Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pembrolizumab in combination with tocilizumab in high-risk hospitalized patients with COVID-19 (COPERNICO): A randomized proof-of-concept phase II study

Matilde Sánchez-Conde[a,b,c,#], Pilar Vizcarra[a,b,c,#], José Manuel Pérez-García[d,e], María Gion[f], María Pilar Martialay[g], Javier Taboada[h], Alberto Alonso-Fernández[i,j,k], Miguel Sampayo-Cordero[e], Andrea Malfettone[e], Isabel Tena[e], Sergio De La Torre[l], Antonio Llombart-Cussac[e,m,n], Javier Cortés[d,e,l,*]

[a] Hospital Universitario Ramón y Cajal; Instituto de Investigación Biomédica del Hospital y Ramón y Cajal, Madrid, Spain
[b] Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain
[c] Centro de Investigación Biomédica en Red de Enfermedades Infecciones (CIBERINFEC), Madrid, Spain
[d] International Breast Cancer Center (IBCC), Quirónsalud Group, Barcelona, Spain
[e] Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain
[f] Hospital Universitario Ramón y Cajal, Madrid, Spain
[g] Complejo Hospitalario Ruber Juan Bravo, Quirónsalud, Madrid, Spain
[h] Hospital Ruber Internacional, Quirónsalud, Madrid, Spain
[i] Servicio de Neumología, Hospital Universitario Son Espases, Palma de Mallorca, Spain
[j] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain
[k] Instituto de Investigación Sanitaria de las Islas Baleares (IdISBa), Palma de Mallorca, Baleares, Spain
[l] Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain
[m] Hospital Arnau de Vilanova, FISABIO, Valencia, Spain
[n] Universidad Católica, Valencia, Spain

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ABSTRACT

Objectives: Severe COVID-19 is associated with immune dysregulation and hyperinflammation (lymphocyte exhaustion and elevated interleukin 6. Pembrolizumab (P; immune-activating anti-programmed cell death-1 antibody) plus tocilizumab (TCZ; anti- interleukin 6 receptor antibody) might interrupt the hyperinflammation and restore cellular immunocompetence. We assessed the efficacy and safety of P + TCZ + standard of care (SOC) in high-risk, hospitalized patients with COVID-19 pneumonia without mechanical ventilation.

Methods: Randomized, controlled, open-label, phase II trial in patients with severe SARS-CoV-2 infection to assess the hospitalization period to discharge.

Results: A total of 12 patients were randomized (P + TCZ + SOC, n = 7; SOC, n = 5). Nine (75%) were males, with a median age of 68 (41-79) years. The median time to discharge for P + TCZ + SOC and SOC was 10 and 47.5 days ($P = 0.03$), with zero (n = 1 patient had P-related grade 5 myositis) and two COVID-19-related deaths, respectively.

Conclusion: The addition of P and TCZ to SOC reduced the hospitalization period, with higher and faster discharges without sequelae than SOC alone.

Introduction

The rapid spread of an enveloped RNA betacoronavirus (2019) (Lu *et al.*, 2020), SARS-CoV-2 (Guan *et al.*, 2020), causing COVID-19, led to a global pandemic (declared by the World Health Organization [WHO] on March 11, 2020) (World Health Organization

* Corresponding author at: International Breast Cancer Center (IBCC), Quirónsalud Group, Carrer de Vilana, 12, Barcelona 08022, Spain.
E-mail address: jacortes@vhio.net (J. Cortés).
# These authors shared first authorship.

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[WHO], 2020a), with more than 266 million cases and 5 million deaths worldwide (WHO, 2021).

The clinical spectrum of patients with COVID-19 appears to be broad, and its severity is unclear, with the SARS-CoV-2 infection and the host response contributing to disease severity (Kwon *et al.*, 2020). Among patients with COVID-19, approximately 80% show asymptomatic infection or mild upper respiratory tract illness, 13.8% develop severe viral acute respiratory distress syndrome (ARDS) (Fan *et al.*, 2017), and a critical group (6.1%) of patients also develop respiratory failure, septic shock, multiorgan dysfunction/failure, cytokine release syndrome, and even death. The mortality rate of hospitalized patients with severe COVID-19 ranges from 22 to 62% (Huang et al., 2020; Ioannou *et al.*, 2020; Wang *et al.*, 2020).

COVID-19 management comprises multiple treatments, some currently used in clinical practice and others still in clinical development, based on the recent WHO interim guidance (WHO, 2020b). However, the optimal management of hospitalized patients with severe COVID-19 with ARDS not requiring mechanical ventilation represents an unmet clinical need (Stasi *et al.*, 2020).

COVID-19 disease has tremendous inflammatory involvement; the inflammatory marker interleukin 6 (IL-6) (Ruan *et al.*, 2020) could play an important role in the COVID-19-induced cytokine storm associated with ARDS (Ruan *et al.*, 2020), with relevant therapeutic implications (Santa Cruz *et al.*, 2021). A progressive decrease in blood lymphocyte counts (cluster of differentiation [CD]4+/CD8+ T cells) (Cascella *et al.*, 2021; Diao *et al.*, 2020, 2020; Rha and Shin, 2021) and elevated exhaustion levels of T cells have also been reported in patients with severe COVID-19 (Kuri-Cervantes *et al.*, 2020; Zheng *et al.*, 2020). Despite this cellular exhaustion, CD8+ T cells exhibiting activated phenotypes (Rha and Shin, 2021), such as the phenotype programmed cell death-1 (PD-1)+ SARS-CoV-2-specific CD8+ T, are involved in producing interferon (IFN)-gamma, indicating that these cells are not completely exhausted (Rha *et al.*, 2021).

Tocilizumab (TCZ), a monoclonal antibody against the IL-6 receptor that blocks its pro-inflammatory effect, has shown significant activity in patients with COVID-19 (Xu *et al.*, 2020). In addition, inhibitors of the PD-1/programmed cell death-ligand 1 (PD-L1) pathway, which regulates the balance between T cell activation, tolerance, and immunopathology, could restore the function in exhausted CD8+ T cells (ability to proliferate, secrete cytokines, kill infected cells, and decrease viral load) (Barber *et al.*, 2006). The engagement of PD-1 with its ligand PD-L1 inhibits T cell activation (Freeman *et al.*, 2000). Therefore, pembrolizumab (P), a humanized monoclonal antibody targeting PD-1, could be an option to diminish the T cell exhaustion observed in patients with COVID-19.

We hypothesized that the blockade of PD-1 with immune-activating drugs (e.g., P) and IL-6 receptor (with TCZ) might restore cellular immunocompetence and interrupt the hyperinflammation at a crucial disease stage (Di Cosimo *et al.*, 2020). Therefore, this study aimed to evaluate the efficacy and safety of P + TCZ and standard of care (SOC) compared with SOC in high-risk hospitalized patients with COVID-19 with pneumonia who were not receiving mechanical ventilation.

Methods

Ethical approval

Hospital Arnau de Vilanova Ethics Committee (Valencia, Spain) approved this study. Written informed consent was obtained from all patients.

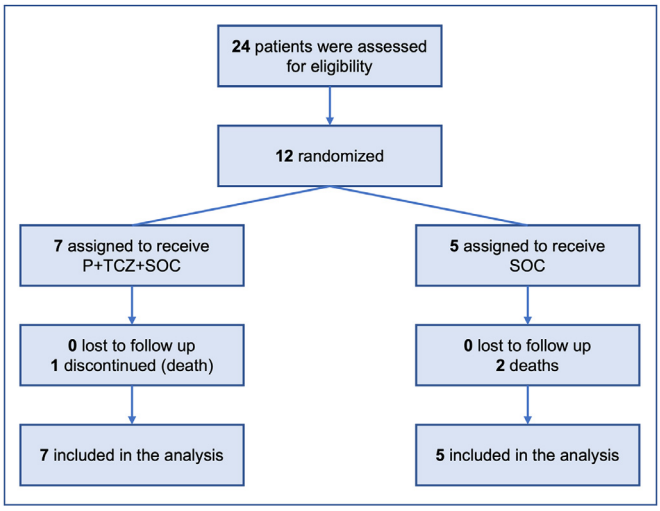

Figure 1. The patient flow diagram.
P, pembrolizumab; SOC, standard of care; TCZ, tocilizumab.

Study design

COPERNICO was a prospective, randomized, controlled, open-label, phase II trial to evaluate the efficacy and safety of P + TCZ + SOC versus SOC in patients with severe COVID-19 pneumonia (NCT04335305).

Patient selection

High-risk hospitalized patients (aged 18-80 years) with laboratory-confirmed SARS-CoV-2 infection, COVID-19 pneumonia without requiring mechanical ventilation, and life expectancy >10 days were included. Additional inclusion criteria included a total lymphocyte count $\leq 0.8 \times 10^6$/ml, peripheral capillary oxygen saturation ≤92% on room air (or ≤94% for patients on a previous TCZ-based regimen), and patients had to meet one or more of the following criteria: increased IL-6, ferritin, D-dimer, C-reactive protein, lactate dehydrogenase, or erythrocyte sedimentation rate or no objective clinical improvement at physician's discretion within 48 hafter treatment initiation. Exclusion criteria included the use/requirement of immunomodulators, antirejection drugs, or other agents with actual/possible antiviral activity against SARS-CoV-2 <24 h before study inclusion and endotracheal intubation, mechanical ventilation, and/or extracorporeal membrane oxygenation. The patient flow diagram is shown in Figure 1.

Study treatment and drug administration

Patients were randomly assigned (2:1) to receive 200 mg P intravenously on day 1 (additional dose on day 21 as per clinical improvement) plus 800 mg/kg TCZ intravenously on day 1 (additional dose after 12 h and on day 28 as per clinical improvement) and SOC (supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, systemic steroids [e.g., dexamethasone], TCZ, and virally targeted agents [e.g., remdesivir] at the physician's discretion), or SOC. Patients were followed up for a period up to 90 ± 14 days after study entry. Patients remained in the study until consent withdrawal, death, or treatment-discontinuation for any other reason.

Study endpoints

The primary endpoint was the length of time to hospital discharge, defined as the time (days) from randomization to the pa-

tient's date of leaving the hospital (discharge date - randomization date + 1).

The secondary endpoints were: (i) percentage of patients who, at the end of study (EoS; 90 ± 14 days after study entry), had been discharged from the hospital (including without sequelae, defined as documented incidence and grade of COVID-19 sequelae at hospital discharge and after that and their association with post-COVID-19 survival); (ii) percentage of patients who had shown respiratory symptoms remission (days of intubation/oxygen therapy independence) that were evaluated at screening and every day during the hospitalization period or had died; (iii) percentage of patients with peripheral capillary oxygen saturation >96% on room air at day 14 (measured as no respiratory support for a time ≥15 min); (iv) change from baseline in modified sequential organ failure assessment (mSOFA) score (multiparameter score which predicts intensive care unit mortality) at days 1, 3, 5, 7, 14, 21, and 28 (after that, once weekly up to hospital discharge only in case of additional dosing of study treatment in the interventional arm). The mSOFA score is calculated considering the following variables: the pressure of arterial oxygen to fractional inspired oxygen concentration, modified SOFA score (Sendagire *et al.*, 2017), Glasgow coma scale, mean arterial pressure, and bilirubin, platelet, and creatinine levels; (v) incidence of adverse events (AEs) until EoS evaluated using the Common Terminology Criteria for Adverse Events version 5.0.

A quantitative reverse transcriptase-polymerase chain reaction assay was performed at screening for a diagnosis of COVID-19 infection and also on day 14 and at hospital discharge to confirm SARS-CoV-2 negativization.

Statistical analysis

Efficacy was assessed in the intent-to-treat set, which included all patients who had undergone randomization. The safety analysis set included all patients who received at least one dose of the study drug. The primary analysis was the likelihood ratio test, based on a univariate Cox regression model. The Breslow method was used for tie correction. The 95% confidence intervals (CIs) for the regression parameter were calculated using the Wald test, using an exponential transformation to create the 95% CIs for the hazard ratio.

The sample size was based on a superiority test of median time to discharge. The two-sided log-rank test had 80% power to detect a 12.5-day decrease in median time to discharge over a 17.5-day median time to discharge for the SOC arm.

An interim analysis for efficacy was performed with 12 patients recruited and at least ten patients discharged. The Pocock efficacy boundaries were used to control for type-I error in the interim and final efficacy analyses. The two-sided nominal α errors for testing the null hypothesis within the analyses were set at 0.0595 for both analyses.

Survival estimates for each time-to-event endpoint were estimated using the Kaplan-Meier method and log-log 95% CIs. The number and proportions of patients in each treatment group and the *P*-value based on chi-square or Fisher's exact test were calculated. The mean difference between the mSOFA scores for the P + TCZ + SOC and SOC arms was analyzed by mixed-effect model repeated measurement analysis, with the absolute mean considering the dependent variables. The results were adjusted for the treatment group and visit number.

All statistical analyses were two-sided, and $P < 0.05$ was considered statistically significant in secondary analyses. Data analysis was carried out using R software version 4.0.2.

Results

From April 1, 2020 through June 30, 2021, 12 patients with confirmed SARS-CoV-2 severe pulmonary infection not yet requiring mechanical ventilation were included in the intention-to-treat population.

Patient disposition and treatment

Patient disposition is shown in Figure 1. All patients (seven patients [58.3%] in the interventional arm [P + TCZ + SOC] and five patients [41.7%] in the control arm [SOC]) required oxygen supplementation.

All patients in the interventional arm received a dose of P and TCZ; 14.3% (one of seven patients) received an additional dose of TCZ after that. In the control group, 20% (one of five patients) received a dose of TCZ as SOC. All patients received steroids. The treatment duration, dose, and type of steroid prescribed were not significantly different between arms (Supplementary Table 1).

Baseline characteristics

Baseline patient characteristics were well balanced between arms (Table 1). The overall population median age was 68 years (range, 47-79): 68 years with P + TCZ + SOC versus 65 years with SOC. A total of 75% of enrolled patients were male (71% with P + TCZ + SOC vs 80% with SOC). The median duration from symptoms onset to randomization was 3 days (range, 0-12).

The rate of patients who completed the first monthly follow-up visit was 71.4% (five of seven patients) with P + TCZ + SOC vs

Table 1
Patient baseline characteristics.

Baseline characteristics, N (%)	P+TCZ+SOC (N = 7)	SOC (N = 5)	Overall (N = 12)
Age, years, median (min-max)	68 (47-79)	65 (41-78)	68 (41-79)
Gender			
Male	5 (71.0)	4 (80.0)	9 (75.0)
Female	2 (29.0)	1 (20.0)	3 (25.0)
Race or ethnic group			
Caucasian	6 (86.0)	4 (80.0)	10 (83.0)
Latin American	1 (14.0)	1 (20.0)	2 (17.0)
Time since symptom onset to randomization, days, median (min-max)	3 (0-12)	3 (1-11)	3 (0-12)
Number of coexisting conditions			
0	1 (14.0)	2 (40.0)	3 (25.0)
1	0 (0)	1 (20.0)	1 (8.0)
≥ 2	6 (86.0)	2 (40.0)	8 (67.0)
Hospitalization status			
Supplemental oxygen	7 (100)	5 (100)	12 (100)
Smoking history			
Never smoked	3 (43.0)	2 (40.0)	5 (41.7)
Ex-smoker (stopped >12 months)	1 (14.0)	2 (40.0)	3 (25.0)
Daily smoker	1 (14.0)	0 (0)	1 (8.3)
Unknown	2 (29.0)	1 (20.0)	3 (25.0)
mSOFA score, median (IQR)	0 (0-0.5)	1 (1-2)	-
Other support			
Antibiotic	3 (43.0)	4 (80.0)	7 (58.3)
Vasopressor	0 (0)	0 (0)	0 (0)
Renal-replacement therapy	0 (0)	0 (0)	0 (0)
Other	1 (14.0)	0 (0)	1 (8.3)

mSOFA, modified sequential organ failure assessment; P, pembrolizumab; SOC, standard of care; TCZ, tocilizumab.

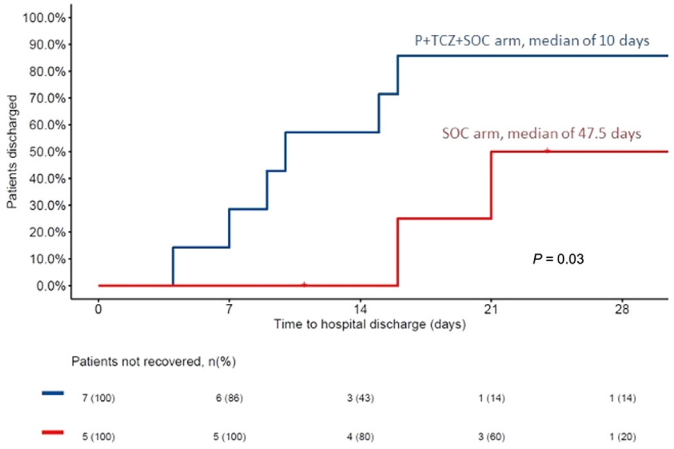

Figure 2. Number of days of hospitalization from randomization to patient discharge.
P, pembrolizumab; SOC, standard of care; TCZ, tocilizumab.

40.0% (two of five patients) with SOC. The second monthly follow-up visit was completed for 42.9% (three of seven patients) with P + TCZ + SOC vs 40.0% (two of five patients) with SOC.

Primary efficacy outcome

The primary endpoint of this study was time to discharge. The median time to discharge was significantly lower with P + TCZ + SOC than SOC: 10 days versus 47.5 days ($P = 0.03$) (Figure 2).

Secondary outcomes

The percentage of patients who were discharged from the hospital through EoS was significantly higher with P + TCZ + SOC (100%, seven of seven patients) versus SOC (60%, three of five patients) ($P = 0.043$) (Supplementary Figure 2). In addition, the number of patients who were discharged without sequelae was higher with P + TCZ + SOC (71.4%, five of seven patients) versus SOC (20%, one of five patients) ($P = 0.079$) (Figure 3a). In each arm, two patients were discharged with dyspnea (one patient in the SOC arm requiring oxygen at night). A statistically significant difference in the median discharge time without sequelae between arms was observed (13 days in P + TCZ + SOC vs not achieved in SOC; $P = 0.044$) (Figure 3b).

Remdesivir was given to 42.9% (three of seven patients) with P + TCZ + SOC and 20.0% (one of five patients) with SOC. These patients were alive at 60 days and were discharged without sequelae (Supplementary Table 2).

In the remaining patients without remdesivir treatment (n = 8), the median time to discharge with and without sequelae was significantly lower with P + TCZ + SOC than SOC; moreover, the rate of patients without receiving remdesivir who were alive at 60 days was 75% with P + TCZ + SOC and 50% with SOC (Supplementary Table 3).

No differences in peripheral capillary oxygen saturation >96% on room air were found through day 14 after treatment initiation (median of 2 days with P + TCZ + SOC vs 3 days with SOC; $P = 0.64$) (Supplementary Figure 3). The mean change from baseline in the mSOFA score was lower in patients with P + TCZ + SOC vs SOC during the entire evaluation ($P = 0.027$) (Supplementary Figure 4). The risk of death was 4.2-times higher with SOC than with P + TCZ + SOC (hazard ratio 4.2; 95% CI: 0.4-48.3) (Supplementary Figure 5).

The rate of patients receiving mechanical ventilation throughout the study did not differ significantly between P + TCZ + SOC (14.3%, one of seven patients) and SOC (80%, four of five patients) ($P = 0.07$; Supplementary Figure 6).

Safety analysis

In the P + TCZ + SOC arm, 71.4% of patients experienced AEs, versus 100% with SOC. Serious AEs occurred in 28.6% of patients with P + TCZ + SOC: one patient experienced clinical worsening of COVID-19 (grade 4), and one patient had P-related myositis (grade 5) and a pulmonary embolism (grade 3) (Table 2). In the P + TCZ + SOC arm, 57.1% of patients experienced treatment-related AEs: hypertransaminasemia (grade ≤2; n = 3), dermatitis and myalgia (both grade 2; n = 1), and myositis (grade 5; n = 1). The latter patient was initially discharged with dyspnea but was subsequently hospitalized again due to worsening dyspnea, myalgia, and proximal weakness of the lower limbs. A thorax computed tomography scan revealed a subsegmental pulmonary embolism, and blood tests revealed a significant elevation of muscle enzymes, including troponin. P-related myositis was suspected, and despite anticoagulant therapy, high-dose steroids, intravenous immunoglobulins, and mechanical ventilation, the patient developed respiratory failure and subsequently died.

In the SOC arm, 80% of patients experienced serious AEs: four patients had clinical worsening of COVID-19 (grade 4), and two died (grade 5). Serious AEs in the SOC arm were retroperi-

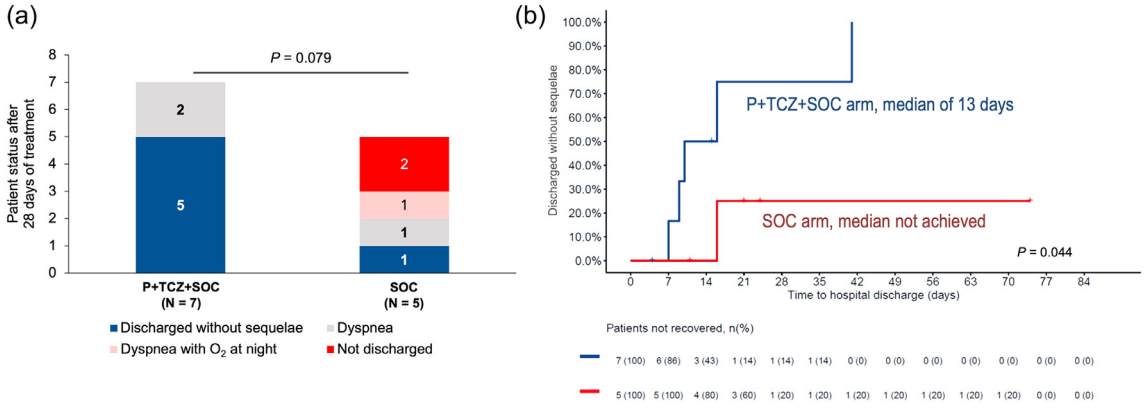

Figure 3. Patients discharged without sequelae (a) Patients discharged with remission of respiratory symptoms (b)
P, pembrolizumab; SOC, standard of care; TCZ, tocilizumab.

Table 2
Summary of AEs in the safety population, occurring in more than 14.3% of patients.

AE, N (%)	P+TCZ+SOC (N = 7)		SOC (N = 5)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any	5 (71.4)	2 (28.6)	5 (100)	4 (80.0)
Hypertransaminasemia	3 (42.9)	0 (0)	1 (20.0)	1 (20.0)
Oral candidiasis	0 (0)	0 (0)	2 (40.0)	0 (0)
Bacterial infection	0 (0)	0 (0)	1 (20.0)	0 (0)
Deep venous thrombosis	0 (0)	0 (0)	1 (20.0)	0 (0)
Fungal infection of nail	0 (0)	0 (0)	1 (20.0)	0 (0)
Hyperglycemia	1 (14.3)	0 (0)	0 (0)	0 (0)
Hypocalcemia	0 (0)	0 (0)	1 (20.0)	0 (0)
Pneumonia bacterial	0 (0)	0 (0)	1 (20.0)	0 (0)
Pseudomonas infection	0 (0)	0 (0)	1 (20.0)	0 (0)
Sepsis	0 (0)	0 (0)	1 (20.0)	0 (0)
Staphylococcus epidermidis	0 (0)	0 (0)	1 (20.0)	0 (0)
Urinary tract infection fungal	0 (0)	0 (0)	1 (20.0)	0 (0)
Serious AEs	2 (28.6)	2 (28.6)	4 (80.0)	4 (80.0)
COVID-19 aggravated[a]	1 (14.3)	1 (14.3)	4 (80.0)	4 (80.0)
Myositis[b]	1 (14.3)	1 (14.3)	0 (0)	0 (0)
Pulmonary embolism	1 (14.3)	1 (14.3)	0 (0)	0 (0)
Hypertransaminasemia	0 (0)	0 (0)	1 (20.0)	1 (20.0)
Hemodynamic instability	0 (0)	0 (0)	1 (20.0)	1 (20.0)
Bronchial aspiration	0 (0)	0 (0)	1 (20.0)	1 (20.0)
Pneumothorax	0 (0)	0 (0)	1 (20.0)	1 (20.0)

[a] In SOC arm, two patients (40%) died during the first month due to clinical worsening due to COVID-19 pneumonia.
[b] In P+TCZ+SOC arm, one patient (14.3%) died after nearly 2 months due to a myositis. The patient was discharged 4 days after treatment initiation.AE, adverse events; P, pembrolizumab; SOC, standard of care; TCZ, tocilizumab.

toneal bleeding (grade 4; n = 1), pneumothorax (grade 4; n = 1), bronchial aspiration (grade 3; n = 1), and hypertransaminasemia (grade 3; n = 1). Supplementary Table 4 presents a summary of the treatment-related AEs.

There were three deaths (25% of the total population): one patient (14.3%) in the P + TCZ + SOC arm due to myositis and two patients (40.0%) in the SOC arm (during hospitalization).

Discussion

Findings from our randomized phase II trial confirmed the safety and efficacy of PD-1 and IL-6 receptor blockade, using the combination of P and TCZ added to SOC in high-risk hospitalized patients with COVID-19 with severe pneumonia but without requiring mechanical ventilation. In addition, this combination improved disease outcomes in terms of reducing hospital discharge time and sequelae.

SOC comprises a complex treatment that several studies have attempted to improve by adding new drugs. In this way, researchers have analyzed the possible benefit of adding TCZ to SOC in patients with COVID-19 regarding the time until hospital discharge and duration of intensive care unit stay (Rosas *et al.*, 2021). This combination showed an immediate activity in a younger population (mean age, 56.8 years) with severe and critical COVID-19, with a mean hospital admission of 15.1 days after receiving TCZ (Xu *et al.*, 2020). Moreover, the addition of TCZ to SOC reported a 10-point increase in the percentage of discharge by day 28 versus SOC (83% vs 73%, respectively) in a high-risk population similar to our study (Hermine *et al.*, 2021).

In our study, the median hospitalization time from randomization to patient discharge with P + TCZ + SOC was reduced by 37.5 days relative to SOC (10 days vs 47.5 days, respectively). Despite the limitations of making indirect comparisons between studies, the time achieved with P + TCZ + SOC is shorter than that previously reported with TCZ+ SOC (that ranged between 15.1 and 20 days) (Rosas *et al.*, 2021; Xu *et al.*, 2020). Furthermore, the percentage of patients who had been discharged by the EoS (including patients without sequelae) after study entry was higher with P + TCZ + SOC than SOC, indicating a good prognosis after the treatment. This earlier discharge with a lower frequency of sequelae could be attributed to the addition of P, which may have a protective role through the PD-1 blockade; although, the efficacy of P as a single agent has not been assessed in patients with COVID-19. Only a single case report showed a long-responder patient with metastatic melanoma treated with P, who was infected with SARS-CoV-2 and fully recovered without sequelae (Pala *et al.*, 2021). A recent publication indicates that PD-L1 dysregulation is associated with COVID-19 pathogenesis, showing PD-L1 upregulation in several types of immune cells (monocytes, neutrophils, gamma delta T cells, and CD4+ T cells) of patients with COVID-19 (Sabbatino *et al.*, 2021), which is likely mediated by elevated IL-10 levels (Lamichhane *et al.*, 2017) and ultimately leads to disease progression (Sabbatino *et al.*, 2021). On the other hand, the presence of neutralizing antibodies against type-I IFN at the onset of critical disease neutralizes the ability of the type-I IFN to block SARS-CoV-2 infection (Bastard *et al.*, 2020).

The presence of these neutralizing antibodies could explain the induction of a hyperactivation status, which causes an excessive immunopathology (Di Cosimo *et al.*, 2020; Schub *et al.*, 2020). In this way, a decrease in PD-L1 expression on CD4+ IFN-stimulated T cells in patients with COVID-19 has been reported (Sabbatino *et al.*, 2021), and the use of immune checkpoint inhibitors may induce immune system activation. These suggest that the immune checkpoint inhibition mediated by anti-PD-1 antibody has a generally consistent treatment effect through a controlled activation immune system in shortening the time to recovery in adults hospitalized with COVID-19 pneumonia.

In our study, two (40%) patients died in the SOC arm due to COVID-19, whereas none (0%) died due to COVID-19 with P + TCZ + SOC. Although there were no differences in mortality between arms, probably due to the small sample size, this finding might also be attributed to the addition of P (activating the immune response). Recently, the use of immunosuppressive medications before hospital admission for COVID-19, such as chronic

steroids, has been associated with higher mortality and risk of complications, reinforcing the notion that immune system activation could improve the outcome of these patients (Calderón-Parra *et al.*, 2021).

An mSOFA score ≥3 at hospitalization has been described as an independent mortality predictor in patients with COVID-19 (Zou *et al.*, 2020). This score shows clinical deterioration mainly due to respiratory failure and the need for oxygen support (Guaraldi *et al.*, 2020; Morrison *et al.*, 2020). A study of patients with COVID-19 treated with TCZ showed improvements in mSOFA score in survivors versus nonsurvivors, indicating a clinical response to TCZ (Morrison *et al.*, 2020). Similar results were obtained in another study with a higher mSOFA score in nonsurvivor patients; interestingly, in this study, the percentage of patients treated with TCZ was higher among survivors (56.6%) than nonsurvivors (40.0%) (Sosa-García *et al.*, 2020). In our study, the mean change from baseline in the mSOFA score was significantly lower in patients treated with P + TCZ + SOC than SOC alone, which may be associated with these drugs' effect on reducing mortality of COVID-19.

Overall, in our study, toxicities reported with P + TCZ + SOC were consistent with those previously reported. Of interest, one death secondary to P (myositis) occurred in the P + TCZ + SOC arm. Despite TCZ association with secondary bacterial or fungal infections (Khiali *et al.*, 2020), no pulmonary infections were reported in our study, which could be explained by P, which is implicated in T cell proliferation and activation (Barber *et al.*, 2006).

Limitations

Similar to many randomized clinical studies carried out on patients with COVID-19 during the early stages of the pandemic, our trial was not blinded. Unfortunately, the emergency situation caused by the pandemic made it impossible to set up a double-blind study rapidly.

The study design only covers a specific group of patients with COVID-19 (high-risk hospitalized patients with pneumonia without mechanical ventilation) and cannot inform about the role of P and TCZ in a broader or more heterogeneous population with COVID-19. Moreover, the study has a small sample size, making it difficult to obtain conclusive results.

The lack of evidence of COVID-19 outcomes in patients with P alone makes it difficult to determine its additive role in managing the disease. An additional arm with P plus SOC could have clarified the role of anti-PD1 antibodies in treating severe COVID-19.

Conclusion

In this randomized, controlled, open-label, phase II trial, the addition of P + TCZ to SOC in high-risk hospitalized patients with severe COVID-19 with pneumonia not yet requiring mechanical ventilation significantly reduced the length of hospitalization and the rate of discharge without sequelae. However, more studies are needed to elucidate the role of immune checkpoint inhibition alone or combined with IL-6 receptor blockade in patients with COVID-19 and other severe viral diseases.

Declaration of Competing Interest

M.S.C. reported having a consulting role for Gilead Sciences, MSD, and ViiV; receiving travel compensation from Gilead Sciences; and receiving research funding from Gilead Sciences and MSD.

J.P.G. reported having a consulting role for Roche, Lilly, and Daichii-Sankyo; receiving travel compensation from Roche; to being a part-time employee of MEDSIR during the study period. M.G. reported having a consulting role for Roche and Pfizer. M.S.C. reported receiving honoraria from MEDSIR, Syntax for Science, and Nestlé; receiving research funding from MEDSIR, Syntax for Science, and Roche; receiving travel compensation from MEDSIR, Syntax for Science, and Roche; serving as a consultant to MEDSIR, Syntax for Science, and Nestlé; to being on the speaker bureau for MEDSIR, Syntax for Science, Roche; and to being part-time employee of MEDSIR during the conduct of the study. A.M. is a full-time employee of MEDSIR. S.T. is a full-time employee of Lilly. A.L.C. reported playing a leadership role at Eisai, Celgene, Lilly, Pfizer, Roche, Novartis, and MSD; intellectual property for MEDSIR and Initia-Research; having a consulting role for Lilly, Roche, Pfizer, Novartis, Pierre-Fabre, GenomicHealth, and GSK; being part of the speaker bureau for Lilly, AstraZeneca, and MSD; receiving research funding from Roche, Foundation Medicine, and Pierre-Fabre, and Agendia,; and receiving travel compensation from Roche, Lilly, Novartis, Pfizer, and AstraZeneca during the study period.

J.C. reported serving as a consultant to Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp&Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead Sciences, Menarini, Zymeworks, and Reveal Genomics; receiving honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp&Dohme, and Daiichi Sankyo; receiving institutional research funding from Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F.Hoffman-La Roche, Guardanth health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Puma C, and Queen Mary University of London; providing intellectual property to MEDSIR, Nektar Pharmaceuticals, and Leuko (relative); and receiving travel compensation from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, and AstraZeneca. The remaining authors declare no competing interests.

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Author contributions

J.C. and A.L.-C. conceptualized, administered, and supervised the study. A.M. designed the study protocol with help from J.M.P.-G., A.A.-F., and I.T. M.S.-C. analyzed the data. Funding acquisition was the responsibility of J.C. and A.L.-C. All authors were involved in further manuscript drafts and revised the manuscript critically for content. All authors gave final approval of the version to be published. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request. Source data are provided with this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.08.007.

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