Phase I Clinical Trial. Safety of Baricitinib to prevent respiratory insufficiency in oncohematological patients affected by Coronavirus Disease-19: BARCOVID19 study

Gabriela Sanz-Linares
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L’Hospitalet de LL, Spain

Alberto Mussetti
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Adalia Albasanz-Puig
Hospital Universitari de Bellvitge - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain, Spain - Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Inst

Ifaki Salvador
Hospital Universitari de Bellvitge - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain, Spain

Anna Sureda
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Carlota Gudiol
Hospital Universitari de Bellvitge - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain, Spain - Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Inst

Ramon Salazar
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Mar Marin
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Margarita García
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Valentín Navarro
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Irma De la Haba
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Eva Coma
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Xavier Dura
Hospital Universitari de Bellvitge - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain, Spain

Sandra Fontanals
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Gala Serrano
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Claudia Cruz
Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Rafael Mañez
Hospital Universitari de Bellvitge - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain, Spain - Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Inst

Gabriel Moreno-González ( gabriel.moreno@bellvitgehospital.cat )
Hospital Universitari de Bellvitge - Catalan Institute of Oncology - Bellvitge Biomedical Research Institute, L´Hospitalet de LL, Spain

Article

Keywords: COVID-19, SARS-CoV-2, baricitinib, JAK inhibitors, therapeutics strategies, oncohematological, immunosuppression
Abstract

Background

Oncohematological patients, due to their secondary immunodeficiency, are at a higher risk of mortality related to COVID-19 infection. Baricitinib, a JAK2 inhibitor, has a dual effect in this context, reducing the inflammatory response to the virus and diminishing virus endocytosis.

Methods

This phase I safety run-in cohort study aimed to determine the dose-limiting toxicity of baricitinib in terms of the rate of serious events in oncohematological patients with COVID-19. The drug was administered on an inpatient basis at an oral dose of 4 mg daily for 5 to 7 days, associated with the institutional standard of care (SOC).

Results

Six patients with solid tumors or hematological malignancies were enrolled in the study. Sixty percent of the patients received active anticancer treatment at the time of inclusion. Lymphopenia and elevation of acute-phase reactants were the most frequent laboratory findings that improved during the treatment course. All patients received corticosteroids, but only 3 of them received remdesivir as the SOC. The most common adverse events were bacterial infections, including pneumonia, urinary tract infections, and bacteremia. The mortality rate due to disease progression and respiratory insufficiency is 33%. The severe adverse event rate was less than 33%, with no adverse events or mortality caused by baricitinib.

Conclusions

The results of the present study demonstrate that baricitinib is a safe treatment for patients with oncohematological diseases and COVID-19. However, its efficacy and superiority to standard treatment will require further testing in phases 2 and 3 trials.

Trial registration:

AEMPs: 20–0356 EudraCT: 2020-001789-12

Background

Severe acute respiratory coronavirus 2 or SARS-CoV2 is the cause of the coronavirus disease (COVID-19). Patients with this disease may have diverse presentations, with respiratory symptoms being the most frequent. These symptoms may vary from an incidental finding in an asymptomatic patient to a lower respiratory tract infection that can progress with an aggressive inflammatory response and vascular permeability in the lung tissue, inducing severe acute respiratory distress syndrome (ARDS) and respiratory failure with a high mortality rate.1–3

During the first month of the global pandemic, COVID-19 had a mortality rate of 28% in patients receiving anticancer therapy, more frequently in those diagnosed with gastrointestinal, breast, and lung cancer, and in patients with hematological malignancies.4

Although the mortality rate between oncological and hematological patients was considerable, slight differences were observed. In the oncology population, the overall mortality rate varies between 24% and 29%, reaching the highest peak (47%) among patients presenting with ARDS,5–7 whereas, in the hematological population, it varies between 29–46%, with a mortality rate of 39% among those needing hospitalization.8–10

It is noticeable that during this pandemic, the mortality rate has diminished, either in the context of vaccination, new target treatments or the changes of the virus strains. In the OnCovid registry, the case fatality rate estimated in the period from February to March 2020 was 29.8%, whereas in January-February 2021, it was only 14.5%.11 However, better treatment strategies are needed.

Artificial intelligence based on knowledge of previous coronavirus outbreaks and informatics algorithms that cross-reference information about antiviral or immunomodulatory drugs, proposed baricitinib, a reversible Janus-associated kinase 1 and 2 (JAK) inhibitor, as a
promising option.\textsuperscript{12–14} It combines an immunomodulatory effect and antiviral activity, theoretically preventing endocytosis and viral assembly.\textsuperscript{15}

Previous publications showed baricitinib as a safe option at least in the general population, that could improve the outcome in patients with COVID\textsuperscript{19,16,17}. To inquire about this issue, we designed a phase I/II clinical trial to evaluate its potential role in preventing the progression of respiratory insufficiency in those patients.\textsuperscript{18} Here, in this article, we evaluate the safety of the use of baricitinib in oncohematological patients with COVID-19.

**Methods**

The complete protocol was previously published,\textsuperscript{18} and can be summarized as follows:

1. **Characteristics of participants**: This study was conducted at the Institut Català d’Oncologia (L'Hospitalet de Llobregat, Catalonia Region, Spain). The inclusion and exclusion criteria were reviewed in a previous publication.\textsuperscript{18} All patients must have a laboratory-confirmed SARS-CoV-2 infection by quantitative reverse transcriptase polymerase chain reaction (PCR).

2. **Aim, design, and setting of the study**: the study design of the Phase I safety run-in cohort is shown in Fig. 1. This phase included six to twelve patients.

   If 3 or more severe adverse events (SAEs) were registered in the first 6 patients enrolled with a dose of 4 mg once a day (OID), the dose would be reduced to 2 mg OID, requiring the inclusion of 6 more patients.

   In cases where only two SAEs were registered, 6 more patients would be included with a 4 mg OID dose, and finally, these 12 patients would be evaluated for the presence of SAEs. If 3 or more SAEs were present in this new cohort of 12 patients, the dose would be reduced to 2 mg OID, and if only 2 SAEs were registered, the 4 mg OID dose would be maintained.

   Given that a reduction in the dose (2 mg OID) was needed, if 3 or more SAEs were registered, the study would be stopped, concluding that the drug was not safe in this population. If only 1 or 2 SAEs occur in the cohort of 12 patients, a 2 mg dose will be considered secure.

   The minimum duration of therapy was five days, allowing extended treatment to seven days, depending on the clinical benefit. The SOC included individualized antibiotics based on clinical suspicion, including the management of febrile neutropenia, prophylaxis of thromboembolic disease administered to all participants except if contraindicated due to thrombocytopenia, remdesivir administration only in patients with severe pneumonia (O\textsubscript{2} saturation < 94%) with less than 7 days of onset of symptoms and with supplemental oxygen requirements but not using a high-flow nasal cannula, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). All patients were evaluated daily, although laboratory tests (blood analysis, chest radiography, and microbiological samples) were performed on days 0, +2, +7, and +14.

   The study protocol was reviewed and approved by the Bellvitge University Hospital Research Ethical Committee with the number AC014/20 on October 22nd, 2020, according to the good clinical practices (CPMP/ICH/135/1995), and the current legislation that regulates its operation. All patients signed informed consent according to the Declaration of Helsinki.

3. **Outcomes and statistical analysis**: The primary objective was to determine the dose-limiting toxicity of baricitinib in terms of the rate of drug-related serious adverse events (AE). These were classified according to the Common Terminology for Adverse Events version 5.0 (CTCAE).\textsuperscript{19} An incidence of severe AE grades 3–4 CTCAE inferior to 33% will be considered sufficient to follow with the next part of the study.

**Results**

The total sample consisted of six patients (one female and five males), with a median age of 66 years (range 57–79), who attended our institution between December 29, 2020, and March 25, 2021. Three patients had solid tumors, and three patients had hematological diseases. The demographic data are shown in Table 1.
<table>
<thead>
<tr>
<th>Demographic data.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>66.6 (57–79)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (83.33%)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td><strong>Karnofsky Performance Status Scale, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>2 (33.33%)</td>
</tr>
<tr>
<td>70</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>60</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td><strong>Active neoplasms, n (%)</strong></td>
<td>2 (33.33%)</td>
</tr>
<tr>
<td>Acute myeloid leukemia – High risk</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Undifferentiated non-small cell lung carcinoma (stage IV)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Rectal adenocarcinoma (stage IV)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (Rai III – Binet C)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Colon adenocarcinoma (stage IV)</td>
<td></td>
</tr>
<tr>
<td><strong>Active anticancer therapy (at least 1 cycle before infection), n (%)</strong></td>
<td>2 (33.33%)</td>
</tr>
<tr>
<td>None</td>
<td>3 (50.00%)</td>
</tr>
<tr>
<td>Chemotherapy + monoclonal antibodies</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Protein kinase inhibitor + monoclonal antibodies</td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy, n (%)</strong></td>
<td>5 (83.33%)</td>
</tr>
<tr>
<td>No</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Screening serology, n (%)</strong></td>
<td>6 (100%)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>HSV-2</td>
<td>4 (66.66%)</td>
</tr>
<tr>
<td>VZV</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>EBV</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>CMV</td>
<td>5 (83.33%)</td>
</tr>
</tbody>
</table>

HSV-1: Herpes simplex virus type 1. HSV-2: Herpes simplex virus type 2. VZV: Varicella zoster virus. EBV: Epstein-Barr virus. CMV: Cytomegalovirus.

AML risk-stratification according to Döhner et al, 2017.24

CCL Risk-stratification according to Rai and Binet classification, Hallek, 2019.25

Four patients (66%) received chemotherapy or immunotherapy at the time of infection, and only one patient (16%) received radiotherapy. The patients received active treatment with pembrolizumab, pemetrexed, and carboplatin for non-small-cell lung carcinoma (1); bimetinib, encorafenib, and cetuximab for rectal adenocarcinoma (1); ibrutinib-ofatumumab for chronic lymphoblastic leukemia (1); and panitumumab, oxaliplatin, and fluorouracil for colon adenocarcinoma (1).
The whole population had a positive PCR for SARS-CoV2 and negative PCR for other viruses, such as influenza and respiratory syncytial virus. The patients had a median basal oxygen saturation of 90% (range, 86–98%). At the time of inclusion, oxygen supplementation was administered through a nasal cannula or Venturi mask in four out of six patients.

As shown in Table 2, the laboratory findings included lymphopenia with elevated acute-phase reactants, such as lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin. All the patients had a normal renal function and no kidney disease parameters. Chest radiography showed bilateral infiltrates compatible with viral infection in all cases.

<table>
<thead>
<tr>
<th>Table 2: Biological and laboratory parameters</th>
</tr>
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<tbody>
<tr>
<td>Day of Inclusion</td>
</tr>
<tr>
<td><strong>Respiratory, n (range)</strong></td>
</tr>
<tr>
<td><strong>Basal oxygen saturation %</strong></td>
</tr>
<tr>
<td><strong>Hematology, n (range)</strong></td>
</tr>
<tr>
<td><strong>Absolute lymphocytes count x 10E9/L</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin g/L</strong></td>
</tr>
<tr>
<td><strong>Platelets x 10E9/L</strong></td>
</tr>
<tr>
<td><strong>LDH: Lactate dehydrogenase. CRP: C-reactive protein. IL: interleukin. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase.</strong></td>
</tr>
</tbody>
</table>

After confirming that all patients met the inclusion criteria and none of the exclusion criteria, baricitinib (4 mg) was initiated. SOC treatment was administered according to the local SARS-CoV2 protocol and was reviewed by an infectious disease specialist. Including the following Dexamethasone (6 mg orally for 6 days), remdesivir (200 mg intravenously on day + 1 and 100 mg intravenously from day + 2 to day + 5), and tocilizumab (600 mg single dose if > 75 kg or 400 mg single dose if < 75 kg) were administered. Dexamethasone was administered to the whole population, but only three patients required remdesivir, while none required tocilizumab.

On day + 2, none of the patients showed signs of acute renal or liver failure (Table 2). This allowed the patients to continue baricitinib treatment at the same dose. All patients received treatment until day + 7, according to the principal investigator. Only one patient required support with a high-flow nasal cannula on day + 3 of baricitinib treatment, with subsequent worsening of respiratory symptoms.

On day + 14, a decrease in the mean values of inflammatory parameters was observed.

The most common AE were bacterial-associated infections (5 of 6 patients), including bilateral bacterial pneumonia (3 patients), urinary tract infection (1 patient), bacteremia (1 patient), or bronchial prosthesis infection (1 patient). Treatment with piperacillin-tazobactam, amoxicillin-clavulanic acid, and ceftriaxone was administered according to the microbiological results, as summarized in Table 3.
Table 3
Adverse events and related treatment.

<table>
<thead>
<tr>
<th>CASE</th>
<th>ADVERSE EVENTS</th>
<th>CT-CAE GRADE*</th>
<th>BARICITINIB RELATED</th>
<th>SPECIFIC COVID-RELATED TREATMENT</th>
<th>SUPPORT TREATMENT</th>
<th>HOSPITAL STAY (days)</th>
<th>DEATH</th>
<th>CAUSE OF DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E. coli urinary tract infection</td>
<td>G3</td>
<td>NO</td>
<td>Prednisone (from day +1)</td>
<td>Ceftriaxone</td>
<td>11</td>
<td>YES</td>
<td>POD</td>
</tr>
<tr>
<td></td>
<td>K. pneumoniae bilateral pneumonia</td>
<td>G3</td>
<td>NO</td>
<td></td>
<td>Cefepime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>G2</td>
<td>NO</td>
<td></td>
<td>General measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>POD</td>
<td>G5</td>
<td>NO</td>
<td></td>
<td>Palliative care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Enterococcus faecium bacteremia</td>
<td>G2</td>
<td>NO</td>
<td>Dexamethasone day +1)</td>
<td>Teicoplanin</td>
<td>43</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deep venous thrombosis</td>
<td>G2</td>
<td>NO</td>
<td></td>
<td>No treatment due to thrombocytopenia.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bronchial prosthesis infection (Corynebacterium striatum)</td>
<td>G2</td>
<td>NO</td>
<td>Remdesivir and Dexamethasone (day +2)</td>
<td>Teicoplanine + piperacillin-tazobactam</td>
<td>15</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemoptysis</td>
<td>G2</td>
<td>NO</td>
<td></td>
<td>Amchafibrin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Bilateral pneumonia</td>
<td>G3</td>
<td>NO</td>
<td></td>
<td>Piperacillin-tazobactam</td>
<td>26</td>
<td>YES</td>
<td>Respiratory insufficiency</td>
</tr>
<tr>
<td></td>
<td>Respiratory insufficiency</td>
<td>G4</td>
<td>NO</td>
<td>Remdesivir (day +1) and dexamethasone (day +2)</td>
<td>High-flow nasal cannula support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bilateral pneumonia</td>
<td>G3</td>
<td>NO</td>
<td>Dexamethasone (day +1)</td>
<td>Amoxicillin-clavulanic</td>
<td>11</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NONE</td>
<td></td>
<td></td>
<td>Remdesivir (day +1) and Dexamethasone (day +2)</td>
<td></td>
<td>11</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>

AML: Acute Myeloid Leukemia. CLL: Chronic Lymphocytic Leukemia. POD: progression of the disease.

CT-CAE: Common Terminology Criteria for Adverse Events v5.19

The deep venous thrombosis described in Case 2 (Table 3) was justified by the presence of a peripherally inserted central catheter (PICC), which was not attributable to the investigational drug. Heparin was not administered because of low platelet levels. No other thrombotic complications were observed during the hospital stay.

As none of the AE were directly attributed to baricitinib, the incidence of AE and SAE due to the drug was considered to be less than 33%.

Two of six patients died, with a mortality rate of 33%. The first patient diagnosed with acute myeloid leukemia presented with oncological disease progression, and palliative care treatment was initiated at the patient's discretion. The second patient presented with respiratory insufficiency, even with a high-flow nasal cannula, and given the advanced stage of his oncologic disease, no further treatment was administered. None of the mortality cases were directly attributed to the study drug.

**Discussion**

During this pandemic, the incidence of mortality has diminished, as shown in some studies. Immunocompromised patients continue to be a high-risk population, especially those with no serological response to vaccines.11 The worldwide epidemiological situation during the COVID-
19 pandemic led to drug repurposing, allowing testing of different medicines for the treatment of this disease. Baricitinib was identified as a potential treatment in this setting, given its potential to interrupt the intracellular assembly of the virus and reduce inflammation in ARDS.

Nevertheless, despite its potential benefits, baricitinib itself may cause infectious side effects, as described in previous studies in rheumatologic patients, especially herpes zoster virus reactivation. Other side effects include thrombosis, gastrointestinal perforation, and major cardiovascular events.

Studies of baricitinib have shown interesting results. In a pilot study on baricitinib safety, combined with lopinavir/ritonavir, non-serious adverse effects were observed, except transaminase elevation in one patient due to the antiviral treatment received. The same group reported a statistically significant decrease in the fatality rate and intensive care unit (ICU) admissions, and a higher discharge rate in a cohort of patients treated with baricitinib plus lopinavir/ritonavir compared to a cohort treated with hydroxychloroquine plus lopinavir/ritonavir.

Another study conducted on patients diagnosed with COVID-19 pneumonia and oxygen requirements treated with baricitinib (2–4 mg OID) and hydroxychloroquine (200–500 mg ODI) showed a reduction in inflammatory parameters such as C-reactive protein (CRP) and improved patients’ oxygen requirements and symptoms, leading to recovery in 80% of patients.

Investigators from the ACTT-2 study group concluded that baricitinib in combination with remdesivir was superior to remdesivir alone in reducing recovery time and improving clinical status, particularly among patients with oxygen supplementation requirements. In this study, 4% of the patients in the experimental group and 3% in the control group were oncologic patients.

The COV-BARRIER study showed that baricitinib, in addition to SOC (including dexamethasone and remdesivir), had a statistically significant reduction in mortality in hospitalized adults with COVID-19, although no significant reduction in overall disease progression was observed.

Although these previous studies concluded that baricitinib is a safe option, diminishing the probabilities of fatality rates and ICU admission, oncologic patients were underrepresented, and no specific safety trial has been conducted on this population.

All the patients enrolled in our study had oncohematological diseases, and most of them were receiving active treatment. Baricitinib was administered for seven consecutive days without dose adjustment due to renal or hepatic failure, concomitant interactions with cancer therapy, or unacceptable adverse events.

Although patients had G3 to G5 AE, as described above, none of them could be identified as AE of the study drug. Concomitant infections were attributed to immunosuppression caused by the underlying disease, active oncological treatment, or an established association between SARS-CoV2 infection and bacterial pneumonia.

Four of six patients received oxygen support at the time of diagnosis. Complete withdrawal was possible in two of them. One patient continued with the same oxygen support until death due to comfort with palliative care, and only one patient presented with progression of respiratory symptoms, with consequent decease.

Given that the drug-related SAE percentage is less than 33%, baricitinib is considered a safe option for oncological patients. The original study design was intended to continue with an open-label, phase II randomized trial to evaluate the efficacy of the drug in this population. Nevertheless, recruitment had to be stopped due to a lack of patients and logistical reasons. Considering that baricitinib is currently used alone or in association with other drugs for COVID19 infection, it is fundamental to show that this drug can be administered safely to oncohematological patients.

This study had some limitations. Initially, it was intended to be a Phase I/Phase II cohort, but due to some schedule delays, a sudden decrease in oncohematological patients with severe COVID19 avoided following with the subsequent phase 2 of the study. Being a small cohort, we cannot ensure that there are no interactions with other anticancer treatments not present in this cohort, which may have led to different results.

In summary, our study demonstrated that baricitinib could be safely administered to oncohematological patients to treat moderate-to-severe COVID-19. Further studies with larger populations are needed to evaluate the benefits of its use in this scenario.

List Of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
</tbody>
</table>
Declarations

Data Access Statement: Data supporting this study are included within the article and/or supporting materials.

Ethics approval and consent to participate: the study protocol was reviewed and approved by the Bellvitge University Hospital Research Ethical Committee with the number AC014/20 on October 22nd, 2020, according to the good clinical practices (CPMP/ICH/135/1995), and the current legislation that regulates its operation. All patients signed informed according to the Declaration of Helsinki.

Consent for publication: not applicable.

Availability of data and materials: data supporting this study are included within the article.

Competing interests: the authors declare that they have no competing interests.

Funding: the study creation was supported from an institutional crowd funding initiative through different media: twitter channel (@ICOnoticies), regional radio and television interviews. Further information can be found at www.contraelcoronavirus.org/ico.

Authors’ contributions: GM designed the study. GSL, AM, and GM drafted the manuscript. All authors participated in the revision and approved the final manuscript.

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Trial Registration: the study was approved by the European clinical trial with EudraCT number 2020-001789-12 and the Spanish Medical Agency (AEMPs) with number 20-0356.

References


Figures
Figure 1

See image above for figure legend.