BMJ Open

Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial

Rafael León López,[1,2] Sheila Cárcel Fernández ,[1,2] Laura Limia Pérez,[2,3] Alberto Romero Palacios,[4] María Concepción Fernández-Roldán,[5] Eduardo Aguilar Alonso,[6] Inés Pérez Camacho,[7] Jesús Rodriguez-Baño,[8,9] Nicolás Merchante,[10] Julián Olalla,[11] M Ángeles Esteban-Moreno,[12] Marta Santos,[13] Antonio Luque-Pineda ,[14,15] Julian Torre-Cisneros[2,3]

To cite: León López R, Fernández SC, Limia Pérez L, *et al*. Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial. *BMJ Open* 2020;**10**:e039951. doi:10.1136/bmjopen-2020-039951

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039951).

Received 01 May 2020
Revised 01 August 2020
Accepted 13 August 2020

For numbered affiliations see end of article.

Correspondence to
Antonio Luque-Pineda;
antonio.luque@imibic.org

ABSTRACT

Introduction About 25% of patients with COVID-19 develop acute respiratory distress syndrome (ARDS) associated with a high release of pro-inflammatory cytokines such as interleukin-6 (IL-6). The aim of the SARICOR study is to demonstrate that early administration of sarilumab (an IL-6 receptor inhibitor) in hospitalised patients with COVID-19, pulmonary infiltrates and a high IL-6 or D-dimer serum level could reduce the progression of ARDS requiring high-flow nasal oxygen or mechanical ventilation (non-invasive or invasive).

Methods and analysis Phase II, open-label, randomised, multicentre, controlled clinical trial to study the efficacy and safety of the administration of two doses of sarilumab (200 and 400 mg) plus best available therapy (BAT) in hospitalised adults with COVID-19 presenting cytokine release syndrome. This strategy will be compared with a BAT control group. The efficacy and safety will be monitored up to 28 days postadministration. A total of 120 patients will be recruited (40 patients in each arm).

Ethics and dissemination The clinical trial has been approved by the Research Ethics Committee of the coordinating centre and authorised by the Spanish Agency of Medicines and Medical Products. If the hypothesis is verified, the dissemination of the results could change clinical practice by increasing early administration of sarilumab in adult patients with COVID-19 presenting cytokine release syndrome, thus reducing intensive care unit admissions.

Trial registration number NCT04357860.

Strengths and limitations of this study

- Early use of sarilumab can reduce the progression of respiratory failure and prevent the saturation of intensive care units.
- The trial will study two doses of the drug. One could be selected for phase III trials with a larger sample.
- Limitations include not being a blind trial and having a limited sample size.
- The stock of sarilumab is limited in Spain. The government distributes the drug to ensure the treatment of patients with rheumatoid arthritis. Pharmacies must request authorisation for dispensation of the drug on a case-by-case basis.
- The incidence of new cases is decreasing in Spain.

INTRODUCTION

SARS-CoV-2 is the virus responsible for COVID-19. Scientific evidence on the pathogenesis of severe COVID-19, which occurs with respiratory distress, indicates that there is a disordered inflammatory response, an imbalance in the renin–angiotensin system (RAS) and a characteristic coagulopathy.[1–3] Typically, patients present lymphopenia at the expense of CD4+ and CD8+ T cells. The deregulated and aberrant immune response affects innate immunity, T-cell activation and cytokine production.[1 4] The end point of this deregulation is diffuse alveolar damage (DAD) characterised by generalised inflammation of the lung with endothelial injury, thrombosis and angiogenesis.[5]

At serum level, this deregulation translates into elevated levels of numerous cytokines

and chemokines, such as interleukin (IL)-6 (IL-6), IL-8 and tumour necrosis factor alpha (TNFα).[4] A recent meta-analysis has shown a strong correlation between IL-6 levels and the most severe forms of the disease.[6] Furthermore, there is an inverse relationship between IL-6 levels and absolute lymphocyte counts related to DAD.[7] For this reason, IL-6 blockade is considered a therapeutic target to control cytokine release syndrome (CRS) related to COVID-19.[8]

Sarilumab is a human anti-IL-6 receptor monoclonal antibody licensed for the treatment of rheumatoid arthritis. It is a safe and well-tolerated drug.[8] The most common side effects are respiratory tract infections, neutropenia, hypercholesterolemia and mild hepatotoxicity. The most serious side effects are gastrointestinal infections and perforations.[9]

This clinical trial tests the hypothesis that early blockade of IL-6 could halt the progression to severe respiratory failure in hospitalised patients infected with SARS-CoV-2. For this purpose, we investigated the efficacy and safety of early treatment with sarilumab added to standard treatment to prevent progression to severe pulmonary forms of COVID-19.

METHODS AND ANALYSIS

Design

This is a phase II, open-label, randomised, multicentre, controlled clinical trial. The patients will be assigned to three treatment groups (figure 1):

1. Control group: 40 patients will receive the best available therapy (BAT) for a maximum of 14 days.
2. Treatment group 1 (T1): 40 patients will receive BAT for a maximum of 14 days+200 mg of sarilumab subcutaneously (single dose).
3. Treatment group 2 (T2): 40 patients will receive BAT for a maximum of 14 days+400 mg of sarilumab subcutaneously (single dose).

At the time the protocol has been written, and in the absence of scientific evidence, BAT is considered any combination of drugs authorised in Spain for this indication. This variable will be taken into account in the efficacy analysis.

Study population and setting

Ten university hospitals located in Andalusia, Spain, will participate in the trial. The trial will include hospitalised patients with confirmed SARS-CoV-2 infection causing respiratory disease and presenting high serum levels of IL-6 or D-dimer (DD). Patients who meet all the inclusion criteria and have no exclusion criteria will be prospectively included in the study. Following hospital admission, patients may be randomised as soon as they meet the inclusion criteria, even in the emergency department. The inclusion and exclusion criteria for the trial are described in box 1.

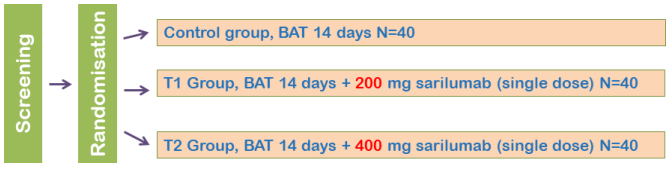

Figure 1 Flow diagram. BAT, best available therapy.

Box 1 Study selection criteria

Inclusion criteria

- Age ≥18 years and <75 years.
- Hospitalisation with COVID-19 (positive PCR in a respiratory tract simple) in absence of respiratory distress (defined as requiring high-flow nasal oxygen or mechanical ventilation).
- Interstitial pneumonia confirmed by chest radiography or CT scan.
- IL-6 levels>40 pg/mL. In the absence of IL-6, D-dimer >1500 or >1000 if progressive increments between at least two determinations are documented after admission.
- In women of childbearing age, a negative pregnancy test.
- Signed informed consent.

Exclusion criteria

- SOFA score >6 points.
- Patient who, in the researcher's opinion, is not subsidiary of invasive mechanical ventilation.
- Neutrophil count $<2\times10^3$/µL.
- Platelet count $<100\times10^9$/L.
- ALT or AST levels >5 times the upper limit of normal.
- Severe renal failure (CrCl <30 mL/min).
- Active bacterial infection.
- Active tuberculosis or history of not completing treatment against tuberculosis.
- Antecedents of diverticulitis.
- Hypersensitivity to sarilumab or its excipients.
- Treatment with TNF antagonists.
- Treatment with anti-IL6 in the previous 30 days.
- Chronic treatment (>1 month*) with corticosteroids at doses>0.5 mg/kg/day of prednisone or equivalent. Topical and inhaled corticosteroids are acceptable.
- Concomitant treatment with immunomodulators, including dexamethaxone, vitamin D or statins. Macrolides such as azithromycin are acceptable.
- Patients on immunosuppressive treatment for any cause.
- HIV-infected patients with CD4 <200/mm^3.
- Past or current history of autoimmune disease.
- Patients receiving immunomodulatory antibody therapy, including immunoglobulins.
- Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than five half-lives of the product under investigation.
- Pregnancy.
- Any other condition that, in clinical judgement, prevents the patient's adherence to the protocol.

*Based on: National Corticosteroids: Oral. NICE; 2012. Liu D *et al*, 2013.[24] Institute for Health and Clinical Excellence (NICE) Clinical Knowledge Summaries.
ALT, alanine transaminase; AST, aspartate transaminase; CrCl, creatinine clearance; SOFA, sequential organ failure assessment; TNF, tumour necrosis factor.

Withdrawal criteria

Patients may withdraw from the study at any time, for any reason and without prejudice to future medical

treatment. Patients who do not comply with the study procedure or have not been followed up will be considered a study 'withdrawal'. The reasons for withdrawal will be examined in full accordance with bioethical principles regarding the guarantee of patients' rights. The criteria for withdrawal from the study are described below.

1. Patient request.
2. Violation or deviation from the protocol (eg, breach of administration of treatment, need for prohibited treatment).
3. Researchers decision, based on clinical reasons.
4. Administrative decision of the investigators, promoter or regulatory authorities.
5. Loss to follow-up.
6. Suspected unexpected serious adverse reaction.
7. Serious adverse event that at the discretion of the promoter or investigator is not acceptable.
8. Any adverse event (AE) considered intolerable by either the patient or the investigator.
9. Pregnancy.

The inclusion and exclusion criteria can be modified in consecutive versions of the protocol, based on the scientific evidence that is published during the development of the trial, after justification and approval by the reference ethics committee.

Study variables

Outcome variables

The primary outcome variable is the development of acute respiratory distress syndrome (ARDS) requiring high-flow nasal oxygenation or mechanical ventilation, both non-invasive and invasive.

The secondary outcome variables are: all-cause (crude) mortality at day 28, time (in days) to clinical improvement, time (in days) until oxygenation improvement for at least 48 hours, proportion of patients who require invasive mechanical ventilation, negativisation of PCR to SARS-CoV-2, cytokine kinetics and side effects.

Time to clinical improvement is defined as number of days until 2 points rise in the seven category ordinal scale.

Clinical improvement will be assessed on a seven-category ordinal scale consisting of the following categories: 1, not hospitalised with the resumption of normal activities; 2, not hospitalised, but unable to resume normal activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, requiring high-flow oxygen therapy; 6, hospitalised requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation or both and 7, death.

Time (in days) until improvement in oxygenation for at least 48 hours: (1) time to verify an increase in the SpO_2/FiO_2 ratio with respect to the worst SpO_2/FiO_2 prior to treatment with sarilumab and stratified according to levels of IL-6 or DD; (2) time until the absence of oxygen need to maintain a saturation in ambient air of ≥93%; (3) number of days in need of supplemental oxygen.

Other variables

The following demographics and clinical information will be collected from all patients: age, sex, weight, height, body mass index, comorbidities, previous treatment, history of the current disease, respiratory rate (breaths/min), basal oxygen saturation (%), arterial pO_2 (mm Hg), pO_2/FiO_2 rate, oxygen saturation/FiO_2 rate, blood pressure (mm Hg), heart rate (beats/min), consciousness level, temperature (°C), clinical improvement, organ failure assessment score (sequential organ failure assessment), microbiological test, analytical parameters (haematimetry, glucose, creatinine, aspartate transaminase, alanine transaminase, C-reactive protein, albumin, lactate dehydrogenase [LDH], ferritin, troponin I, protein kinase, procalcitonin, lipid profile, IL-6, DD, prothrombin time, international normalized ratio [INR]). All concomitant medication and AEs will be recorded and monitored in accordance with regulatory procedures. SARS-CoV-2019 in nasopharyngeal swab and a panel of cytokines (IL1-α,IL1-β, IL-6, IL-8, IL-10, IL-12, IL-18, IL-38, INFγ, TNFα, CCL2, CCL3, CCL4, MIF y PAI-1) RAGE (receptor for advanced glycation endproducts), Ang-2 and protein C will be determined before randomisation and on days 5, 10, 14, 21 and 28.

Randomisation and masking

A total of 120 patients will be recruited (40 in each group). Patients who meet the selection criteria will be randomised to be included in the control group or the two experimental groups. Randomisation will be carried out by means of electronic case report forms (eCRFs). The ratio will be 1:1:1 for each group (balanced randomisation). The study design is open, but the investigator will not know the treatment assignment until the patient signs the informed consent form and randomisation is performed, thus minimising selection bias. Patients will be identified by a code that includes the centre code followed by the patient number (XX-YY).

Study medication

The investigational medication (IM) is sarilumab (ATC code: L04AC14), a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 (IL-6Rα) receptors and inhibits the transmission of IL-6 mediated signals involving signal transducer glycoprotein 130 (gp130) and activator of transcription 3 (STAT-3).

The commercial subcutaneous medication available in Spain (SANOFI-AVENTIS) will be used. Administration of the IM will be carried out according to the technical sheet and the local practice of each centre.

The BAT will include any combination of drugs included in the current protocol of the Spanish Ministry of Health (https://www.mscbs.gob.es/

Table 1 Chart of study procedures

	Study period											
	Baseline	Postrandomisation										
	Day 0	Day 1	Days 2–4	Visit 1 Day 5	Days 6–9	Visit 2 Day 10	Days 11–13	Visit 3 Day 14	Days 15–20	Visit 4 Day 21	Days 22–27	Visit 5 Day 28
Recruitment												
Review of inclusion and exclusion criteria	X											
Informed consent	X											
Randomisation	X											
Baseline data, demographics data and comorbidities*	X											
Clinical data												
Respiratory rate, saturation, applied oxygen (FiO_2) SpO_2/FiO_2 ratio	X	X	X	X	X	X	X	X	X	X	X	X
Arterial pO_2, pO_2/FiO_2 ratio	X			X		X		X		X		X
SOFA score	X	X	X	X	X	X		X		X		X
7-point ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory data												
PCR COVID-19 (nasopharyngeal swab)	X			X		X		X		X		X
Analytical parameters†	X			X		X		X		X		X
Samples for cytokine determination	X			X		X		X		X		X
Pregnancy test	X											
Drugs												
Intramuscular administration	X											
Interaction assessment, AR, SAR, SUSAR, AE, SAE	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication record	X	X	X	X	X	X	X	X	X	X	X	X
Radiological tests												
Chest X-ray or CT scan	X											
Biological samples												
Samples for Biobank	X			X		X		X		X		X

*Age, sex, weight, height, body mass index, comorbidities, previous treatment (including therapeutic family; for example, ACEI, angiotensin II receptor antagonist, statins), current disease history, BP (mm Hg), HR, levels of consciousness, temperature (°C), National Early Warning Scope.
†Haematimetry, glucose, creatinine, aspartate transaminase, alanine transaminase, C reactive protein, albumin, LDH, ferritin, troponin I, protein kinase, procalcitonin, pregnancy test (at visit 0), lipid profile, interlekin-6, D-dimer, prothrombin time, INR.
AE, adverse event; SAE, serious adverse event; SOFA, sequential organ failure assessment; SUSAR, suspected unexpected serious adverse reaction.

profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos.htm) and complementary notes issued by the Spanish Agency of Medicines and Medical Products (www.aemps.gob.es). It includes Remdesivir.

Study procedures

The duration of follow-up for each patient will be 28 days and will start from the moment the patient is randomised. A total of six visits will be scheduled during the trial: baseline, days 5, 10, 14, 21 and 28. The scheduled follow-up is shown in table 1. The visit following the end of treatment will be considered as the end-of-treatment visit. Visit 5 (day 28 after randomisation) will be considered the final study visit. The final study visit can be moved forward to the day of hospital discharge. Additionally, data on clinical improvement (on a 7-point ordinal scale), axillary temperature, oxygen saturation (or pO_2) and oxygen therapy will be collected daily.

Nasopharyngeal swabs will be performed on days 0, 5, 10, 14, 21 and 28. Plasma will also be obtained on days 0, 5, 10, 14, 21 and 28. The samples will be locally preserved (frozen at −80°C) until dispatched to the Biobank of the Reina Sofía University Hospital of Córdoba, Spain.

The principal investigator will be responsible for the detection and documentation of AE throughout the study. All AEs must be notified during all phases of the study and followed up until resolution or until an adequate explanation is found, although the patient has completed study treatment. Periodic reports will also be submitted on AEs that occurred during the study, including causality assessment, severity and intensity.

Statistical analysis

Since this is a phase II study, a sufficient number of patients are included to perform an initial analysis of efficacy and safety. We have calculated an overall sample size of 120 patients, 40 patients for each arm, to detect a 30% reduction in the primary outcome with an alpha error of 0.05, a beta risk of 0.2 and assuming that the modified intention-to-treat population will be 90% of the randomised patients.

Clinical data will be collected in an eCRF. All analyses will be performed using PASW Statistics software V.15.0 (IBM Corporation) and R software (V.3.5.0). Frequencies will be calculated for the qualitative variables and compared using the χ^2 test or Fisher's test. For quantitative variables, the mean and SD will be calculated. Normality will be analysed using the Kolmogorov-Smirnov test and comparisons will be made using the Student's t-test or the Mann-Whitney test depending on whether or not they follow a normal distribution, respectively. For the comparison of three or more groups, the analysis of variance or Kruskal-Wallis tests will be used. The analyses will be based on the intention-to treat population (randomised patients receiving treatment). The time until the primary outcome variable is reached will be plotted on a Kaplan-Meier curve and compared using a log-rank test. A Cox regression analysis will be performed for the primary efficacy variable and the results reported in terms of the HR with 95% CIs.

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

This clinical trial will be conducted in accordance with the protocol and the ethics principles of the Declaration of Helsinki (Fortaleza, 2013) and in accordance with the applicable regulatory requirements, in particular, the ICH Tripartite Guideline 'Standards of Good Clinical Practice', Royal Decree 1090/2015 regulating clinical trials with medications in Spain and Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use. The protocol, the informed consent form, the patient information form and any documents applicable to the study have required approval by the appropriate regulatory agencies. The Committee for Biomedical Research Ethics of the Reina Sofia University Hospital approved the trial. Authorisation has also been obtained from the Spanish Agency of Medicines and Medical Products (AEMPS, 20-0262). The trial is registered in accessible public databases such as the Spanish Clinical Studies Registry (REec), EUDRACT (2020-001531-27) and ClinicalTrials. gov.

DISCUSSION

Worldwide, the number of people infected with SARS-CoV-2 has continued to increase steadily to the millions. Although the vast majority of patients are asymptomatic or develop mild forms, a proportion develop severe forms of ARDS with high mortality.[9] The interaction between the virus and the immune system plays an essential role in the pathogenesis of this severe clinical presentation.[10]

To enter respiratory epithelial cells, SARS-CoV-2 spike protein (S-protein) binds to the cellular ACE2 for which the collaboration of transmembrane serine protease 2 and cathepsin B/L are required. ACE2, a carboxypeptidase widely expressed in the respiratory tract, is the cornerstone of RAS and modulates the effect of angiotensin 2 on respiratory tissue. Excess angiotensin 2 is related to immune system activity and lung thrombogenesis.[11–13] The expression of ACE2 in the respiratory epithelium differs among patients depending on their genetic factors, sex, age and lifestyle. These variables may explain the variability of the clinical expression of COVID-19.[11 14]

However, prior to the evidence on the relationship between RAS and COVID-19, it had already been observed that ARDS produced by SARS-CoV-2 was clinically similar to the CRS caused by chimeric antigen receptor T-cell therapy.[15] The overproduction of pro-inflammatory cytokines, such as IL-6, IL-2, IL-17, TNF, IL-10, IFN-γ-protein10 or macrophage inflammatory protein 1, is a clinical marker of severity with intense pulmonary inflammation and thrombus formation.[1] IL-6 plays an essential role in this pathogenesis and has attracted therapeutic interest because it can be therapeutically blocked.[14–16] There is evidence that IL-6 levels are related to mortality.[17] It is logical to think that antiviral treatment is insufficient to control immune deregulation in severe cases. The use of a humanised monoclonal antibody against the IL-6 receptor (IL-6R) has been proposed in patients with COVID-19 requiring invasive ventilation who present elevated levels of IL-6.[18] As is usual in science, there is no lack of dissenting opinions regarding this hypothesis.[19–21]

At the healthcare level, improving the management of critical patients is not sufficient. It is necessary to detect patients at risk of progression to ARDS early on and to investigate therapeutic strategies that prevent the progression of the disease. This is the only way we will be able to reduce the need for mechanical ventilation, avoid collapsing intensive care units and reduce mortality.[22 23]

Therefore, it seems rational to speculate that, if done early, blocking IL-6 could play a protective role in mitigating the elevated immune response to the virus and preventing the cytokine storm. We propose that the early use of sarilumab, in addition to standard therapy, can attenuate the detrimental host immune response in patients with elevated markers of inflammation by reducing the development

of severe respiratory failure and other organ damage. In conclusion, the SARICOR study aims to reduce the severity and mortality associated with COVID-19.

Author affiliations
[1]Intensive Care Unit, Hospital Universitario Reina Sofia, Cordoba, Andalucía, Spain
[2]IMIBIC, Cordoba, Andalucía, Spain
[3]Internal Medicine Unit, Hospital Universitario Reina Sofia, Cordoba, Andalucía, Spain
[4]Infectious Diseases Unit, Hospital Universitario de Puerto Real, Puerto Real, Andalucía, Spain
[5]Infectious Diseases Unit, Hospital Universitario Virgen de las Nieves, Granada, Andalucía, Spain
[6]Intensive Care Unit, Hospital Infanta Margarita, Cabra, Andalucía, Spain
[7]Infectious Diseases Unit, Hospital Regional Universitario de Malaga, Malaga, Andalucía, Spain
[8]Infectious Diseases Unit, Hospital Universitario Virgen Macarena, Sevilla, Andalucía, Spain
[9]Spanish Network for Research in Infectious Diseases, Carlos III Health Institute, Madrid, Comunidad de Madrid, Spain
[10]Infectious Diseases and Microbiology Unit, Hospital Universitario Virgen de Valme, Sevilla, Andalucía, Spain
[11]Internal Medicine Service, Hospital Costa del Sol, Marbella, Andalucía, Spain
[12]Infectious Diseases Unit, Complejo Hospitalario Torrecardenas, Almeria, Andalucía, Spain
[13]Infectious Diseases Unit, Hospital Universitario de Jerez de la Frontera, Jerez de la Frontera, Andalucía, Spain
[14]Clinical Trials Unit, IMIBIC, Cordoba, Spain
[15]Hospital Universitario Reina Sofia, Cordoba, Andalucía, Spain

Acknowledgements We gratefully acknowledge the collaboration of Aurora Paez, José Carlos Garrido and Jesús Fernández from the Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)/Reina Sofía University Hospital/University of Córdoba. JRB and JTC have received support from the Spanish Network for Research in Infectious Disease (REIPI, RD16/0016). ALP is supported by SCReN (Spanish Clinical Research Network) funded by the ISCIII-Sub-Directorate General for Research Assessment and Promotion through project PT13/0002/0010-PT17/0017/0012 and PT17/0017/0032.

Contributors JT-C, RLL and AL-P collaborate in the design of the protocol and the informed consent form.The protocol was reviewed and agreed with SCF, LLP, ARP, MCF-R, EAA, IPC, JR-B, NM, JO, MAE-M and MS, who contributed in the definition of the eligibility criteria. JT-C contributed in the refinement, final review and approval of the protocol and the informed consent form.

Funding COVID-19 Research Programme. Ministry of Health and Families, Regional Government of Andalusia. Project code COVID-0013-2020.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Sheila Cárcel Fernández http://orcid.org/0000-0002-8102-9520
Antonio Luque-Pineda http://orcid.org/0000-0002-4353-3662

REFERENCES

1 Wang J, Jiang M, Chen X, *et al*. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. *J Leukoc Biol* 2020;108:17–41.
2 Hamming I, Timens W, Bulthuis MLC, *et al*. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
3 Cheng H, Wang Y, Wang G-Q. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol* 2020;92:726–30.
4 Laing AG, Lorenc A, Barrio DMD I, *et al*. A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nat Med* 2020.
5 Ackermann M, Verleden SE, Kuehnel M, *et al*. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–8.
6 Henry BM, de Oliveira MHS, Benoit S, *et al*. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020;58:1021–8.
7 Li S, Jiang L, Li X, *et al*. Clinical and pathological investigation of patients with severe COVID-19. *JCI Insight* 2020;5:e138070.
8 Ascierto PA, Fox BA, Urba WJ, *et al*. Insights from immuno-oncology: the Society for immunotherapy of cancer statement on access to IL-6-targeting therapies for COVID-19. *J Immunother Cancer* 2020;8:e000878.
9 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
10 Sarzi-Puttini P, Giorgi V, Sirotti S, *et al*. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol* 2020;38:337–42.
11 Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020;81:537–40.
12 Vaduganathan M, Vardeny O, Michel T, *et al*. Renin-Angiotensin-Aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;382:1653–9.
13 Zhang X, Li S, Niu S. Ace2 and COVID-19 and the resulting ARDS. *Postgrad Med J* 2020;96:403–7.
14 Benetti E, Tita R, Spiga O, *et al*. Ace2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population. *Eur J Hum Genet* 2020;17:1–13.
15 Cytokine storm drugs move from CAR T to COVID-19. *Cancer Discov* 2020;10:OF8.
16 Köhler BM, Günther J, Kaudewitz D, *et al*. Current therapeutic options in the treatment of rheumatoid arthritis. *J Clin Med* 2019;8:938.
17 Chen X, Zhao B, Qu Y, *et al*. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin Infect Dis* 2020:ciaa449.
18 SIMIT. *Interpretation of "New Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Version 7)" 2020.Vademecum per la cura delle persone con malattia da COVI-19*. 39. SIMIT, 2020.
19 Maggi E, Canonica GW, Moretta L. COVID-19: unanswered questions on immune response and pathogenesis. *J Allergy Clin Immunol* 2020;146:18–22.
20 Sinha P, Matthay MA, Calfee CS. Is a "Cytokine Storm" Relevant to COVID-19? *JAMA Intern Med* 2020.
21 Wilson JG, Simpson LJ, Ferreira A-M, *et al*. Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis. *JCI Insight* 2020;5.
22 Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *JAMA* 2020;323:1499–500.
23 Xie J, Tong Z, Guan X, *et al*. Critical care crisis and some recommendations during the COVID-19 epidemic in China. *Intensive Care Med* 2020;46:837–40.
24 Liu D, Ahmet A, Ward L, *et al*. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9:30.