

An Open-label Randomized Multicenter Study to Evaluate the Efficacy of Early Administration of Tocilizumab (TCZ) in Patients With COVID-19 Pneumonia.

Massimo Costantini,¹ Carlo Salvarani,^{2,3} Marco Massari,⁴ Silvio Cavuto,⁵ Nicola Facciolongo,⁶ Paolo Bruzzi,⁷ Fabrizio Boni,⁸ Giovanni Dolci,³ Luisa Savoldi,⁵ Luca Braglia,⁵ Caterina Turrà,⁹ Domenico Franco Merlo.⁵

¹ Scientific Director, Azienda USL-IRCCS di Reggio Emilia (Italy);

² SOC Reumatologia Azienda USL-IRCCS di Reggio Emilia;

³ Università degli Studi di Modena e Reggio Emilia;

⁴ SOC Malattie Infettive Azienda USL-IRCCS di Reggio Emilia;

⁵ SC Infrastruttura Ricerca e Statistica, Azienda USL-IRCCS di Reggio Emilia;

⁶ SOC Pneumologia, Azienda USL-IRCCS di Reggio Emilia;

⁷ SC Epidemiologia Clinica, IRCCS Ospedale Policlinico San Martino, Genova;

⁸ SOC Internistica Multidisciplinare, Ospedale Civile Guastalla, Azienda USL-IRCCS di Reggio Emilia;

⁹ SOC Farmacia Azienda USL-IRCCS di Reggio Emilia.

Corresponding author:

Massimo Costantini, MD

Scientific Director

Azienda USL-IRCCS di Reggio Emilia

Viale Umberto I, 50. 42123 Reggio Emilia (Italy)

Email: massimo.costantini@ausl.re.it

Abstract

Background

No evidence is available in support of the efficacy of any specific treatment for SARS-CoV2 infection, and the treatment is basically symptomatic, with supportive care for seriously ill patients. In severe patients infection is associated with a "cytokine storm" characterized by the increase in plasma concentrations of various cytokines, including the pro-inflammatory cytokine interleukin-6 which plays a key role in this aberrant immune response. Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the human Interleukin-6 Receptor. High levels of IL-6 are implicated in the pathogenesis of various inflammatory and autoimmune disorders. Long-term treatment with TCZ in these patients is safe and well tolerated. These observations have led to hypothesize the efficacy of TCZ in severe SARS-CoV2 infection.

Methods

This is a randomized, open label, parallel, phase 2 trial comparing early administration of TCZ in hospitalized patients with COVID-19 pneumonia to standard of care. Clinical aggravation is defined by an arterial partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio <150 at one of the arterial blood gas (ABG) measurements.

The study population includes patients with recent-onset COVID-19 pneumonia who require hospital care, but not invasive or semi-invasive mechanical ventilation, and with a $\text{PaO}_2/\text{FiO}_2$ between 200 and 300. The dosage schedule of TCZ is 8 mg/kg (maximum 800 mg) intravenously repeated after 12 hours.

The primary endpoint is defined by the appearance, within 2 weeks of randomization, of one of these 3 events: a) entry into ICU with invasive mechanical ventilation; b) death from all causes; c) clinical aggravation documented by the finding of a $\text{PaO}_2/\text{FiO}_2$ ratio $< 150\text{mm/Hg}$ at one of the ABG measurements. For a 50% relative reduction in the primary endpoint (from 20% to 10%), with a power of 80% and an alpha error of 0.05, a sample of 199 patients per group is required.

Discussion

Randomized controlled trials remain essential, also in a contest of emergency, to provide evidence-based quality care to millions of patients. Nevertheless, this could be difficult due to several factors. This is an ongoing not for profit academic trial, that has received no financial support.

Trial registration: EudraCT (2020-001386-37) and

ClinicalTrials.gov (NCT04346355). Registered 15 April 2020 - Retrospectively registered, <https://clinicaltrials.gov/ct2/show/NCT04346355?term=tocilizumab&cond=COVID&draw=2&rank=7>

Keywords COVID-19, Tocilizumab, randomized clinical trial

Background

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) is a virus of the Coronaviridae family identified for the first time at the end of 2019 which is the cause of the current epidemic of CoronaVirus Disease 19 (COVID-19). [1] The outbreak began in the Chinese city of Whuan, rapidly spread to more than 100 countries until it was declared a "public health emergency of international concern" by the World Health Organization on January 30, 2020. [2] On March 11, 2020, the WHO made the assessment that the COVID-19 a pandemic. [3] In Italy it is affecting the whole country, with the highest rate of incident cases, Intensive Care Unit (ICU) admissions and mortality in the Northern regions. As of April 30, 2020, 205,463 COVID-19 cases were recorded in Italy and 27,967 have died. In the most severe cases the infection causes interstitial pneumonia with respiratory failure which may require non-invasive or mechanical ventilation.

So far, no evidence is available in support of the efficacy of any specific treatment for COVID-19 . [4] The treatment of coronavirus infection is basically symptomatic, with supportive care in ICUs for seriously ill patients. SARS-CoV2, like the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus infection (MERS-CoV), is capable of inducing an excessive, aberrant and ineffective immune response in the host, associated with a serious lung disease, usually an interstitial pneumonia, which can lead the patient to death. [5-8] Some patients with SARS-CoV2 develop Acute Respiratory Distress Syndrome (ARDS) with a characteristic radiological picture.

In many patients with severe disease, SARS-CoV2 infection is also associated with a "cytokine storm" characterized by the increase in plasma concentrations of various cytokines, including the pro-inflammatory cytokine interleukin-6 (IL-6) which plays a key role in this aberrant immune response.[5-10] Available data from the recent literature on SARS-CoV2 infection in China have shown that this exaggerated inflammatory response represents one of the most important negative prognostic factors in these patients. A systematic review and meta-analysis on 9 studies demonstrated that patients with severe SARS-CoV2 had a significantly higher serum IL-6 levels compared to non-severe patients. [11] Given the association of elevated IL-6 with severe SARS-CoV2 and mortality, clinicians should use this as a potential marker to recognize severe disease.

In surviving patients, this excessive immune response can lead to chronic lung injury and pulmonary fibrosis with disabilities and reduced quality of life. [12,13] An in vitro study has shown that, in mouse astrocytes, the induction of IL-6 already occurs after 2 hours after infection and is closely related to viral replication. [14] It can then be hypothesized that therapies targeting cytokines involved in this excessive inflammatory response may have an important role in delaying lung damage in patients with SARS-CoV2 infection.

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the human Interleukin-6 Receptor (IL-6R) which binds to both its soluble and membrane form (sIL-6R and mIL-6R), blocking "signaling" in both IL-6R receptors. IL-6 is produced by various cell types, including monocytes and fibroblasts and is involved in numerous processes including T cells activation, acute phase protein induction, stimulation and differentiation of cell growth of hematopoietic precursors, liver proliferation, dermal and neural cells, and bone and lipid metabolism. [15] High levels of IL-6 are implicated in the pathogenesis of various inflammatory and autoimmune disorders, such as Rheumatoid Arthritis (RA), Giant Cell Arteritis (GCA), psoriasis and Castleman's disease. Long-term therapy experiences with TCZ in RA and GCA have shown that TCZ is a safe and well tolerated therapy. [16-18] Furthermore, 50-70% of patients with induced Cytokine Release Syndrome (CRS) in patients treated with Chimeric Antigen Receptor-T (CAR-T) cell therapy show a response to TCZ therapy. [19] These observations have led to hypothesize the efficacy of TCZ in severe COVID-19, and several trials are ongoing worldwide to address this hypothesis.

The general objective of this study is to evaluate whether TCZ can reduce the number of patients with SARS-CoV2 pneumonia who require mechanical ventilation. This is an objective of primary interest for patients, but also in terms of public health given the need to reduce access to ICUs.

Methods/design

The study is registered in the EudraCT database (2020-001386-37) and in the ClinicalTrials.gov Protocol Registration and Results System (NCT04346355). The main results of this trial will be published following the Consolidated Standards of Reporting Trials (CONSORT) statement [20]. The sponsor is the Azienda USL-IRCCS di Reggio Emilia, Italy.

Study aims

Primary aim

Evaluate the efficacy of TCZ administered early in patients with COVID-19 pneumonia compared to patients who receive standard therapy in the two weeks after entering the study.

Secondary aims

1. Compare the effectiveness of TCZ in terms of admission to ICU with invasive mechanical ventilation in two groups:
 - a. patients to whom TCZ is administered early as per protocol;
 - b. patients treated with standard of care and to whom TCZ can be administered at clinical worsening as rescue therapy (for an arterial partial pressure of oxygen / fraction of inspired oxygen ($\text{PaO}_2 / \text{FiO}_2$) ratio <150).
2. Compare the effectiveness of TCZ in terms of all-cause mortality in two groups:
 - a. patients to whom TCZ is administered early as per protocol.
 - b. patients to whom TCZ is administered at clinical worsening (for a $\text{PaO}_2/\text{FiO}_2$ ratio <150) or in the first 24 hours after admission to ICU.
3. Evaluate TCZ toxicity
4. Evaluate the levels of IL-6 and serum C-Reactive Protein (CRP) and their correlation with the outcome
5. Evaluate the levels of ferritin, Lactate Dehydrogenase (LDH) and D-dimer and their correlation with the outcome
6. Evaluate the progress of the $\text{PaO}_2/\text{FiO}_2$ ratio and their correlation with the outcome
7. Evaluate the trend over time of the lymphocyte count and their correlation with the outcome

Design and clinical centers

This is a randomized, open label, parallel, phase 2 trial comparing early administration of TCZ in hospitalized patients with COVID-19 pneumonia to late administration of TCZ (when COVID-19 pneumonia aggravates).

Patients allocated to the experimental arm will receive TCZ therapy within 8 hours from entering the study + standard therapy while those allocated to the control arm will receive standard therapy. In the event of clinical aggravation or entry into the ICU, patients will receive TZC. Clinical aggravation is defined by an arterial partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio <150 at one of the scheduled arterial blood gas (ABG) measurements or at an emergency measurement confirmed by a second ABG within 4 hours.

COVID-19 patients will be recruited in 24 clinical centers located in five Italian Regions: Emilia Romagna, Liguria, Lombardia, Toscana, Piemonte, and Veneto.

Study population

The study population includes patients with recent-onset COVID-19 pneumonia who require hospital care, but not invasive or semi-invasive mechanical ventilation procedures at enrolment. The inclusion criteria are:

- age > 18 years;
- Informed consent for participation in the study;
- Real time Polymerase Chain Reaction (Real-time PCR) diagnosis of Sars-CoV2 infection;
- Hospitalization due to clinical/instrumental diagnosis (high resolution chest computed tomography scan or chest x-ray or pulmonary ultrasound);
- Presence of acute respiratory distress syndrome with a $\text{PaO}_2/\text{FiO}_2$ ratio between 200 and 300 mm/Hg;
- Presence of exaggerated inflammatory response defined by the presence of at least 1 of the following criteria: at least one body temperature measurement $> 38^\circ\text{C}$ in the past two days; serum CRP greater than or equal to 10 mg/dl; CRP increase of at least twice the basal value.

The exclusion criteria are:

- Patient with acute respiratory distress syndrome with $\text{PaO}_2/\text{FiO}_2$ ratio < 200 mm/Hg or in non-invasive ventilation or in invasive ventilation or presence of shock or presence of concomitant organ failure that requires admission to the ICU;
- Severe heart or kidney failure;
- Pregnant or breastfeeding patient;
- Patient who, in the opinion of the clinician or by the patient's express will, will not go to intensive care regardless of the evolution of the lung picture;
- Known hypersensitivity to TCZ or its excipients;
- Patient being treated with immuno-depressors or anti-rejection drugs;

- Known active infections or other clinical conditions that contraindicate TCZ and cannot be treated or resolved according to the physician's judgment;
- Glutamate-pyruvate transaminase (GPT) or glutamine oxaloacetic transaminase (GOT) > 5 times the upper limit of the norm;
- Neutrophils < 500/mmc;
- Platelets < 50.000/mmc;
- Diverticulitis or intestinal perforation
- Suspicion of latent tuberculosis

Treatment protocol

Rationale for using Tocilizumab

The indications authorized in the European Union (EU) for Tocilizumab -in association with Methotrexate (MTX)- for which the drug presents efficacy and safety tests are as follows:

- treatment of severe, active, and progressive RA in adults not previously treated with MTX;
- treatment of moderate to severe active RA in adult patients who have not responded adequately or are intolerant to previous therapy with one or more Disease-Modifying Antirheumatic Drugs or Tumor Necrosis Factor antagonists;
- treatment of Systemic Juvenile Idiopathic Arthritis active in patients > 2 years who have not responded adequately to previous therapy with Nonsteroidal Anti-Inflammatory Drugs and systemic corticosteroids;
- treatment of juvenile idiopathic polyarthritis in combination with MTX;
- treatment of severe or life-threatening CRS induced by CAR-T lymphocytes (chimeric antigen receptor t cell) in adults and paediatric patients > 2 years.

For CRS, the posology indicated in the data sheet is a dose of 8 mg / kg iv in patients weighing > 30 kg (or 12 mg / kg iv in patients weighing <30 kg) from administer in 60 minutes. Each administration should not exceed 800 mg.

In the absence of clinical improvement in the signs and symptoms of CRS after the first dose, up to 3 additional doses may be administered. The interval between two consecutive doses must be at least 8 hours.

To date, there are no published clinical studies on the use of TCZ in patients with SARS-CoV2 infection, but only some very recent anecdotal evidence that seems to show the efficacy of Tocilizumab in some cases of severe lung involvement by SARS-CoV2. An independent clinical study is underway in China (Reg. No.: ChiCTR2000029765, <http://www.chictr.org.cn/showprojen.aspx?proj=49409>) aimed at demonstrating the

efficacy and safety of Tocilizumab via intravenously in patients suffering from pneumonia caused by COVID-19 with high levels of IL-6 in which the administration of TCZ is 4-8 mg / Kg iv by infusion in two infusions after 12 hours, without exceeding the total 800 mg.

Based on the mechanism of action of the drug, its possible action to contain the cytokine "storm" that seems to characterize severe SARS-CoV2 pneumonia, in which a hyper inflammatory response has a primary and negative prognostic role and the available evidence, early treatment with TCZ is hypothesized to be effective in patients with lung involvement secondary to SARS-CoV2.

Experimental therapy with TCZ. Duration, dosage, and treatment schedule

Given the little experience and in analogy with the CRS in which most of the responses occur after two administrations, the following dosage schedule will be applied to the study population:

1. Tocilizumab 8 mg/kg (maximum dose per single infusion: 800 mg) to be administered by intravenous infusion lasting 60 minutes according to the following dosage schedule:
 - 1st infusion after randomisation (for patients enrolled in the experimental arm)
 - 2nd infusion 12 hours after the first infusion

Standard of care therapy

All patients, regardless of the assignment arm, will continue to receive ongoing therapy, including that for Sars-CoV2 infection.

For the duration of the study, the following will not be allowed:

- the concomitant use of IL-1 blockers, Janus Kinase Inhibitor (JAK) inhibitors, and TNF inhibitors
- the start of the steroid in the two weeks of study. The steroid may be continued if the patient already takes a steroid at the time of hospitalization.

In case of interruption of the study due to transfer of the patient to intensive care or to clinical aggravation as per protocol, the patient can receive steroid therapy.

- in the experimental arm immediately after leaving the study
- in the control arm after the TCZ therapy foreseen by the therapeutic scheme.

Assessments

Endpoints of the study

The primary endpoint is defined by the appearance, within 2 weeks of randomization, of one of these 3 events:

- a) entry into ICU with invasive mechanical ventilation;
- b) death from all causes;

c) clinical aggravation documented by the finding of a PaO₂/FiO₂ ratio < 150mm/Hg to one of the programmed ABG measurements or to an ABG emergency measurement and confirmed by a second examination within 4 hours.

The assessment of secondary endpoints is done in the order in which the secondary objectives of the study are presented:

- 1) entry into ICU with invasive mechanical ventilation;
- 2) all-cause mortality;
- 3) toxicity measured according to internationally recognized standard.

Clinical assessments

Evaluations are scheduled in the 2 weeks of the study or until the patient leaves the study due to death, transition to intensive care or clinical aggravation.

Day 1 is the day of randomization regardless of the time it was made (00-24). Exams done for the assessment of eligibility prior to randomization can be used for day 1. The required exams are those required by the protocol. The doctor is free to prescribe additional tests at his discretion. In case of early termination of the study due to ICU transfer or clinical aggravation, the evaluations foreseen by the protocol are suspended.

Timing of the programmed arterial EGAs and laboratory evaluations are described in Table 1. During the planned days of assessments temperature, saturation and respiratory frequency will be collected for all patients.

Registration and randomisation procedures

Eligible patients will be registered in a centralized database developed by the Information Technologies Service of the Azienda USL-IRCCS of Reggio Emilia. Randomisation will take place on a competitive and balanced basis by participating clinical center. Random lists stratified by center will be prepared using permuted blocks of various sizes in random order. Randomisation will be carried out by telephone access to the Clinical Trials and Statistics Unit of the Azienda USL-IRCCS 7 days a week, 24 hours a day. This operation also determines the registration of enrolled patients.

Statistical considerations

Sample size determination

The sample size was calculated congruently with the primary objective and in accordance with the following assumptions. Null hypothesis (H_0): $\pi_{\text{ctrl}} = \pi_{\text{exp}} = 0.20$ (where π_{ctrl} and π_{exp} are the "failure" rates in the control and experimental group respectively);

1. Alternative hypothesis (H_1): $\pi_{\text{ctrl}} = 0.20$ & $\pi_{\text{exp}} = 0.10$ which corresponds to a 50% reduction;
2. Statistical test: chi-square (asymptotic);
3. two-sided test;
4. alpha error = 0.05;
5. statistical power = 0.80;
6. allocation ratio: 1: 1

Based on these assumptions, a sample of 199 patients per group is required, 398 in total.

The sample size was calculated using PROC POWER implemented in the SAS / STAT package of the SAS software, version 9.4 for Microsoft OS.

Statistical analysis

Efficacy analyses

The statistical analyses are described by aim as follow:

Primary aim:

The primary efficacy analysis will be conducted on the randomized population for the purposes set out in the primary objective, following the intention-to-treat principle.

A secondary analysis will be conducted "per protocol" for completeness and with descriptive purposes.

The failure rate of the two arms will be compared using the chi-square test (in an asymptotic form). The Rate Ratio (RR) will also be calculated, with the related bilateral 95% confidence interval, to facilitate the comparison of the rates mentioned above from a descriptive point of view.

Secondary aims:

1. the rate of patients admitted to ICU with invasive mechanical ventilation will be analysed as stated for the primary aim;
2. the all-cause mortality rate will be analysed as stated for the primary aim;
3. toxicity will be described by tables and listings;
4. Level of IL-6 will be compared between groups using the t-test for unpaired data; in case of heteroskedasticity, the test will be fixed using the Satterthwaite method. [21] The 95% 2-sided

confidence interval will be provided for the mean of each IL-6 level. The same analysis will be conducted for the C-Reactive protein.

5. Levels of ferritin, LDH and D-dimer will be analysed as stated for the level of IL-6;
6. the progress of the PaO₂/FiO₂ ratio will be evaluated using the analysis of variance for repeated measures. [22] The underlying model will be estimated by the REsidual (restricted) Maximum Likelihood (REML) method. [23,24] An unstructured R-side covariance matrix will be assumed, shifting to a simpler AR(1) structure in case of estimation troubles.
7. the trend over time of the lymphocyte count will be evaluated using the analysis of variance for repeated measures for Poisson variables. [25] The underlying models will be estimated by the Generalized Estimating Equations method. [26,27] An unstructured within-subject correlation structure will be assumed, shifting to a simpler AR(1) structure in case of estimations troubles. To effectively describe the possible trend, a regression model over time will be also estimated assuming the same correlation structure.

The conventional level of 0.05 for statistical significance will be adopted to evaluate the p-values. Statistical analysis will be carried out by using R and SAS System.

Safety analysis

Safety analyses will be performed only on the safety population defined above.

For each patient and for each type of toxicity described according to Common Terminology Criteria for Adverse Events, the worst grade found during treatment will be used for descriptive analysis. These data will be described using lists and tables.

Safety and Pharmacovigilance

Any adverse event (AE) that the Investigator becomes aware of after completing the observation and clinical evaluation period and that is judged as possibly related to the treatment must be reported until the closure of the study.

During the study, all adverse events and associated adverse events should be followed proactively. Every effort should be made to obtain a resolution for all events, even if the events continue after the interruption / completion of the study. The investigator is responsible for following all Serious Adverse Events (SAEs) until resolution, until the subject returns to basic status or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond participation. at the studio.

The reference safety information necessary to evaluate and classify an adverse reaction, based on nature and severity, including frequency, is included in the updated Investigator's Brochure for Tocilizumab and provided by the marketing authorization holder.

Data Safety Monitoring Committee (DSMC)

The study has a committee of independent experts who will evaluate the conduct of the study, the safety data and, if necessary, the critical efficacy endpoints on a weekly basis. Based on its assessment, the DSMC provides the sponsor with recommendations regarding the modification, continuation or conclusion of the study.

Discussion

This pragmatic randomized controlled trial aims to provide evidence of the effectiveness of early administration of TCZ in patients with COVID-19 pneumonia in a context of a public health emergency of unprecedented scale. The protocol was written in the second half of March 2020 following the initial lockdowns of February 21st of eleven municipalities in the Province of Lodi, Lombardy Region and the extension of March 9th to the entire country. Based on limited observational and anecdotal evidence, the study was designed by clinicians full-time involved in clinical settings, under the exponential growth of new COVID-19 cases. The study design was conceived to keep the workload of physicians and clinical staff to a minimum, with a few additional assessments to the current clinical practice.

All the work was done via tele and videoconference. Despite the rush dictated by the need to quickly draft, finalize, and approve the research protocol, we have followed rigorous research standards, including the implementation of a remote site initiation visit, a 24 hours telephone randomization service and helpdesk, the on line monitoring of the performance of the centers to check timely completion of the electronic case report forms. The study is a not for profit academic trials and has received no financial support. Hoffman la Roche has kindly provided the experimental treatment.

Randomized controlled trials remain essential, also in a context of emergency, to provide evidence-based quality care to millions of patients. Nevertheless, this could be difficult due to several factors. First, clinicians are already working extra hours and in extremely challenging situation, leaving little or no time and energies to use in research projects. Furthermore, organizing a multicenter randomized clinical trial usually takes several weeks or months: this is not compatible with the urgent need, during an epidemic, to obtain information on the efficacy of the various treatments that can be used in other patients during the same epidemic.

In addition, both internal and external pressures can affect quality and integrity of research projects. The hope for an effective care in such demanding clinical realities can easily and understandably alter scientific judgments. Literature can be difficult to evaluate and understand as it is evolving at an outstanding pace, often with quick revisions and with scientific papers sometimes highly anticipated by mass media. We were and are not immune from this pressure, but hopefully our awareness of their presence can mitigate their negative consequences. As an example, a peculiar feature of the COVID-19, affecting the design of this and other trials, is the lack of any medical treatment of proven efficacy: this, from a purely scientific perspective, would call for a placebo-controlled randomised trial with an untreated control group, but this option was not deemed practicable by the investigators because of the presumable opposition from the

patients and some Ethics Committees as well. A trial without a control group was a second option, but such a study would not allow an unbiased assessment of the efficacy of the drug under study.

The choice was to design a randomized trial in which both the experimental and the control arms continue to receive the so-called standard therapy, whichever it is, as determined by the treating physician, to which TCZ is added in the standard arm. In the control arm, TCZ is administered when a significant worsening is observed in a patient. This design was partly based also on the available, though limited, knowledge on COVID-19 pathogenesis: it has been reported that a cytokine storm can play a role in the lung damage observed in COVID-19. [10] Thus we decided to include in the trial patients with mild acute respiratory distress syndrome and with an inflammatory phenotype, hypothesizing that tocilizumab could block some inflammatory pathways in the early and intermediate stages of the disease, when lung disruption is not severe and established. The study is a not for profit academic trials and has received no financial support.

Study status

Patient recruitment started on March 31 and as of April 30 enrolled 107 patients. The study had an expected duration of enrolment of two weeks. This estimate was done according to the incidence of new cases of COVID-19 pneumonia at the time of protocol writing. At present, the marked decreasing incidence of cases does not allow to define with precision the duration of enrolment.

Abbreviations

ABG: Arterial Blood Gas

AE: Adverse Event

COVID-19: COronaVirus Disease 19

CRP: C-Reactive Protein

CRS: Cytokine Release Syndrome

GCA: Giant Cell Arteritis

GOT: Glutamine Oxaloacetic Transaminase

GPT: Glutamate-Pyruvate Transaminase

IL-6: interleukin-6

IL-6R: interleukin -6 receptor

LDH: Lactate Dehydrogenase

MERS-CoV: Middle East respiratory syndrome coronavirus infection

MTX: methotrexate

Real-time PCR: Real time Polymerase Chain Reaction

RA: Rheumatoid Arthritis

RR: Rate ratio

SAEs: Serious Adverse Events

SAR: Serious Adverse Reaction

SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus

SARS-CoV2: Severe Acute Respiratory Syndrome - Coronavirus – 2

TCZ: Tocilizumab

TNF: Tumor Necrosis Factor

JAK: Janus Kinase Inhibitor

Declarations

Ethical approval and consent to participate

This study will be conducted in full compliance with the principles of the Helsinki Declaration, or the Italian laws and regulations, whichever provides the greatest protection for the participants. In accordance with Italian law, patients should personally sign the written informed consent to the study and the authorizations to manage personal data. Specific Italian guidelines recently stated that for patients involved in COVID-19 clinical trials, the consent could be obtained orally. [28] Therefore, at the bedside, the physician will explain the study to the patient, describe known side effects and any risks involved in taking part in the study. Moreover, the physician will state that she/he is free to withdraw from the study at any time without prejudice to present and future care, without any obligation to explain the reasons. Consent will be obtained orally and a witness, present to the meeting, will sign the form declaring that the patient received the correct information and gave informed consent to the participation to the trial.

The study protocol was submitted and authorised by the Italian National Regulation Agency-AIFA (#AIFA/SC/P/35938; 27 March 2020) and approved by the Ethics Committee of the IRCCS Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, Rome (#37/2020; 27 March 2020).

Consent to publish

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was obtained for this study. The coordinator centre and all participating centres are using local resources to conduct the trial. Roche did not provide any specific support to the trial apart the furnishing of the drug and its distribution to the centres.

Authors' contributions

CS, MM, NF, FB, GD, DFM and MC conceived the study. MC, CS and DFM drafted the first version of the manuscript. SC, PB, LS and LB contributed to the statistical section of the manuscript. CT revised the pharmacological section of the manuscript. All authors read and approved the final manuscript.

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Table 1: Timing of the programmed arterial blood gas analysis (ABG) and laboratory assessments

	Days from randomisation													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Laboratory assessments ^a	•		•				•							•
Real-time PCR ^b	•		•				•							•
Interleukin-6	•		•				•							•
Procalcitonin	•													
Programmed ABG	•	•	•	•	•	•	•			•				•

^a Laboratory includes Complete Blood Count, Glutamate-Pyruvate Transaminase, Glutamine Oxaloacetic Transaminase, Bilirubin, Creatinine, Real-time PCR, interleukin-6, Lactate Dehydrogenase, Ferritin, D-dimer

^b Real-time PCR: Real time Polymerase Chain Reaction

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