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Early use of canakinumab to prevent mechanical ventilation in select COVID-19 patients: A retrospective, observational analysis

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Abstract

Introduction: The fully-human monoclonal anti-interleukin (IL)-1β antibody canakinumab may inhibit the production of inflammatory mediators in patients with coronavirus disease 2019 (COVID-19) and the hyperinflammatory response potentially leading to acute respiratory distress syndrome.

Objectives: The goal of our retrospective, observational analysis was to evaluate the safety and efficacy of subcutaneous (s.c.) canakinumab in combination with our standard of care (SOC) treatment of selected patients with COVID-19 with respiratory failure and elevated reactive pro-inflammatory markers.

Methods: Eight participants received two doses of s.c. canakinumab 150 mg (or 2 mg/kg for participants weighing ≤40 kg) in addition to SOC. 12 patients received only SOC treatment.

Results: Canakinumab treatment reduced the need for mechanical ventilation and reduced proinflammatory markers, resulting in an amelioration of the final outcome, with respect to the control group who received SOC alone. The treatment was safe and well tolerated; no adverse events were reported.

Conclusion: The use of canakinumab (300 mg, s.c.) in the early stage of COVID-19 with mild-to-moderate respiratory failure was superior to SOC at preventing clinical deterioration and may warrant further investigation as a treatment option for patients with COVID-19 who experience a hyperinflammatory response in the early stage of the disease.

Keywords

biomarkers, canakinumab, case series, interleukin-1β, mechanical ventilation, COVID-19, SARS-CoV-2

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Background

Interleukin (IL)-1β, is a pro-inflammatory cytokine mediating inflammation, including peripheral immune responses during infection, and autoimmune diseases.[1] The fully-human monoclonal anti-IL-1β antibody, canakinumab (Ilaris®, Novartis), inhibits the association of IL-1β

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with the type 1 IL-1 receptor (IL-1RI),[2] thereby neutralizing IL-1β signaling and suppressing inflammation in patients with autoimmune disorders.

Canakinumab is generally well-tolerated,[3,4] and reduces inflammation without major effects on lipid levels or platelet function,[5] suggesting its independent anti-inflammatory activity in patients with atherosclerosis and persistent systemic inflammation. In the double-blind CANTOS trial in patients with atherosclerotic disease and elevated high-sensitivity C-reactive protein (hs-CRP) levels, canakinumab significantly reduced recurrent cardiovascular events and hs-CRP levels, independent of lipid-lowering.[5]

Canakinumab may be of value in those patients with coronavirus disease 2019 (COVID-19), characterized by a hyperinflammatory response leading to acute respiratory distress syndrome.[6,7] The benefit of subcutaneous (s.c.) canakinumab plus standard of care (SOC) treatment in increasing the chance of survival without requiring invasive mechanical ventilation is being evaluated among hospitalized patients with COVID-19-induced pneumonia (ClinicalTrials.gov Identifier: NCT04362813).

Methods

Patients

This retrospective, observational cohort study evaluated the safety and efficacy of s.c. canakinumab treatment of COVID-19 patients hospitalized at the "Annunziata" Hospital, Cosenza, Italy with respiratory failure and elevated reactive pro-inflammatory markers between April 06–30, 2020. The study was approved by the local ethics committee. No registration number was needed for the study.

Patients assigned to canakinumab plus SOC treatment per our local practice, which included lopinavir/ritonavir, hydroxychloroquine, enoxaparin (4000 U s.c. twice-daily [BID]), doxycycline, colchicine, and supportive care were indirectly compared with a control group of COVID-19 patients receiving SOC therapy.

Adults ≥18 years old were eligible for treatment with canakinumab if they were diagnosed with SARS-CoV-2 infection by PCR, pneumonia by chest computed tomography (CT), and with evidence of cytokine release syndrome (CRS) and CRP > 20 mg/L, ferritin >600 ng/L, interleukin 6 >40 pg/mL, and SpO_2 ≤93% on room air or arterial oxygen partial pressure (PaO_2)/fraction of inspired oxygen (FiO_2) <300 mmHg. Informed consent was obtained prior treatment.

Exclusion criteria included: active infection; low white blood cell counts (WCC); a weak immune system; a history of human immunodeficiency virus, hepatitis B, or C infection; recurrent infections; recent receipt of any live vaccine; and presence of malignancies or any chronic auto-inflammatory conditions.

Plasma IL-6 levels were measured before and after initiation of canakinumab using validated enzyme-linked immunosorbent assay (ELISA); markers of the acute-phase response, including CRP, haptoglobin (Hp), and fibrinogen, along with indicators of iron status were also measured.

Canakinumab recipients were treated with two s.c. doses (150 mg BID for a bodyweight of 60–80 kg). A clinical response was defined as survival without ever requiring invasive mechanical ventilation between Day 3 and Day 29 inclusive.

A non-responder was defined if clinical status worsened (need for mechanical ventilation, category 6, 7, and 8 on the WHO 9-point ordinal scale, or death[8]) at any time from Day 3 to Day 29, or if they needed intubation and mechanical ventilation, or ventilation plus additional organ support (pressors, renal replacement therapy, and extracorporeal membrane oxygenation).

Patients were classified by CRS grades according to the revised validated grading system of Lee DW et al.[9,10]; the clinical severity of COVID-19 was assessed according to the Brescia-COVID Respiratory Severity Score (BCRSS)/algorithm,[11] a helpful tool in clinical practice although not yet validated.

Chest computed tomography features of canakinumab group were evaluated by means of a not yet validated semiquantitative visual scoring system.[12]

Participants were followed for up to 24 weeks after completing treatment with canakinumab.

Statistical analysis

Unpaired t test was applied to compare canakinumab + SOC group versus SOC group data; it was performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA.

Results

Eight patients were included in the canakinumab group and 12 in control group. Table 1 reports the characteristics of patients included in the canakinumab group, while the patients' comorbidities, including obesity, the most serious risk factor for adverse COVID-19 outcomes, are reported for both groups in Table 2.

Based on clinical severity assessed according to the Brescia-COVID Respiratory Severity Score (BCRSS),[11] all patients were level 3 (PaO_2 <65 mmHg or SpO_2 <90%, respiratory rate >22) and received non-invasive ventilation (continuous positive airway pressure/bilevel positive airway pressure [CPAP/BiPAP]) or high-flow nasal cannula and dexamethasone, before a start on canakinumab therapy was considered.[11]

Inflammatory markers, NLR and PLR were elevated with respect to the normal range, in all patients at admission (Table 3) and 7 days after canakinumab administration (Table 4).

Table 1. Patient demographics and clinical characteristics of canakinumab group upon presentation.

	Canakinumab + SOC (*N*=8)
Age in years: Median (range)	56 (46-82)
Female gender, n (%)	4 (50.0)
Symptoms, n (%)	
Fever	8 (100.0)
Cough	8 (100.0)
Fatigue	8 (100.0)
Dyspnea	8 (100.0)
Lymphocytopenia	8 (100.0)
Vitamin D deficiency	8 (100.0)
Oxygen status, n (%)	
Respiratory rate > 30 breaths/min	8 (100.0)
Blood oxygen saturation <93%	8 (100.0)
PaO_2FiO_2 <300 mm Hg	8 (100.0)
CRS *, n (%)	
Grade 1	1 (12.5)
Grade 2	2 (25.0)
Grade 3	5 (62.5)
Grade 4	0 (0.0)

Abbreviations: CRS, cytokine release syndrome; PaO2FIO2, arterial oxygen partial pressure/fraction of inspired oxygen.
*According to the revised grading system of Lee DW et al., Blood 2014.[9]

Table 2. Comorbidities detected in the patients of both canakinumab and the control group upon presentation, n (%).

Comorbidity, n (%)	Canakinumab + SOC (*N* = 8)	SOC alone (*N* = 12)
Hypertension	6 (75.0)	7 (58.3)
Diabetes	4 (50.0)	2 (16.7)
Chronic obstructive lung disease	4 (50.0)	1 (8.3)
Obesity	1 (12.5)	3 (25.0)

Table 3. Inflammatory markers on presentation.

	Baseline mean (SD)		
	Canakinumab + SOC (*N*=8)	SOC alone (*N*=12)	*p* value
CRP, mg/L (normal range: 0-5)	153.8 (23.7)	180.8 (30.2)	0.047
Fibrinogen mg/dL (normal range: 150-450)	856.3 (58.8)	708.3 (74.5)	0.0002
LDH, U/L (normal range: 50-248)	969.9 (47.2)	1028 (149.6)	0.302
D-dimer, mg/L (normal range: 0.0-0.50)	2.813 (0.290)	2.208 (0.636)	0.022
Ferritin, ng/mL (normal range: 11-307)	1493 (91.5)	1303(155.2)	0.006
Procalcitonin, ng/mL (normal range: 0.00-0.09)	1.413 (0.290)	1.714 (0.511)	0.149
Interleukin-6, pg/mL (normal range: 0.0-6.4)	188.1 (29.3)	251.3 (41.8)	0.002
Haptoglobin, mg/dL (normal range: 30-200)	572.5 (53.1)	653.3 (53.7)	0.004
Neutrophil-to-Lymphocyte Ratio (NLR)	3.075 (0.21)	3.40 (0.39)	0.047
Platelet-to-Lymphocyte Ratio (PLR)	175.3 (9.5)	188.30 (13.5)	0.029

CRP: C-reactive protein; LDH: lactate dehydrogenase; SOC: standard of care. Unpaired t test was applied to compare canakinumab + SOC group versus SOC group data.

Table 4. Inflammatory markers measured 7 days after the administration of canakinumab in the canakinumab + SOC group.

	7 days post treatment mean (SD)		
	Canakinumab + SOC (*N*=8)	SOC alone (*N*=12)	*p* value
CRP, mg/L (normal range: 0-5)	35.00 (16.99)	112.5 (31.3)	<0.0001
Fibrinogen mg/dL (normal range: 150-450)	350.0 (84.7)	670.8 (156.3)	<0.0001
LDH, U/L (normal range: 50-248)	450.0 (124.9)	769.6 (108.7)	<0.0001
D-dimer, mg/L (normal range: 0.0-0.50)	0.700 (0.35)	1.492 (0.30)	<0.0001
Ferritin, ng/mL (normal range: 11-307)	581.3 (234.9)	1000 (157.0)	0.0001
Procalcitonin, ng/mL (normal range: 0.00-0.09)	0.012 (0.005)	0.829 (0.247)	<0.0001
Interleukin-6, pg/mL (normal range: 0.0-6.4)	48.00 (9.75)	118.8 (20.6)	<0.0001
Haptoglobin, mg/dL (normal range: 30-200)	369.9 (105.6)	548.3 (72.2)	0.0003
Neutrophil-to-Lymphocyte Ratio (NLR)	2.213 (0.431)	2.917 (0.366)	0.001
Platelet-to-Lymphocyte Ratio (PLR)	110.1 (8.34)	207 (4.69)	<0.0001

CRP: C-reactive protein; LDH: lactate dehydrogenase; SOC: standard of care. Unpaired t test was applied to compare canakinumab + SOC group versus SOC group data.

Table 5. CT score[12] in Canakinumab + SOC treated patients, n (%).

CT visual score	Canakinumab + SOC (*N* = 8)	SOC alone (*N* = 12)
2 (5%–25% involvement)	2 (25.0)	2 (16.7)
3 (26%–49% involvement)	4 (50.0)	6 (50.0)
4 (50%–75% involvement)	2 (25.0)	4 (33.3)

CT: computed tomography; SOC: standard of care.

Common chest computed tomography (CT) features of both groups included ground glass opacity (GGO) in all patients, interlobular septal thickening (90%), consolidation (60%), and crazy-paving pattern (40%). In the canakinumab group, using a semiquantitative visual scoring system, 2 patients had a CT parameter score of 2, 4 a score of 3, and 2 patients (those with fatal outcome) had a score of 4[12] (Table 5). Conventional CT parameters of patients in the SOC group included: GGO in all patients, consolidation in 7 patients, mixed pattern in 5 other patients, interstitial thickening in 8 patients, and crazy-paving pattern in 5 patients.

In the canakinumab group, either an adverse event or clinically significant change in laboratory measures was recorded in only two patients. In contrast to the control group, 6 of 8 patients receiving canakinumab experienced a faster and more stable improvement in clinical conditions, accompanied by a reduction of inflammatory markers, a gradual improvement in respiratory function, a lower oxygenation request within 7–14 days, and no exitus.

Six of the 8 patients did not need invasive mechanical ventilation between day 3 and day 29, and 2 were defined as non-responders, with deteriorating health and the need for mechanical ventilation. In the control group, four patients required invasive mechanical ventilation. The requirement for oxygen supplementation in canakinumab recipients gradually lowered, in contrast to the SOC group.

No unexpected adverse events (AEs) were reported in patients treated with canakinumab.

Discussion

The inflammatory response and the cytokine storm play a critical role in COVID-19[13], suggesting that an immunomodulatory agent may reduce the systemic inflammatory response and benefit patients. Seven days after canakinumab treatment, the proinflammatory markers were significantly reduced in the canakinumab + SOC group with respect to the control.

A correlation between CRP levels, lung lesion diameter, and disease severity has been observed; in early-stage COVID-19 CRP levels were positively correlated with the diameter of lung lesions and severe presentation.[14] Increased levels of LDH are common in severe COVID-19,[15] and may be reflective of disease severity; Liu et al. have reported that patients with IL-6 >32.1 pg/mL or CRP >41.8 mg/L were more likely to have severe complications,[13] suggesting that IL-6 and CRP could be used as independent factors to predict COVID-19 severity.

Moreover, cytokine storm is closely associated with severe deterioration in some patients[16]; controlling the inflammatory response with immunomodulators may therefore improve the prognosis of patients with SARS-CoV-2 infections.

At presentation, all patients in our study had lymphopenia, an increase of NLR, consistent with the findings by other authors,[15,17] elevated levels of infection-related biomarkers, and a rising neutrophil count together with a falling lymphocyte count during the severe phase. Mean IL-6 concentrations were higher in patients with complicated COVID-19 compared to those with non-complicated disease, as already reported.[18] Of note, one subject in the canakinumab group and three in the SOC group were obese patients. Patients in intensive care unit were all affected by obesity with a BMI >35 and with concomitant diabetes and/or arterial hypertension. Diabetic patients were undergoing a therapy with oral hypoglycemic agents before hospitalization and, at presentation, they showed a severe glyco-metabolic situation. During hospitalization they were administered s.c. insulin (Humalog) and oral sitagliptin (Januvia). Patients affected by hypertension required an adjustment of the pharmacologic anti-hypertensive therapy during hospitalization, as blood pressure was not under control at presentation. The new therapy allowed a gradual stabilization of the blood pressure. Despite the small number of patients included, this case series confirm obesity, uncontrolled glycemic level, and high blood pressure as the main risk factors for the development of a most severe COVID-19 pathology. Canakinumab has been evaluated in other patients with respiratory symptoms. In a retrospective analysis of ten patients with bilateral pneumonia, hyperinflammation, and respiratory failure requiring supplemental oxygen, canakinumab reduced the systemic inflammatory response and improved oxygenation.[19]

Currently, canakinumab is being investigated in a proof-of-concept trial (ClinicalTrials.gov Identifier: NCT04365153) to evaluate whether, by acting on the cytokine storm, it can reduce the progressive deterioration of respiratory and cardiac function in SARS-CoV-2-infected patients with myocardial injury and high levels of inflammation.[20]

Our analysis presents obvious limitations due to design of the study. It is an observational retrospective study on a limited number of heterogeneous patients, hospitalized in the same center, that were recruited following the emergency time situation. For such a reason, a prior power calculation of the sample size selected for the study was not feasible. Nevertheless, this design resulted appropriated to promptly investigate the clinical response in the situation of the COVID-19 health emergency, when a safe and effective intervention is needed to reduce the burden of the intensive care units.

In our analyses, the use of canakinumab in the early stage of COVID-19 with mild-to-moderate respiratory failure reduced the need for mechanical ventilation and proinflammatory markers. Moreover, at 24 weeks follow-up no symptoms of post-infection (dyspnea, cough, and chest pain) were detected in the canakinumab group, with the exception of persistence of mild asthenia. In 50% of patients in the control group, difficulty thinking or concentrating, tiredness or fatigue, and cough, frequently persisted. Therefore, administration of canakinumab reduced the manifestation of post-covid symptoms. Canakinumab was superior to SOC at preventing clinical deterioration and may warrant further investigation as a treatment option for patients with COVID-19 and hyperinflammatory response in the early stage of the disease.

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Declaration of conflicting interests

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Ethics approval

Ethical approval for this study was obtained from "Annunziata" Hospital, Cosenza, Internal Committee, according to the Italian Law (CIRCOLARE MINISTERIALE N. 6, 2 September 2002, published on G.U. n. 214, 12 September 2002), which specifies that observational studies need to be notified to the local ethics committee which will be then proceed either to a formal approval or to a simple acknowledgment of the ongoing study. A letter of permission that authorizes the study has been obtained by "Annunziata" Hospital, Cosenza.

Informed consent

Written informed consent was obtained from all subjects before the study.

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