVET	Assistance Publique Hôpitaux de Marseille	Centre Hospitalier Intercommunal de Toulon La Seyne-sur-mer
Trial Identifier	EudraCT 2020-001825-29	EudraCT 2020-001754-21	2020-001963-10
Phase & Intention	Phase 2/3, to assess the effect of anakinra in addition to standard treatment on the need for mechanical ventilation in patients with severe COVID-19 and CSS pneumonia	Phase 3, to assess ANAKINRA or TOCILIZUMAB alone or in combination with RUXOLITINIB in severe stage 2b and 3 COVID-19 disease	Phase 3, to compare clinical and biological efficacy of a therapeutic strategy using ANAKINRA with or without RUXOLITINIB for serious cases of SARS-CoV-2 infection, oxygen dependent, needing or not an invasive ventilation on systemic inflammation
Study design	RCT, open label	RCT, open label	RCT, open label
Status of trial	Ongoing	Ongoing	Ongoing
Duration/End of Study	Start April 2020	Start May 2020	Start May 2020
Study details			
Number of Patients	180	150	54
Disease severity	Hyperinflammation and respiratory distress in patients with SARS-CoV-2	Severe stage 2b and 3 COVID-19 disease	Serious cases of SARS-CoV-2 infection, oxygen dependent, needing or not an invasive ventilation on systemic inflammation
Setting	Hospital	Hospital	Hospital
Location/Centres	Spain	France	France
Intervention drug name and dosage	Anakinra	Anakinra alone Tocilizumab alone	Anakinra with or without Ruxolitinib

Active substance	**Anakinra**	**Anakinra alone** (and **Anakinra plus Ruxolitinib**	**Anakinra alone** (and **Anakinra plus Ruxolitinib**)
		or in combination with Ruxolitinib	
Comparator (drug name and dosage)	Hydroxychloroquine; Azythromicine; Lopinavir/Rotonavir	See above	See above
Duration of observation/ Follow-up	Up to 28 days	Up to 28 days and 12 months	Up to 28 days
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary: Treatment success, defined as number of patients not requiring mechanical ventilation by Day 15. Number of patients not requiring mechanical ventilation (day 28); Time to mechanical ventilation (days); Time to oxygen saturation normalization; Stay in ICU and hospitalization (days) Secondary: Total mortality rate (day 28); Mortality 48 hours, 7 days, in ICU and hospital; Viral clearance / viral shedding; Frequency and severity of AEs	Primary: Ventilation free days at D28 (VFD28) (an increase of 5 days VFD28 is expected) Secondary: Number of patients admitted in ICU (for stage 2b); Number of days in ICU (for stage 3); -Death at D28 for all patients; Number of days in hospital; Visceral insufficiency improvement (SOFA score); Number of days without fever at D7 (without antipyretics for 48h); No increase in the number of bacterial or fungal sepsis; Biological parameters; Immunological parameters; Lung tomodensitometry and ventilation capacity	Primary: Biological criteria: validation if at least 3 parameters are met including CRP and/or Ferritin 1) CRP: decrease > 50% 2) Ferritinemia: decrease > 1/3 3) Serum creatinine: decrease > 1/3 4) AST/ALT: decrease > 50% 5) Eosinophils > 50 /mm3 6) Lymphocytes > 1000 /mm3 Secondary: Number of days of oxygen dependency; number of admission in the intensive care for patient of regular unit (patient enrolled at stage 2b); mortality at D28; number of days in the intensive care unit; total number of days in the hospital; organ failure score SOFA progress; number of days without fever at D7; number of bacterial or fungal sepsis
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

5 REFERENCES

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