Effectiveness of Interleukin-6 Receptor Inhibitors in the Management of Patients with Severe SARS-CoV-2 Pneumonia: An Open-Label, Multicenter Sequential and Cluster Randomized Trial

No specific treatment is currently available for patients with severe pneumonia due to SARS-CoV-2 infection. Approximately 1 out of 5 hospitalized patients might need critical care. An exacerbated inflammatory response can contribute to worsening the clinical course in these patients. In this clinical trial, we aim to elucidate whether treatment with an IL-6 inhibitor improves clinical outcomes, particularly reducing rates of ARDS, mechanical ventilation and shortening hospital admissions. Equipoise: Since the interaction between patient and physician is currently driven by an urgent need to introduce novel modes of action (to prevent end stage patients from dying), a placebo group would not be possible in clinical practice. Thus the randomization is introduced after the "control group" has been completed. Bias: We will statistically attempt to adjust for this possible selection bias, by using modelling techniques referred to as causal inference methodology (e.g. propensity scores); the prospective design, however, will enable all other risks of bias to be handled as explicitly as in a typical superiority randomized trial.

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Background

Coronavirus disease 2019 (COVID-19) is caused by the newly discovered coronavirus, SARS-CoV-2 (1). The median time from onset of symptoms of COVID-19 to development of acute respiratory distress syndrome (ARDS) has been reported as short as 9 days (2). No effective prophylactic or post-exposure therapy is currently available. According to data from the Danish Health Authority (www.sst.dk/corona), as of March 21st, 2020, there were 1326 patients infected with the disease in Denmark, more than 250 are admitted to a hospital, and >50 of them have required intensive care. Nearly 350.000 cases and 15.000 deaths have been reported globally. These numbers are likely to markedly increase during the coming weeks, challenging the capacity of health systems worldwide.

In patients infected with SARS-CoV-2, it has been described that disease severity and outcomes are related to the characteristics of the immune response (7). Interleukin (IL)-6 and other components of the inflammatory cascade contribute to host defense against infections. However, exaggerated synthesis of IL-6 can lead to an acute severe systemic inflammatory response known as 'cytokine storm'. In the pathogenesis of SARS-CoV-2 pneumonia, a study found that a cytokine storm involving a considerable release of proinflammatory cytokines occurred, including IL-6, IL-12, and tumor necrosis factor α (TNF-α) (3). Studies on the Middle East respiratory syndrome caused by another coronavirus (MERS-CoV), indicate that cytokine genes of IL-6, IL-1β, and IL-8 can be markedly upregulated (3). Similarly, patients with SARS-CoV-2 pneumonia admitted to an intensive care unit had higher plasma levels of cytokines including IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and TNF-α (3). These findings indicate that the magnitude and characteristics of the cytokine response is related to the severity and prognosis of patients with SARS-CoV-2 pneumonia (3).

It has been suggested that IL-6 blockade may constitute a novel therapeutic strategy for other types of cytokine storm, such as the systemic inflammatory response syndrome including sepsis, macrophage activation syndrome and hemophagocytic lymphohistiocytosis (8). Remarkable beneficial effects of IL-6 blockade therapy using a IL-6 receptor inhibitor has been described in patients with severe SARS-CoV-2 pneumonia in a retrospective case series from China (4).

Currently, there are two available drugs based on human monoclonal antibodies against IL-6 receptor, tocilizumab (RoActemra, Roche) and sarilumab (Kevzara, Sanofi). IL-6 receptor inhibitors are currently licensed for several autoimmune disorders and are considered well tolerated and safe in general. The most common side effects reported are upper respiratory tract infections, headache, hypertension, and abnormal liver function tests. The most serious side effects are serious infections, complications of diverticulitis, and hypersensitivity reactions (9, 10).

We hypothesize that IL-6 might play a key role in the cytokine storm associated with serious adverse outcomes in patients infected with SARS-CoV-2 pneumonia, and that blockade of IL-6 would be suitable therapeutic target for these patients. We will investigate the effect of different types of IL-6 inhibition versus no adjuvant treatment compared to standard of care in patients with severe SARS-CoV-2 pneumonia.

Study hypotheses

A single dose of either tocilizumab intravenous (IV) 400 mg; tocilizumab 2x162 mg subcutaneous (SC) or sarilumab 200 mg (SC) is superior to standard of care in terms of time to waning oxygen support.

Objective

Primary objective: To compare the effect of either one of three IL-6 inhibitor administrations, relative to the standard of care, on time to independence from supplementary oxygen therapy, measured in days from baseline to day 28, in patients with severe SARS-CoV-2 pneumonia.

Study Design and Methods

Study type: Interventional (clinical trial); Sequential and Cluster Randomized Trial

Allocation: Sequential enrollment; after a period of one week collecting the control comparator (*D* arm) data, the 3 experimental interventions will be prescribed in randomized order with the day of week as the unit of random allocation independently for clinical site.

Estimated enrollment: 200 patients (1:1:1:1)

Intervention Model: Multi-Arm Parallel-Group Randomized Trial: 3 group single dose treatment assignment arms *vs.* a management as usual comparator-control group:

A: 400 mg tocilizumab IV
B: 2 x 162 mg tocilizumab SC
C: 1 x 200 mg sarilumab SC
D: Comparator control arm receiving no additional treatment (i.e. standard of care = management as usual).

Patients will be sequentially enrolled starting with enrolment of all the comparator-control group participants for one week (aiming at 10 patients a day; at least 50 enrolled over a week) followed by a prespecified daily randomization to either Arm *A*; Arm *B*; Arm *C* different for each treating site.

Standard of care: To be determined by physician in charge of the individual patients based on a clinical assessment. All patients will be screened for latent infections at inclusion to the study, including HIV and hepatitis screening, and quantiferon test.

Masking: None (Open Label)

Follow-up time: 28 days observation after first dosage

Primary purpose: Treatment of SARS-CoV-2 pneumonia

Study population

Ages eligible for study: 18 Years and older (Adult, Older Adult)
Sexes eligible for study: All
Accepts healthy volunteers: No

Inclusion Criteria:

Patients will be offered participation in the study if they fulfill the following criteria:
SARS-CoV-2 infection confirmed by real time-PCR and
Positive imaging: consolidation, ground glass opacities, or bilateral pulmonary infiltration either by CT-scan or chest x-ray; and
Need of oxygen therapy to maintain SO2>94% OR FiO2/PaO2 > 20

and at least two of the following laboratory measures:
CRP level >70 mg/L or CRP level >= 40 mg/L and doubled within 48 hours (without other confirmed infectious or non-infectious cause), Lactatdehydrogenase > 250 U/L, thrombocytopenia < 120 x 10E9/L, lymphocyte count < 0.6 x 10E9/L, D-dimer > 1 ug/mL, serum ferritin > 300 ug/mL

Exclusion Criteria:

Age <18 years, pregnancy suspected or confirmed, severe heart failure, suspected or confirmed bacterial infection, current solid or hematological malignancy, neutropenia, ALAT elevation more than three times the laboratory upper limit, ASA class 5 (after COVID19 admission) or higher at inclusion (prior admission), severe chronic obstructive pulmonary disease or heart failure (NYHA class II or higher), pregnant or lactating women, current treatment with conventional synthetic disease-modifying antirheumatic drugs (DMARDs)/immunosuppressive agents including IL-6 inhibitors, or with Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period, current use of chronic oral corticosteroids in a dose higher than prednisone 10 mg or equivalent per day, by previous history or testing prior to this disease course: active tuberculosis (TB), HIV infection regardless of immunological status, hepatitis, evidence of recent (30 days) invasive bacterial or fungal infections; patients who have received immunosuppressive antibody therapy within the past 5 months, including intravenous immunoglobulin or plans to receive during the study period, IV drug abuse, history of inflammatory bowel disease, diverticulitis, ulcer, perforated gastrointestinal tract, participation in any clinical research study evaluating an investigational product (IP) or therapy within 3 months and less than five half-lives of IP prior inclusion to the study, any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study, suspected or known intolerance or allergy to any of the study drugs, inability to give informed consent. However, patients treated with hydroxychloroquine and azithromycin will be allowed if deemed necessary.

Exit criteria:

Subjects asked to withdraw the study, or according to researchers' suggestions.

Measured Outcomes

Primary outcome: Time to independence from supplementary oxygen therapy in days.

Key secondary outcomes:

1) Number of deaths
2) Days out of hospital and alive at 28-day follow-up
3) Ventilator free days alive and out of hospital within 28 days
4) C-reactive protein (CRP) level (time frame: baseline, peak during treatment, 14 days, 28 days)
5) Number of participants with Serious Adverse Events (SAEs) as assessed by Common Terminology Criteria for Adverse Event (CTCAE) (time frame: during treatment, 14 days, 28 days).

Exploratory outcomes and potential confounders (i.e. pre-exposure covariates)

Variable	**Baseline**	**48hrs +/- 6hrs**	**96 hours +/- 6hrs**	**Day 14**	**Day 28**
Demographics					
Age	x				
Sex	x				
Clinical					
Days after symptom debut at inclusion	x				
Respiratory frequency per minute	x	x	x	X*	X*
Systolic blood pressure < 100 mmHg	x	x	x	X*	X*
Pulse < 125 beats per minute	x	x	x	X*	X*
SaO2	x	x	x	X*	X*
O2 flow (L)	x	x	x	X*	X*
Underlying conditions					
CCI score	x				
Alcohol (minimal use, social use, dependence)	x				
Smoking status	x				
ASA score before admission	x				
ASA score after admission	x				
Any comorbidity	x				
BMI	x				
Hypertension	x				
Diabetes	x				
Coronary Heart Disease	x				
Asthma	x				
Chronic Pulmonary Disease	x				
Chronic nephropathy	x				
Any malignancies	x				
Other	x				
Laboratory Measures					
C-reactive protein mg/L	x	x	x	x	x
Lymphocyte count x 10E9/L	x	x	x	x	x
Platelet count x 10E9/L	x	x	x	x	x
Hemoglobin U/L	x	x	x	x	x

Serum ferritin ug/mL	x	x	x	x	x
Creatinin umol/L	x	x	x	x	x
Lactatdehydrogenase U/L	x	x	x	x	x
Protrombine time < 16 s	x	x	x	x	x
D-dimer ug/mL	x	x	x	x	x
Procalcitonin mg/L	x	x	x	x	x
Other					
SAEs	x	x	x	x	x
Numerical breathing effort (0-100)	x	x	x	x	x
Numerical Breathing Distress (0-100)	x	x	x	x	x
Numerical global health (0-100)	x	x	x	x	x

Abbreviations: CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists Physical Status Classification System score; BMI: Body max index; VAS: visual analogue scale; TESAE: Treatment Emergent Serious Adverse Events. *only if hospitalized

Safety considerations

The investigator will monitor each patient for clinical and laboratory evidence of SAEs on a routine basis throughout the study. SAEs will be listed separately for each period of the trial. The investigator will assess and record SAEs in detail including the date of onset, description, severity, duration and outcome, relationship of the SAE to study drug, and any action(s) taken. SAEs, whether in response to a query, observed by site personnel, or reported spontaneously by the participant will be recorded.

Definitions

Adverse event

- An AE is defined as any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the allocated treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the experimental treatment or product, whether or not the event is considered causally related to the treatment.

  Such an event can result from the treatment as stipulated in the protocol, as well as from accidental or intentional overdose, abuse, or withdrawal. Any worsening of a pre-existing condition is considered an AE. Laboratory abnormalities are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

  A treatment-emergent AE is defined as any AE with onset or worsening reported by a participant during the entire study period.

However, if the pre-existing condition deteriorates unexpectedly during the study, then the deterioration of the condition for which the elective surgery/procedure is carried out will be considered an AE.

- AE Severity
  - The investigator will use the following definitions to rate the severity of each AE:
    - Mild: The AE is transient and easily tolerated by the participant
    - Moderate: The AE causes the participant discomfort and interrupts the participant's usual activities

      Due to the state of emergency only the first two AE types will only be reported for injection site reactions and infusion reactions.
    - Severe: The AE causes considerable interference with the participant's usual activities and may be incapacitating or life-threatening

Serious adverse events

If an AE meets any of the following criteria, it is to be reported to the Sponsor as a serious AE (SAE) within 24 hours of the site being made aware of the SAE.

- Results in death
- Is life-threatening (note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result

in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also in general be considered serious.

Relationship to study treatment

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

- Probably related: An AE has a strong temporal relationship to study intervention or recurs on re-challenge and an alternate aetiology is unlikely or significantly less likely
- Probably not related: An AE has little or no temporal relationship to the study intervention and/or a more likely alternative aetiology exists
- Not related: An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study interventions (*e.g.*, has no temporal relationship to study intervention or has a much more likely alternative aetiology)

Adverse event collection period

Besides injection site reactions or infusion reactions, due to the critical condition of this disease, and the well known character of the drugs being given, only SAEs reported from the time of enrolment until 28 day after randomisation will be collected, whether elicited or spontaneously reported by the participant. Information on AEs is collected at each clinic visit.

In Danish:

1) Vi registrerer kun følgende AE'er: injection site reactions og infusion site reactions (dette gøres fra randomisering til 28 dage efter randomisering)

2) Vi registrerer alle SAE'er (dette gøres fra randomisering til 28 dage efter randomisering). Såfremt patienten i forsøgsperioden overflyttes til Intensivafdelingen, vil der kun blive registreret følgende SAE'er: "død".

   Hvis patienten flyttes tilbage til stamafdeling igen indenfor de 28 dage, genoptages registreringen af alle SAE'er

3) Vi akutrapporterer (indenfor 24 timer) kun følgende SAE'er fra investigator til sponsor: "overførsel til intensivafdeling" og "død"

4) Alle andre SAE'er bliver indsamlet årligt og ved afslutningen af forsøget

5) Sponsor vurderer alle indberettede SAE'er med henblik på SUSAR-rapportering til Lægemiddelstyrelsen og Videnskabsetisk Komité

Adverse event reporting

In the event of a SAE, whether related to study intervention or not, the investigator will notify the Sponsor by emailing/faxing the appropriate SAE forms within 24 hours of being made aware of the SAE. However, due to the critical condition, if the patients deteriorate and gets transferred to ICU; this will be reported - and only SUSARs will be reported beyond this point of care together with death.

Serious adverse reaction (SAR)

It is a SAE for which a causal relationship to the trial/study product is at least possible i.e. a causal relationship is conceivable and cannot be dismissed.

Suspected unexpected serious adverse reaction

A SAR can be a suspected unexpected serious adverse reaction (SUSAR), which means that it may or may not be related, but is unexpected, as it is not consistent with current information. If the Sponsor-Investigator (Lars Erik Kristensen) judge that a SAE is SUSAR they are responsible for reporting it to the Danish Health and Medicines Authority and the local health research ethics committee. A SUSAR that is life threatening must be reported to the national competence authority within 7 days (15 days in case of not life-threatening SUSAR).

Obligations and responsibilities of the Sponsor-Investigator related to safety reporting

When reporting AEs the following parameters must be recorded:

- Study name
- Patient identification (e.g. subject number, initials, sex, age)
- Event (preferably a diagnosis)
- Drug
- Reporter identification (e.g. name, or initials)
- Causality
- Outcome

Reporting to the Danish Health and Medicines Authority

The Sponsor-Investigator will be responsible for all required periodic updates to health authorities and expedited reporting of SAEs occurring during the performance of the study, in accordance with local regulations and the agreed protocol. The approving Danish Health and Medicines Authority may:

- Have special requests beyond SUSAR reporting

The Sponsor-Investigator shall be responsible for providing to the participating investigators and ERB all applicable study related information (including information submitted to the Danish Health and Medicines Authority).

Reporting to Sanofi DK and Roche DK

When the Sponsor-Investigator is aware that the study subject has been exposed to a Roche or Sanofi (R or S) product, the following information must be reported in English to R or S Pharmacovigilance contact:

- All individual SARs
- Indicate on any SAR whether it has been submitted to the Danish Health and Medicines Authority
- In addition to SARs, any other events that have been submitted to the Danish Health and Medicines Authority according to regulatory requirements in Denmark shall be sent to R or S at time of submission to health authorities
- Report any pregnancy in the study subject that occurs during the use of a R or S product
- The Sponsor-Investigator shall provide further information about safety related events to R or S, if the Sponsor-Investigator receives specific requests from R or S

Safety considerations in Danish:
Jf. Lægemiddelstyrel-sens vejledning, er en hændelse, enhver uønsket hændelse hos en patient eller en forsøgsperson i et klinisk forsøg efter behandling med et lægemiddel, uden at der nødvendigvis er sammenhæng mellem denne behandling og den uønskede hændelse.

En bivirkning og en uventet bivirkning. Jf. Lægemiddelstyrelsens vejledning, er en bivirkning enhver skadelig og uønsket reaktion på et forsøgslægemiddel uanset dosis. En uventet bivirkning er en bivirkning, hvis karakter eller alvor ikke stemmer overens med produktoplysningerne.
En alvorlig hændelse eller alvorlig bi-virkning. Jf. Lægemiddelstyrelsens vejledning, er en alvorlig hændelse eller alvorlig bivirkning, som uanset dosis resulterer i død, er livstru-ende, medfører hospitalsindlæggelse eller forlængelse af hospitalsop-hold, resulterer i betydelig eller vedvarende invaliditet eller uarbejds-dygtighed eller fører til en medfødt anomali eller misdannelse.
Bivirkninger registreres fra underskrivelse af samtykke eller administration af forsøgslægemidlet til et 28 dages opfølgning efter single dose (studie afslutning), således at eventuelle sene bivirkninger også registreres.

Alvorlige hændelser og bivirkninger skal rapporteres til sponsor øjeblikkeligt og indenfor 24 timer.
Sponsor sikre at oplysninger om SUSARs, som er dødelige eller livstruende, registreres og indberettes til Lægemiddelstyrelsen hurtigst muligt og senest 7 dage efter, at sponsor har fået kendskab til en sådan formodet bivirkning. Senest 8 dage efter indberetningen vil sponsor meddele Lægemiddelstyrelsen alle relevante oplysninger om sponsors og investigators opfølgning på indberetningen.
Alle andre SUSAR, vil indberettes til Lægemiddelstyrelsen senest 15 dage efter, at sponsor har fået kendskab til disse.

Power and Sample Size Considerations

Assumptions: Under the circumstances to which the trial is conducted, the sample size estimation is only meant as a pragmatic illustration of our primary objective. We consider a clinically significant difference between time to independence from supplementary oxygen therapy of 4 days (SD±7 days).

> *D*: Mean *Time to independence* in days in group 1 (comparator-control arm receiving standard of care): 21 days
> *A-to-C*: Mean *Time to independence* in days in the combined group 2 (pooled IL-6 receptor antagonist): 17 days

Naïvely assuming that we were to randomize into two groups only (1:1) with an alpha level of 5% and beta of 20%, we estimate a n=49 patients per group would be the minimum required to achieve a reasonable statistical power (≥80%) to detect a difference of 4 days to independence from supplementary oxygen therapy. Therefore, we aim to enroll 50 patients per arm including 50 in the comparator-control. Thus, in total, we hope to include 200 patients (50:50:50 *vs.* 50).

Statistical Considerations

Our main objective is to examine whether the IL-6-inhibitor intervention(s) are different from the comparator-control group, therefore we will compare all three experimental intervention groups (combined: *A*&*B*&*C*) with the control group using a single test of statistical significance (P<0.05; two-sided).

Secondarily three specific comparisons are made between specific pairs (i.e. combinations of treatments: *A vs. D*; *B vs. D*; and *C vs. D*) to explore whether any of the specific arms could be more superior (against standard of care treatment) than the other. However, since the number of possible comparisons can be considerable (up to six comparisons for each outcome measure) these tests will be subject to multiplicity testing and elaborated on in the Statistical Analysis Plan).

The comparison between the active and control group in this pragmatic design is potentially biased by the fact that we could be introducing "selection bias"; observational studies almost always have selection bias because prognostic factors are unequally distributed between patients exposed or not exposed to an intervention. However, in this particular study, the clinician does not have access to the novel (IL-6 inhibitor) therapies before the rigorous randomized trial design is introduced in the clinic (i.e. when comparing the three IL-6 inhibitors head-to-head).

The standard approach to dealing with this "risk of selection bias" is to use adjusted or stratified analyses: Its principle is to use measurement of risk factors to create prognostically homogeneous groups. As stated under propensity score adjustments (see below), we will apply propensity analysis, where groups are matched according to the likelihood of membership in exposed (IL-6 inhibitors) or unexposed (comparator-control) groups. Propensity methods will enable us to deal with multiple prognostic factors, even when there are relatively few patients having outcome events (e.g. dying from their condition).

After this – when the clinical departments enter the 3-arm parallel group – randomized trial design period, we will have a stringent protocol, which is randomized. The randomization is not focusing on the individual patients, rather we will consider each day of the week a "cluster" to randomize - thus representing groups of individuals (statistically handled using a random effects factor with day of the week as individual cluster levels). Each clinical center will have its own randomized sequence each day; potentially this could introduce selection bias on a given day, if the clinician having the responsibility for the individual patient do not agree with the content of the present protocol (since the specific IL-6 inhibitor was revealed earlier that particular morning); recalling that all of the three IL-6 inhibitor strategies are novel, this risk of personal judgment for the individual clinicians is considered highly unlikely.

Analysis population: Before looking and analyzing any of the data collected from this trial, we will write an explicit Statistical Analysis Plan (SAP). The main analysis will be conducted based on the intention-to-treat (ITT) population, which will be defined as all participants who were enrolled (and randomized) with completed baseline evaluations collected for any given variable of interest. From this the effect of one (or all of the three) experimental interventions will be assessed by evaluating on the basis of the ITT a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group will be followed up, assessed and analyzed as members of their initial group irrespective of their adherence/compliance or censoring/withdrawals from to the randomized course of treatment.

All statistical models will be adjusted for the following fixed effect factors (*i*) site (i.e. the center handling the patient), (*ii*) the experimental intervention to which the individual patient were randomized (*A*, *B*, or *C*), and finally (*iii*) the day of the week as a random effects factor (i.e. the unit of randomization). In general, binary outcome measures will be analyzed using logistic regression models enabling adjustments for covariates (incl potential confounders). For continuous outcomes Analysis of Covariance (ANCOVA) will be used enabling adjustment for baseline values. Time to events will be analyzed using survival statistics when appropriate. For the primary outcome measure it is anticipated that various transformations (e.g. log_e) will be applied since '*Time to independence from supplementary oxygen therapy*' will probably represent a skewed distribution.

Analysis of effectiveness: All analyses will be done on the ITT population. The study hypotheses can only be accepted if a statistically significant difference between groups (H_A: $\mu_I \neq \mu_C$ rejecting the null hypothesis) for the primary outcome is detected. All statistical tests will be two-sided at an alpha level of 5% with estimates presented with 95% confidence intervals.

Propensity scores to compare the control group with our randomized groups:

Propensity score adjustment (and matching) is used to balance covariates between treated (e.g. any of the three IL-6 inhibitor groups) and untreated observations (the *D* group). A propensity score is the conditional probability that a participant receives "treatment" given the individual's observed covariates. The goal of propensity scoring is to mimic what happens in the standard randomized controlled trials (RCT's) by balancing observed covariates between participants in control and treatment study groups.

In a randomized controlled trial, participants are randomly placed into a treatment and a control group. The treatment group receives the treatment and the treatment outcomes are evaluated *vs*. the control group outcomes. Due to randomization, an RCT has no selection bias when splitting participants up into the control and treatment groups. Randomization balances both observed and unobserved characteristics between the two subject groups. Thus, it accounts for all possible "confounding variables". Unaccounted for confounding variables prevent us from measuring the true impact a treatment has on an outcome. Thus, inevitably a challenge with causal inference from the current design is that treatment *vs* no treatment is not applied randomly, theoretically leading to some selection bias (although there are currently no IL-6 inhibitors available in clinical practice) and thus some confounding variables would potentially need to be taken into account.

Improved confounding variable balance between treatment (IL-6 inhibitors) and the comparator-control group can be achieved (with reasonable certainty) by matching observations from each of

the two groups based on the propensity score, which in this case would be the probability that a patient received the IL-6 inhibitor given the observed covariates. Propensity score analysis seeks to isolate the treatment as the only difference between our treatment and comparator-control groups. Logistic regression will be used to develop propensity scores, which in this trial represent the probability that a patient receives the IL-6 inhibitor based on the participant's observed covariates. Thus, we will create a logistic model in which the variables we would like to balance between, our treatment and control groups, are used as our predictors of treatment, our dependent variable in the logistic regression model.

Study Medications

Description: Tocilizumab IV & SC as well as sarilumab SC are well known anti-rheumatic drugs being used for rheumatoid arthritis and giant cell arteritis. It is available across continents and to reasonable cost due to single dosage regimen, making the results of the trial to rapidly be extrapolated to developing countries.

Dosing and administration: Rational for IV tocilizumab dosing is based on a previous study by Xu X et al (2) 400mg/patient. From experiences from rheumatology care 2 pens of tocilizumab 162 mg/pen or 1 pens of sarilumab 200mg/pen will resemble (equipotent in RA anti-inflammatory treatment) a dosage of tocilizumab 400 mg/iv.

Source: The study drug will be provided as SC pens or IV-vials from the hospital pharmacy.

Adverse events reporting: The applied intervention will be delivered by staff with relevant qualifications, education and certification. Thus, according to the current GCP standard, passive surveillance of harms will be assessed: The recorded adverse events (AE) are injection site reactions and infusion reactions. Otherwise only serious adverse event (SAE) will be reported until end of study or transfer to ICU, in addition suspected unexpected serious adverse events (SUSAR) will be recorded and report these to the Danish Health and Medicines Authority and Health Research Ethics committee according to Danish Law.

Interim Subjective Evaluation

At inclusion of 10%, 30% and 60% in the pooled intervention group. The inclusion will be paused for 12hrs until the study team (PI, co-investigator, site responsible doctors) have evaluated safety and feasibility of the study based on death and TESAE's. At 10% no more than 4 deaths will be accepted and TESAE < 50% of enrolled patients. At 30% no more than 10 deaths will be accepted and TESAE < 50% of enrolled. At 60% no more than 15 deaths will be accepted and TESAE < 40% of enrolled. If deemed feasible the study will continue, when in doubt interaction with the Danish medical authority will solve whether the trial will continue or not.
Due to the extraordinary circumstances extreem positive response rates (days on oxygen in the intervention group < 50% * days of oxygen in the comparator group) will need to be made publicly avialable already at 60% of inclusion. However, the study will continue.

Ethical Considerations

Before screening, all potential trial participants will be informed, both orally and in writing about the purpose of the study, process and potential risks, costs and benefits of participation. In addition, the leaflets '*Før du beslutter dig*' and '*Rettigheder som forsøgsperson i et sundhedsvidenskabeligt forskningsprojekt*' will be handed out.

All participants are informed of their rights to withdraw from the study at any time without this impacting on any future investigations and/or treatments at the hospital or by some of the members of the study group. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing a consent form before trial participation can take place.

All patients will be screened for latent infections at inclusion to the study, potentially including HIV, hepatitis screening, and quantiferon test, however, status for these latent infections will most likely be unknown at the point of entry. Patients will be well informed about this, and test results will only be given based on patient request, and in a responsible manner – offering full support and relevant treatment if positive. A follow-up control at 28-days after discharge will be offered to all patients and treating clinicians will follow-up for the results from the baseline infection screening. Treatment or prophylactic therapies will be implemented when relevant.

IL-6 inhibitor treatment has been approved for rheumatoid arthritis and plenty of clinical evidence placing it as a rather safe treatment. Where bacterial infection, elevated liver tests and neutropenia are the most common. All patients will therefore receive broad spectrum antibiotic therapy before administration of study drugs (which is also part of routine care normally) . And they will be monitored with blood tests to screen for these side effects prior and after administration of study drug. High lever test and low neutrophils are part of the exclusion criteria. The blood tests drawn in this study in addition to what is expected from routine care is considered minimal (<4x 10 ml) – and can pose some extra burden on the patient. Storage of biological material of blood tests are not part of the present study and access material will be disposed as per routine care. The trial will be conducted in accordance with the ICH-Good Clinical Practice and the Helsinki Declaration. Written informed consent forms will be stored locally and quarantined in order not to create chains contamination.

Data access

Prior to informed consent investigators/researchers will study patient journals for laboratory results; positive COVID-19 PCR; Imaging (x-ray) status; and clinical status at admission, without sharing or recording any specific information. Then informed consent will be offered, and if accepted investigator will interview and deep dive more into the patient record to see if the patients fulfill eligibility criteria for this study, and subsequently data will be recorded as described in this protocol. After informed consent investigators, delegates, sponsors, monitors and Danish authorities might access the patient record for purposes deemed necessary for conducting, monitoring, and governing the study.
GDPR legislature will be complied with and the projects way of storing and logging data has been approved by the Danish data authorities Danish IRB/Data Approval: journal-nr.: P-2020-294 and by the local data center at the hospital CIMT.

Funding

PI took the initiative to the current study, which is a IIT (investigator initiated trial). The study is funded by 3.9 mio DKK from Lundbeck foundation to cover salaries and analysis plus administration. The Danish government kindly supplied the study drug. No funding goes directly to any of the researcher but is administrated by the hospital administrations in Capital Region of DK. Neither PI or any other in the study team has any financial connection with funding parties or any financial gain/contracts from/with Pharmaceutical companies manufacturing the drugs being tested in the current study.

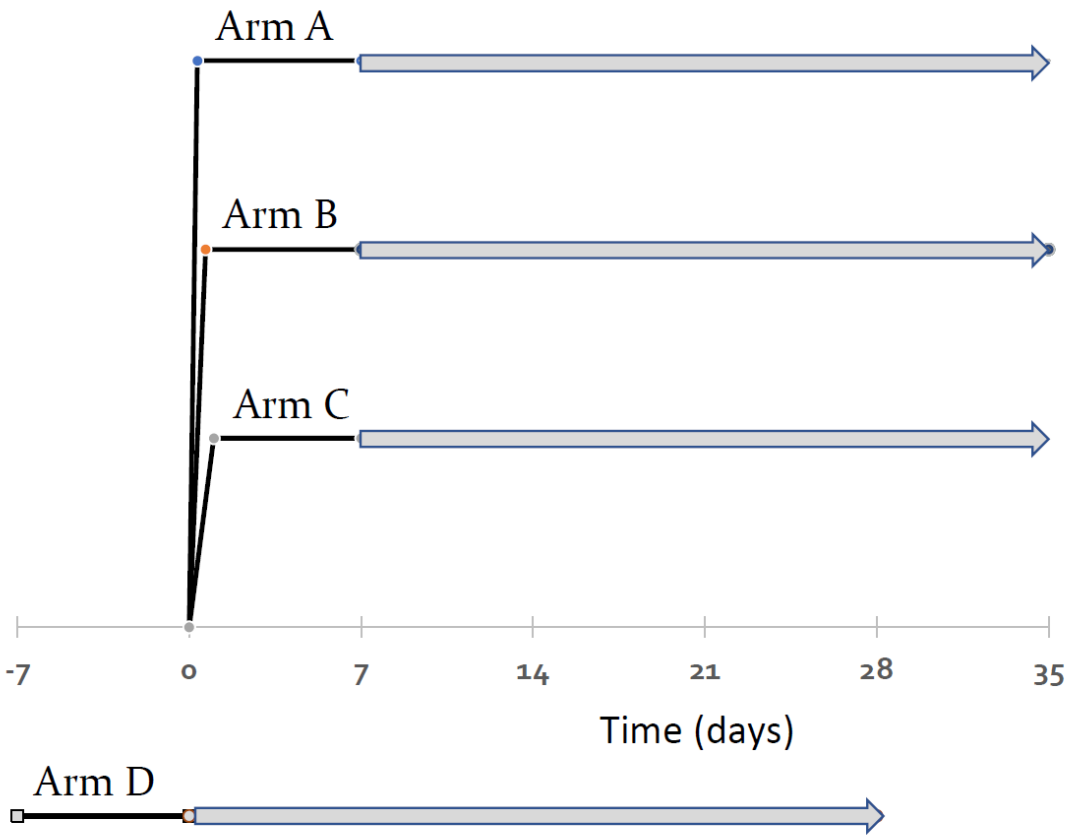
Randomization and Group Allocation Concealment

A clinician enrolling and/or consenting patients into a prospective (randomized) trial like this must believe that the available evidence does not indicate that the new intervention being studied is either superior or inferior to the existing standard treatment. However, since the consequences around the management of patients with severe SARS-CoV-2 pneumonia is so serious, an individual's equipoise can be altered by personal experience, anecdotal evidence or even by single case studies. Thus, the term clinical equipoise will be used here to reflect the views of the wider medical community, rather than the individual clinician.

Although preliminary evidence suggests a promising effect of IL-6 inhibitors (that could potentially be lifesaving), there is no consensus in the medical community. In order for patients to agree to participate in this clinical trial, they need to be well informed and understand there is equipoise, since this new mode of action (IL-6 inhibition) might shorten their need for supplementary oxygen therapy despite we do not know about any unintended adverse effects, otherwise this will inevitably result in inadequate recruitment.

Among medical researchers there is a strong believe that we need to introduce some new modes of action (e.g. IL-6 inhibitors) to reduce the mortality and the burden to society; thus when introduced

it is anticipated that all clinicians will reach out to these, in order to do more good than harm to their patients. As a consequence it has been decided by the trial steering committee that we will start by enrolling all patients during the first week of the trial to enter group *D* (comparator-control arm receiving standard of care; approximately 50 patients), which will subsequently be followed by a more rigorous trial design where the last 150 individuals will be randomly allocated on the basis of study site and "*Cluster Days*".



As illustrated in the figure, we will use SAS Proc Plan to generate the random sequence generation determining which of the three IL-6 inhibitors should be prescribed to patients (within a specific clinical site), conditioning on the specific day of the week. Participants will be randomized to treatment *A*, *B*, or *C* when enrolled: the unit of randomization is based on the specific day of recruitment (hopefully corresponding to patients as well) will be randomized in a 1:1:1 manner. The randomization will be stratified by clinical site (e.g. C_1, C_2, …., to $C5$) with a block size varying between three and six.

The study utilizes a computer-generated allocation concealment process, which ensures that the group to which the day (and thus specific patients) is allocated is not known before the day starts, and the first patient is entered into the study on the specific day. Randomization and allocation are done electronically in the e-CRF at the inclusion visit. The randomization sequence is created by an independent biostatistician (RC) using a "random number" generator, SAS statistical software. Each specific day, at each clinical center (and thus patients enrolled that day) will be given their study number and randomization group when the responsible physician "clicks" on the "enroll button," which will be available at the baseline visit. The randomization number and assigned intervention will then be visible on the screen for the local pharmacy for the rest of that specific day.

/*SAS code to illustrate a list of sequence generations over 28 random days. List like this will be performed for each center*/

```
Title 'Clinical Centr#1 out of C';
                proc plan seed=20200323;
                factors block=5 random treat=6 random/noprint;
                output out=Strat1
                treat nvals=(1 2 3 3 2 1)
                random;
run;

Title 'Days in stratum #1';
Proc print Data=Strat1;
Run;
```

Study Timeline

Approvals by authorities: 1 week
Recruitment: 4 weeks (50 patients/week)
First patient first visit: 26/03/2020
Last patient last visit: estimated calendar dates 02/06/2020

DATA owner ship:

All data gathered in the current study under this protocol is owned solely by PI (Lars Erik Kristensen) until the date of completion of study including analysis + up to 4 days – where after all data will be made publicly available in open access to the cause of greater good.

Author group for the protocol

Lars Erik Kristensen (PI), Hanne Rolighed Christensen, Celeste Porsbjerg, Christian Sylvest Meyhoff, Jesper Sonne, Birgitte Lindegaard Madsen, Zitta Barrella Harboe, Casper Roed, Tanja S Jørgensen, Marius Henriksen, Robin Christensen.

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APPENDIX:

Procedures for accountability of study medication
Ready-to-use pens containing tocilizumab or sarilumab for SC administration and vials containing tocilizumab concentrate for IV infusion will be provided to each site by the hospital pharmacy. The number of pens/vials provided will depend on the expected enrolment at each site. Upon receipt, the site will record the number of pens/vials received, the date of receipt, and the batch number(s) of each medication on a study medication log. The study medication will be stored at +2 to +8°C and protected from light in a locked cabinet and/or in a room with restricted access (dependant on the facilities at each site) until use. It will be clearly marked that the medications are for use in the current clinical study only. In addition, the three study medications will be clearly separated in order to minimise mistakes.

For each administration of study medication, the patient identifier will be recorded in the source documents, as will the dose of study medication administered, the date of administration, and the batch number of the study medication. If the planned dose for some reason was not administered, the approximate dose administered and a reason for the deviation will be recorded in the source documents. Appropriate information will be transcribed to a study medication log for reconciliation purposes.

Following administration of study medication to each patient, used vials/pens will be kept individually in separate containers (e.g., small plastic bags) and marked with patient identifier and date of administration (either on the vial/pen itself or on the bag) and saved for reconciliation purposes. After reconciliation and verification by the study monitor, used vials/pens will be discarded according to standard routines at each site.

Vejledning i opstart af il-6 receptor antagonist hos forsøgsperson.

Forprøver/undersøgelser før opstart af tocilizumab og sarilumab:

- CRP, hæmoglobin, trombocytter, leukocytter inkl. differentialtælling, ALAT, kreatinin, albumin.
- Screening for hepatitis B (HBs-antigen, HBs-antistof, HBc-antistof) og hepatitis C (anti-HCV), quantiferontest.
- HIV- kan overvejes. Med mindre disse tilstande er usandsynlige anamnestisk
- Røntgen af thorax (max 6 måneder gammelt).
- Lipidprofil (total kolesterol, LDL-kolesterol, HDL-kolesterol og triglycerider).
- Bloddyrkning
- Antibiotika dække (enligt lokal klinisk praksis – grundet forhøjet CRP
- For fertile kvinder: Der skal foreligge negativ graviditets test inden administration af il-6 receptor antagonist og der skal anvendes sikker antikonception eller abstinens fra udskrivningstidspunktet og i minimum 3 måneder frem.

DOSING and MONITORING guide

TOCILIZUMAB

Intravenous

1.Tocilizumab/Roactemra is supplied as a sterile, preservative-free solution for intravenous (IV) infusion in single use vials (USE 400 mg/20mL).

2.Do not dilute vials until after successfully obtaining intravenous access.

3. Dilute to 100 mL in 0.9% NaCl for intravenous infusion using aseptic technique.

4.Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discoloration are noted, the product should not be used. Fully diluted tocilizumab solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

5.The fully diluted tocilizumab solution for infusions should be stored at 36 – 46 degrees Fahrenheit or at room temperature and can be stored for up to 24 hours. The solution should be protected from light.

6.Tocilizumab solution does not contain preservatives; therefore, unused product remain in the vials should NOT be used.

Subcutaneous

1.Tocilizumab for subcutaneous administration is supplied as two prefilled syringe/pens which delivers 0.9ml (162 mg) of tocilizumab.

2.Remove from the refrigerator approximately 30-60 minutes prior to injection.

SARILUMAB

Subcutaneous

1.Sarilumab for subcutaneous administration is supplied as a prefilled syringe which delivers 0.9ml (162 mg) of tocilizumab.

2.Remove from the refrigerator approximately 30-60 minutes prior to injection.

MONITORING

Intravenous Tocilizumab

1.Allow the fully diluted tocilizumab solution to reach room temperature prior to infusion.
2.The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
3.Tocilizumab should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of tocilizumab with other drugs.
4.Obtain vital signs (temperature, blood pressure and pulse) upon arrival, after initiation of the infusion, upon discontinuing the infusion and before the patient departs the facility. However, if the patient has a history of prior acute infusion reaction, monitor vital signs every 10 minutes for 30 minutes and for 30 minutes after the infusion.
5.Total infusion time is 60 minutes with an additional 15 minutes to flush 20 mL of normal saline to clear the infusion line of medication.

Subcutaneous Sarilumab or Tocilizumab

1.Inject into the front of the thigh (preferred), abdomen (except for 2-inch area around the navel), or the outer area of the upper arms (if administered by a caregiver). Rotate injection sites (≥1 inch apart); do not administer into tender, bruised, red, or hard skin.

Managing Infusion Reactions

1.Acute infusion reaction can occur during the administration of tocilizumab/sarilumab or within 24 hours of infusion/injection. If the patient reports mild reactions (such as flushing, chills, etc.), slow down the IV infusion rate and assess the patient. Notify the supervising provider of the reaction.
2.For more severe reactions (such as hives, difficulty breathing, chest pain, high or low blood pressure, swelling of face and hands, fever, chills or anaphylaxis) or when mild reactions persist despite slowing the infusion, stop the infusion and treat the acute reaction. Tocilizumab should not be given to patients who have experienced anaphylaxis or other severe hypersensitivity and not re-challenged.

MONITORING After administration of all types (tocilizumab iv; sarilumab sc; tocilizumab sc)

Vitals (HR; Sat; resprate; Blood pressure and temperature) should be measured 30min and 1 hrs after. Thereafter every 6th hour until 24 hours post administration.

RETNINGSLINJE FOR INDHENTNING AF SAMTYKKE

Grundet den særlige situation der er på hospitalet i forbindelse med isolering af patienter med COVID-19 vil vi indhente samtykke fra forsøgspersonerne, på en af nedenstående måder:

1. At få en kopi af underskrevet samtykkeerklæring – fx ved brug af kamera: Forsøgspersonen kan underskrive samtykkeblanketten som vanligt. Da den underskrevne blanket herefter ikke må forlade isolationsstuen, kan underskriften dokumenteres i form af et fotografi af den underskrevne blanket, fx gennem en rude.

2 Såfremt forsøgspersonen ikke kan underskrive samtykkeerklæringen selv, fx på grund af problemer med at have elektronisk udstyr i lokalet, eller at få dokumentation for samtykket ud af lokalet, kan vidne underskrive på vegne af forsøgspersonen: Såfremt forsøgspersonen mundtligt samtykker, kan et vidne på vegne af forsøgspersonen underskrive samtykkeblanketten. Vidnet er i denne sammenhæng en person tilknyttet forsøget, dette værende investigator eller andre med specielt delegeret opgave fra investigator (de delegerede er beskrevet i en log), at indhente samtykke

For begge ovennævnte løsningsforslag gælder, at dokumentation (foto hhv. vidnesignatur) arkiveres i investigators del af Trial Master Filen (TMF). Det skal endvidere sikres, at databeskyttelsesforordningen og databeskyttelsesloven overholdes, selvom dokumentation for samtykket midlertidigt er anderledes end det plejer at være.

Vi vil forsøge mulighed 1 før mulighed 2. Såfremt situationen normaliseres, skal korrekt underskrevet samtykkeblanket indhentes fra forsøgspersonen hurtigst muligt.

1 RETNINGSLINJER FOR AFGIVELSE AF MUNDTLIG DELTAGERINFORMATION

Læger der går på afdelingen og møder patienterne i deres daglige virke tager kontakt til patienterne så snart de bliver opmærksomme på at det er en COVID-19 patient, som kunne indgå i forsøget.
Den skriftlige information uddeles til patienten på afdelingen så snart lægen er blevet opmærksom på at patienten kunne indgå i forsøget.
3-6 timer efter at patienten har modtaget den skriftlige information bliver de tilbudt en 30. minutters samtale fra behandlende læger, dette værende investigator eller delegerede (de delegerede er beskrevet i en log). Patienten får her opså oplyst at vedkommende har ret til at medbringe en bisidder.
Inden informationssamtalen træffes aftale om tid og sted for samtalen, og der oplyses om, at der er tale om en forespørgsel om deltagelse i et sundhedsvidenskabeligt forskningsprojekt.
Forsøgspersonen eller stedfortræder vil blive gjort opmærksom på, at det er muligt at medbringe en bisidder til samtalen, og der oplyses om retten til betænkningstid efter informationen.
Samtalen afholdes på isolationsstuen under rolige forhold og vil blive tilpasset den individuelles behov.
Under samtalen vil der være mulighed for, at forsøgspersonen/stedfortræder har tilstrækkelig tid til at lytte til den mundtlige information og stille spørgsmål.
Der gives en forståelig fremstilling af forskningsprojektet uden brug af tekniske eller værdiladede vendinger.
Samtalen tilpasses modtagerens individuelle forudsætninger m.h.t. alder, modenhed, erfaring m.v.,
<Hvis der inkluderes børn i forsøget indsættes følgende:
"Der inkluderes ikke børn i forsøget."
N/A
<Hvis der inkluderes unge mellem 15-17 år, indsættes følgende:
"Der inkluderes ikke unge mellem 15-17 år i forsøget". >
N/A
Samtalen tager udgangspunkt i den skriftlige deltagerinformation, og vil bl.a. indeholde oplysning om:

- Eventuelle forudsigelige risici, bivirkninger, komplikationer, ulemper, samt at der kan være uforudsigelige risici og belastninger knyttet til deltagelse i forsøget.
- Andre behandlingsmetoder (hvis forsøget også har behandlingsmæssigt sigte).
- At oplysninger fra om helbredsmæssige forhold, rent private forhold og andre fortrolige oplysninger kan videregives til og behandles af personer, som skal foretage en lovpligtig kvalitetskontrol af forsøget

- Forhold, som forsøgspersonen i øvrigt skønnes at være uvidende om, men som har betydning for forsøgspersonens stillingtagen, fx at vederlag til deltagerne er skattepligtige.
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Forsøgspersonen (eller stedfortræder) får oplyst retten til at frabede sig yderligere helbredsoplysninger. Denne mulighed er også tilgængelig på samtykkeerklæringen. **DET VIDENSKABSETISKE KOMITÉSYSTEM**

Standard udarbejdet af Det Videnskabsetiske Komitésystem, version 2, december 2011.

Forsøgspersonen/stedfortræderen har op til 24 timers betænkningstid, men det er vores opfattelse, at jo tidligere samtykke gives i processen jo bedre.

Efter informationssamtalen vil forsøgspersonen eller stedfortræder blive informeret,

- Hvis der under gennemførelsen af forsøget fremkommer nye oplysninger om effekt, risici, bivirkninger, komplikationer eller ulemper,
- Hvis forskningsprojektets forsøgsdesign ændres væsentligt i forhold til forsøgspersonens sikkerhed (gælder forsøgspersoner, der aktivt deltager i forsøget),
- Hvis der under gennemførelsen af forskningsprojektet fremkommer væsentlige oplysninger om forsøgspersonens helbredstilstand, medmindre forsøgspersonen utvetydigt har givet udtryk for, at den pågældende ikke ønsker dette,
- Om de resultater, der er opnået samt om eventuelle konsekvenser for den enkelte. Dette forudsætter, at det er praktisk muligt og forsøgspersonen ønsker dette.
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Projektidentifikation: EudraCT