CLINICAL SCIENCE

Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study

Emanuel Della-Torre ,[1,2] Corrado Campochiaro ,[1,2] Giulio Cavalli,[1,2] Giacomo De Luca,[1,2] Angela Napolitano,[2,3] Salvatore La Marca,[2,3] Nicola Boffini,[1] Valentina Da Prat,[4] Gaetano Di Terlizzi,[4] Marco Lanzillotta,[1,2] Patrizia Rovere Querini,[2,5] Annalisa Ruggeri,[6] Giovanni Landoni,[2,7] Moreno Tresoldi,[4] Fabio Ciceri,[2,6] ALberto Zangrillo,[2,7] Francesco De Cobelli,[2,3] Lorenzo Dagna ,[1,2] SARI-RAF Study Group

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For numbered affiliations see end of article.

Correspondence to
Dr Emanuel Della-Torre and Professor Lorenzo Dagna, Università Vita-Salute San Raffaele, IRCCS San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy; dellatorre.emanuel@hsr.it, dagna.lorenzo@unisr.it

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ABSTRACT

Objectives To assess the safety and efficacy of interleukin (IL)−6 blockade with sarilumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation.

Methods We conducted an open-label study of sarilumab in severe COVID-19 pneumonia (PaO_2/FiO_2 <300 mm Hg) with hyperinflammation (elevated inflammatory markers and serum IL-6 levels). Sarilumab 400 mg was administered intravenously in addition to standard of care and results were compared with contemporary matched patients treated with standard of care alone. Clinical improvement, mortality, safety and predictors of response were assessed at 28 days.

Results Twenty-eight patients were treated with sarilumab and 28 contemporary patients receiving standard of care alone were used as controls. At day 28 of follow-up, 61% of patients treated with sarilumab experienced clinical improvement and 7% died. These findings were not significantly different from the comparison group (clinical improvement 64%, mortality 18%; p=NS). Baseline PaO_2/FiO_2 ratio >100 mm Hg and lung consolidation <17% at CT scan predicted clinical improvement in patients treated with sarilumab. Median time to clinical improvement in patients with lung consolidation <17% was shorter after sarilumab (10 days) than after standard treatment (24 days; p=0.01). The rate of infection and pulmonary thrombosis was similar between the two groups.

Conclusions At day 28, overall clinical improvement and mortality in patients with severe COVID-19 were not significantly different between sarilumab and standard of care. Sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation at baseline.

Key messages

What is already known about this subject?
- Severe inflammation identifies a subset of patients with COVID-19 with dismal prognosis.
- Interleukin 6 (IL-6) represents a promising therapeutic target for patients with severe COVID-19 pneumonia and hyperinflammatory phenotype.

What does this study add?
- This is the first study to describe the safety of IL-6 blockade with intravenous sarilumab in patients with hyperinflamed COVID-19 pneumonia and to identify predictors of treatment response.

How might this impact on clinical practice or future developments?
- This study indicates that sarilumab is safe and effective in a specific subset of patients with severe hyperinflamed COVID-19 presenting with low percentage of lung consolidation on CT scan.
- Our study suggests that quantification of lung consolidation should be considered when treating patients with COVID-19 with IL-6 blocking agents as well as when designing clinical trials with alternative experimental drugs.

INTRODUCTION

In late December 2019, a new infectious coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in the city of Wuhan, China, and rapidly spread worldwide.[1–4] COVID-19 clinical manifestations vary from mild influenza-like symptoms in the majority of patients to acute respiratory distress syndrome (ARDS), multiorgan failure, and ultimately death in 1%–5% of cases.[5–8] Because there is currently no effective treatment for SARS-CoV-2 infection, management of life-threatening COVID-19 pneumonia is limited to supportive invasive or non-invasive oxygen therapy and to empiric antiviral drugs.

Severe COVID-19 is characterised by significantly elevated plasma level of the proinflammatory cytokines interleukin (IL)-1, IL-6, tumour necrosis factor α and granulocyte-macrophage colony-stimulating factor (GM-CSF) suggesting that hyperinflammation may represent a primary instigator of

SARS-CoV-2 related ARDS as well as a potential rationale therapeutic target.[1–16] In particular, elevated serum IL-6 levels have been associated to poorer outcome in these patients and with a mortality of nearly 20% at 14 days.[5–8 12 17 18] IL-6 is a cytokine with pleiotropic activity implicated in physiological haematopoiesis, immune response to pathogens and inflammatory disorders that closely resemble severe COVID-19 manifestations, such as the macrophage-activation syndrome and haemophagocytic lymphohistiocytosis.[19–21] Also, interference with IL-6 pathway has been approved for treating 'cytokine release syndrome' following chimeric antigen receptor T-cell therapy, another life-threatening condition sharing multiple analogies with the 'cytokine storm' observed in COVID-19.[22]

Based on this evidence, we considered IL-6 blockade with sarilumab—a recombinant human IL-6Rα antagonist—in addition to standard of care to treat patients with severe COVID-19 with hyperinflammatory phenotype and compared outcomes with concomitantly hospitalised patients receiving standard therapies alone.

METHODS

Study population

This open-label observational study was conducted from 14 March 2020, through 2 April 2020 at San Raffaele Hospital (Milan, Italy) during the COVID-19 outbreak in Lombardy

Table 1 Baseline demographic and clinical characteristics of the patients' cohort

	Total (n=56)	Sarilumab (n=28)	Comparison group (n=28)	P value
Age (years)	56 (51–60)	56 (49–60)	57 (52–60)	0.37
Male sex, n (%)	44 (78)	24 (85)	20 (71)	0.32
Duration of symptoms before enrolment (days)	7 (7–10)	7 (6–10)	7 (7–10)	0.81
Hospitalisation before enrolment (days)	2 (1–3)	2 (1–3)	3 (1–3)	0.51
Coexisting conditions, n (%)				
Arterial hypertension	17 (30)	6 (21)	11 (39)	0.24
Tobacco smoking	10 (18)	5 (18)	5 (18)	0.99
Dyslipidaemia	8 (14)	4 (14)	4 (14)	0.99
Coronary artery disease	6 (21)	2 (8)	4 (14)	0.66
Type 2 diabetes	9 (16)	3 (11)	6 (21)	0.46
Chronic obstructive pulmonary disease	2 (4)	1 (4)	1 (4)	0.99
Chronic renal failure	3 (5)	1 (4)	2 (8)	0.99
Oxygen support, n (%)				
Non-invasive positive-pressure ventilation	41 (73)	21 (75)	20 (71)	0.99
High-flow oxygen (FiO_2 ≥40 mm Hg)	15 (27)	7 (25)	8 (28)	0.99
Respiratory status, n (%)				
PaO_2/FiO_2 ratio 200–300	4 (7)	1 (4)	3 (11)	0.61
PaO_2/FiO_2 ratio 100–200	22 (39)	10 (36)	12 (43)	0.78
PaO_2/FiO_2 ratio <100	30 (54)	17 (60)	13 (46)	0.42
Fever >38°C, n (%)	37 (66)	20 (64)	17 (54)	0.57
Laboratory values				
Neutrophils (normal 1800–7000 cells/µL)	6000 (4000–8600)	6350 (3850–8525))	5400 (4000–8650)	0.81
Lymphocytes (normal 1000–4800 cells/µL)	900 (700–1200)	950 (700–1175)	800 (600–1200)	0.51
Platelets (normal 130–400 cells/µL)	242 (185–315)	255 (182–300)	221 (176–409)	0.79
LDH (normal 125–220 IU/L)	479 (394–594)	468 (397–585)	495 (389–635)	0.64
CRP (normal <6 mg/L)	152 (116–210)	143 (101–224)	152 (122–208)	0.54
Ferritin (normal 30–400 ng/mL)	1376 (1023–6927)	1849 (1006–2904)	1234 (1066–2987)	0.97
IL-6 (normal <7 pg/mL)	60 (36.4–126)	67.5 (37.5–127)	46 (34–117)	0.68
D-dimer (normal 0.27–0.77 µg/mL)	1.41 (0.78–2.29)	1.27 (0.59–1.99)	2 (0.88–5.96)	0.07
Creatine kinase (normal 20–195 IU/L)	115 (62–214)	135 (69–216)	87 (29–162)	0.17
AST (normal 5–35 IU/L)	57 (39–86)	57 (42–79)	55 (28–98)	0.61
ALT (normal 6–59 IU/L)	47 (30–73)	47 (34–73)	49 (24–88)	0.83
Radiological features*				
Consolidation (cc)	516 (289–828)	504 (288–846)	622 (266–993)	0.97
Consolidation (%)	15.8 (7.1–26.1)	16.6 (7.4–28.3)	14.2 (5.2–37.2)	0.72
Ground glass (cc)	1129 (954–1378)	1194 (963–1384)	992 (843–2138)	0.41
Ground glass (%)	33.9 (30.3–44.6)	34.5 (31.1–43.8)	32.2 (19.8–55.6)	0.77
Unaffected lung (cc)	1289 (801–2761)	1241 (781–2467)	1467 (484–3203)	0.86
Unaffected lung (%)	44.6 (26.1–60)	44.3 (26.5–59.2)	47.6 (10.1–74.85)	0.97

Continuous data are reported as median (IQR). Categorical data are reported as number of patients (n) and percentage (%). A p value < 0.05 was considered statistically significant.

*CT scan was performed at baseline in n=20 patients treated with sarilumab and in n=8 patients treated with standard of care.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin 6; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen ratio.

region. Patients enrolled were prospectively followed up with daily data collection into an electronic case report form (COVID-BioB Study, ClinicalTrials.gov NCT04318366).[23] Patients eligible to sarilumab were required to have (1) confirmed SARS-CoV-2 infection by reverse-transcriptase PCR on nasal-pharyngeal swab, (2) radiologically documented bilateral pneumonia and (3) severe hyperinflamed COVID-19 as defined in online supplementary material. Contemporary patients fulfilling the inclusion criteria and matched for age, sex, comorbidities, inflammatory markers, respiratory parameters and radiological findings on lung CT scan were identified and used as a comparison group.

Study design and treatments

Eligible patients received a single intravenous infusion of sarilumab 400 mg in addition to local standard of care. Specifically, two single-dose prefilled syringes, each containing 200 mg sarilumab, were added to 100 mL 0.9% sodium chloride and infused intravenously over 1 hour. Treatment with sarilumab was initiated on a compassionate indication within 24 hours from the fulfilment of inclusion criteria. All patients received oral therapy with lopinavir/ritonavir, hydroxychloroquine and a course of azithromycin as per local institutional standard of care at the time of admission (see online supplementary material). Supportive therapies with supplemental oxygen and/or non-invasive ventilation (NIV) with continuous positive airway pressure (with a positive end expiratory pressure (PEEP) of 10 cm of H_2O) were provided at the discretion of the clinicians. To better evaluate the effects of sarilumab on disease progression and lung inflammation, patients underwent a lung CT scan before treatment and either before discharge at clinical worsening. Quantification of 'normal parenchyma', 'ground-glass' and 'consolidation' areas was performed as detailed in online supplementary material according to published algorithms.[24 25] All patients provided written informed consent for off-label use of sarilumab. There has been no patient or public involvement in the conception, design and conduction of the present study.

Outcomes

Data on haemoglobin saturation, oxygen-support requirements, PaO_2/FiO_2 ratio, fever, laboratory values and adverse events were recorded daily from enrolment through day 28 of hospitalisation, intensive care unit (ICU) admission, discharge, or death, whichever came first. The main objective was to describe the overall survival and clinical improvement, including changes in oxygen-support requirements (ambient air, low-flow oxygen, high-flow oxygen, NIV, invasive mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO)), hospital discharge, MV-free survival and death using a six-category ordinal scale as recommended by the WHO R&D Blueprint Group (http://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/). The six-point scale consisted of the following categories: (1) not hospitalised; (2) hospitalised,

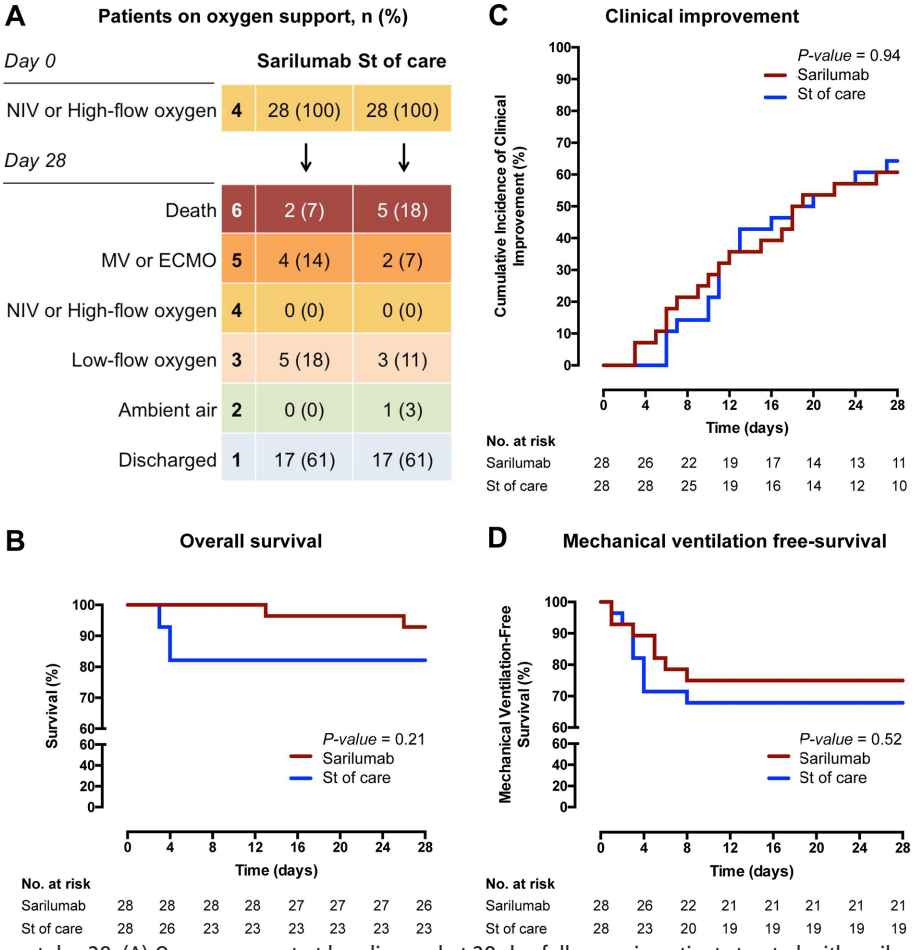

Figure 1 Main outcomes at day 28. (A) Oxygen support at baseline and at 28-day follow-up in patients treated with sarilumab and standard of care. Data are reported as number of patients and percentage. Cumulative incidence of (B) overall survival, (C) clinical improvement and (D) mechanical ventilation-free survival at 28 days is outlined in Kaplan-Meier curves. ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; NIV, non-invasive ventilation; St of care, standard of care.

Table 2 Summary of patient outcomes

	Sarilumab (n=28)	Comparison group (n=28)	P value
Clinical improvement, n (%)	17 (60)	18 (64)	0.99
Time to clinical improvement (days)	18 (9–28)	19 (11–28)	0.89
Death, n (%)	2 (7)	5 (18)	0.42
Time to death (days)	19 (13–26)	4 (3–4)	**0.006**
Live discharge, n (%)	17 (60)	17 (60)	0.99
Time to discharge (days)	12 (8–20)	13 (10–20)	0.35
Mechanical ventilation, n (%)	6 (21)	7 (25)	0.99
Time to mechanical ventilation (days)	5 (1–6)	3 (2–4)	0.52
Fever resolution, n (%)	28 (100)	28 (100)	0.99
Time to fever resolution (days)	1 (1–1)	4 (1–4)	**<0.0001**
CRP normalisation, n (%)	24 (86)	17 (61)	0.06
Time to CRP normalisation (days)	6 (4–7)	12 (9–15)	**<0.0001**
Adverse events			
Infections	6 (21)	5 (18)	0.99
Neutropenia	4 (14)	0 (0)	0.11
Increase in liver enzymes	4 (14)	0 (0)	0.11
Thromboembolism	2 (7)	2 (7)	0.99

Categorical data are reported as number of patients (n) and percentage (%).
Increase in liver enzymes indicates an increase in serum levels of alanine aminotransferase and aspartate aminotransferase more than three times the upper limit of normal. A p value < 0.05 was considered statistically significant.
Bold indicates significant values.
CRP, C-reactive protein.

not requiring supplemental oxygen; (3) hospitalised, requiring supplemental oxygen; (4) hospitalised, requiring nasal high-flow oxygen therapy, NIV or both; (5) hospitalised, requiring MV, ECMO, or both; and (6) death. Clinical improvement was defined as discharge from hospital, a decrease of at least two points from baseline on the six-category ordinal scale, or both. Additional outcomes included time to C reactive protein (CRP) normalisation, time to fever resolution, time to PaO_2/FiO_2 ratio improvement, and duration of hospitalisation in survivors. Independent predictors of clinical response to sarilumab were also assessed. Safety outcomes included adverse events that occurred during treatment.

Statistical analysis

Statistical analyses are detailed in online supplementary material.

RESULTS

Baseline characteristics of the patients' cohorts

Twenty-eight patients with severe COVID-19 pneumonia and inflammatory phenotype were treated with sarilumab in addition to local standard of care. Twenty-eight concomitant matched patients were treated with standard of care alone. As shown in table 1, there were no significant differences between the two groups in baseline demographic characteristics, laboratory test results, respiratory parameters, radiological findings and distribution of ordinal scale scores at the time of enrolment. Of note, all patients were on high-flow oxygen supplementation and most were also on NIV due to moderate ARDS (PaO_2/FiO_2 ratio=100–200 mm Hg with a PEEP ≥5 cm H_2O; 39%) or severe ARDS (PaO_2/FiO_2 ratio <100 mm Hg with a PEEP ≥5 cm H_2O).

Clinical outcomes and effects on systemic inflammation

Clinical outcomes at 28-day follow-up are summarised in figure 1 and table 2. Specifically, the survival rate was numerically higher in the sarilumab group (26/28 patients, 93%) than in the comparison group (23/28 patients, 82%) but this difference was not statistically significant (HR 0.36; 95% CI 0.08 to 1.68; p=0.21; figure 1B). Of note, median time to death was significantly longer in the former group (19 days, IQR 13–26 vs 4 days, IQR 3–4; p=0.006). Reported causes of death were refractory hypoxia and multiorgan failure in the sarilumab group, massive pulmonary embolism (one patient), refractory hypoxia and multiorgan failure (two patients each) in the comparison group. Multiorgan failure occurred after ICU admission in patients with concomitant bacterial infections. The median time to clinical improvement, the median length from hospitalisation to discharge and the MV-free survival at 28 days were similar between the two groups (figure 1C,D).

At 28-day follow-up, CRP normalised in 24/28 patients (86%) treated with sarilumab and in 17/28 patients (61%) in the comparison group (p=0.06), and all patients in both groups became afebrile. Treatment with intravenous sarilumab was associated with a significantly earlier reduction of serum CRP and fever resolution (table 2 and online supplementary figure 1).

Safety

A total of 12/28 patients (43%) in the sarilumab group and 10/28 patients (36%) in the control group reported adverse events between baseline and day 28 (table 2). Six patients (21%) in the sarilumab group and five (18%) in the comparison group experienced bacterial infections during permanence in ICU. Infections in the sarilumab group occurred after a median of 11 (6–14) days from the infusion and were polymicrobial in 4/6 cases. No polymicrobial infections were observed in the comparison group. Germs isolated from the blood stream of both groups included *Enterococcus faecalis*, *Staphilococcus haemoliticus*, *Staphilococcus hominis*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*. Germs isolated from the blood stream of patients treated with sarilumab included *Candida albicans*, *Propionibacterium acnes*, *Pseudomonas aeruginosa* and *Corynebacterium pseudodiftericum*. One case of pulmonary thromboembolism and deep vein thrombosis was observed in either group (sarilumab and standard of care). A transitory elevation of liver enzymes >3 times the upper limit of normal (ULN) and a reduction of the absolute neutrophil count $<1000\times10^3$ cells/μL were reported in four patients treated with sarilumab. In all four cases, neutropenia persisted until discharge or at 28 days of follow-up without evidence of concomitant infection. No infusion-related adverse reactions were reported.

Predictors of clinical outcomes in patients treated with sarilumab

At univariate analysis, serum IL-6 level, PaO_2/FiO_2 ratio, the percentage of lung consolidation and total volume of consolidated lung were associated with clinical improvement in patients treated with sarilumab (table 3). Of note, serum IL-6 levels did not correlate with the other predictors of clinical improvement whereas a strong negative correlation was found between PaO_2/FiO_2 ratio and lung consolidation (figure 2A and online supplementary figure 2). No other clinical, serological or radiological variables were associated with clinical improvement at univariate analysis (table 3). The PaO_2/FiO_2 ratio, the percentage of lung consolidation and total volume of consolidated lung also represented independent predictors of clinical improvement at

Table 3 Baseline univariate predictors of clinical improvement in patients treated with sarilumab

	Improved (n=17)	Not-improved (n=11)	P value
Age (years)	56 (48–57)	56 (49–69)	0.36
Sex (male/female)	15/2	9/2	0.99
Time to sarilumab (days)	10 (9–11)	9 (8–10)	0.17
Non-invasive mechanical ventilation, n (%)	11 (65)	11 (100)	0.06
Coexisting conditions, n (%)			
Arterial hypertension	2	4	0.17
Tobacco smoking	2	3	0.35
Dislipidaemia	3	1	0.99
Coronary artery disease	2	0	0.51
Type 2 diabetes	1	2	0.54
Chronic obstructive pulmonary disease	1	0	0.99
Chronic renal failure	0	1	0.99
PaO_2/FiO_2 ratio (mm Hg)	112 (84–138)	81 (50–104)	**0.002**
Axillary temperature, °C	38 (37.7–38.2)	38 (37.5–38.0)	0.61
Laboratory values			
CRP (normal <6 mg/L)	154 (110–256)	122 (100–329)	0.86
Ferritin (normal 30–400 ng/mL)	1849 (1006–5333)	1737 (931–4570)	0.89
LDH (normal 125–220 IU/L)	456 (394–539)	429 (409–608)	0.31
IL-6 (normal <7 pg/mL)	58 (28–113)	99 (37–130)	**0.03**
AST (normal 5–35 IU/L)	55 (36–77)	63 (46–84)	0.37
ALT (normal 6–59 IU/L)	47 (34–72)	47 (31–74)	0.21
Creatine kinase (normal 20–195 IU/L)	141 (67–352)	115 (56–183)	0.51
D-dimer (normal 0.27–0.77 µg/mL)	1.08 (0.54–1.71)	1.2 (0.81–2.3)	0.25
Platelets (normal 130–400 cells/µL)	257 (192–307)	254 (167–557)	0.75
Lymphocytes (normal 1000–4800 cells/µL)	1000 (700–1250)	900 (600–1000)	0.43
Neutrophils (normal 1800–7000 cells/µL)	6300 (4500–16500)	6700 (3500–8600)	0.99
Radiological features*			
Consolidation (cc)	348 (264–566)	1034 (745–1422)	**0.002**
Consolidation (%)	10.7 (6–19.7)	34.9 (20.1–45.9)	**0.013**
Ground glass (cc)	1218 (906–1580)	1098 (1004–1232)	0.64
Ground glass (%)	33.7 (30–49.4)	34.5 (30.6–40.3)	0.98
Unaffected lung (cc)	1875 (846–3070)	908 (436–1551)	0.12
Unaffected lung (%)	55.6 (27–61)	27.9 (16–46.3)	0.06

Variables associated with clinical improvement (defined as discharge from hospital or two points improvement from baseline on the six-category ordinal scale) at 28 days in patients treated with sarilumab were studied by univariate analysis. Continuous data are reported as median (IQR). Categorical data are reported as number of patients (n) and percentage (%). A p value <0.05 was considered statistically significant.

*CT scan was performed at baseline in n=13 patients who improved after sarilumab, in n=7 patients who did not improve, in n=18 patients who survived at 28-day follow-up, and in the n=2 patients who died.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin 6; LDH, lactate dehydrogenase; PaO2/FiO2 ratio, partial pressure of arterial oxygen/fraction of inspired oxygen ratio.

multivariate analysis, showing an HR of 0.87 (95% CI 0.86 to 0.99; p=0.03), of 0.89 (95% CI 0.88 to 0.98; p=0.01) and of 0.88 (95% CI 0.86 to 0.98; p=0.01), respectively.

To further address the performance of these variables, cut-off values were generated by receiver operating characteristic (ROC) curves. A baseline PaO_2/FiO_2 ratio of 100 mm Hg differentiated patients experiencing clinical improvement with a sensitivity of 100% and a specificity of 58% (area under the ROC curve (AUC) 0.78; 95% CI 0.62 to 0.95; p=0.01). Clinical improvement was observed in 91% of cases with a baseline PaO_2/FiO_2 ratio >100 mm Hg and in 41% of cases with a PaO_2/FiO_2 ratio <100 mm Hg. Median time to clinical improvement was shorter in patients with a baseline PaO_2/FiO_2 ratio >100 mm Hg (7 (5–15) days vs 28 (18-28) days; HR 0.18; 95% CI 0.02 to 0.26; p=0.0001; figure 2B). A percentage of lung consolidation of 17% at CT scan predicted clinical improvement after sarilumab with 100% sensitivity and 75% specificity (AUC 0.91; 95% CI 0.76 to 1; p=0.006). Clinical improvement was observed in 100% of cases with <17% of consolidated lung and in only 33% of cases with lung consolidation >17% (figure 3). Median time to clinical improvement was shorter in patients with <17% of consolidated lung (10 (7–17) days vs 28 (21–28) days; HR 0.11; 95% CI 0.03 to 0.31; p=0.0003; figure 2C). A total volume of lung consolidation of 600 cc at CT scan also demonstrated excellent performance in predicting clinical improvement after sarilumab (100% sensitivity; 83% specificity; AUC 0.95; 95% CI 0.87 to 1; p=0.002; online supplementary figure 2).

Results of univariate analysis for clinical improvement in patients treated with standard of care are reported in online supplementary table 1. Of note, while disease progression in patients treated with sarilumab and with standard of care was comparable regardless of baseline PaO_2/FiO_2 ratio, a significantly shorter time to clinical improvement was observed in patients treated with sarilumab having a baseline percentage of

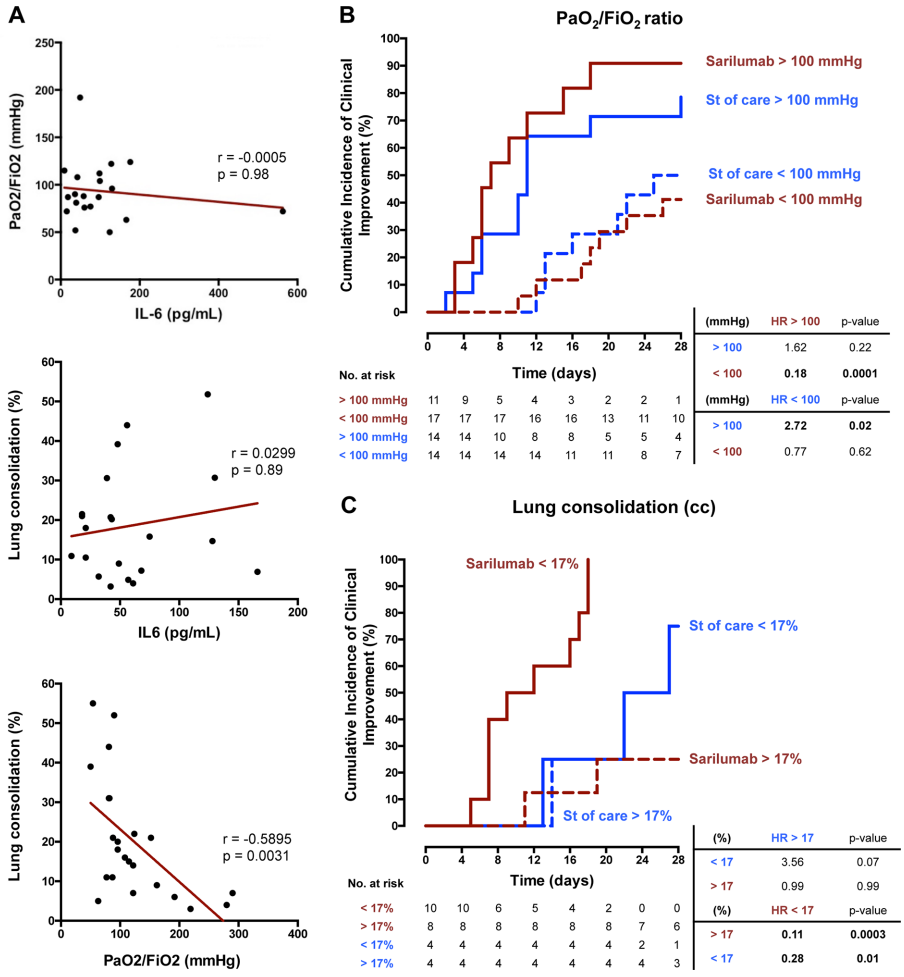

Figure 2 Predictors of clinical improvement in patients treated with sarilumab. Correlation studies between predictors of clinical improvement identified by univariate analysis in patients treated with sarilumab (A). Cumulative incidence of clinical improvement in patients treated with sarilumab and standard of care defined as discharge from hospital or two points improvement from baseline on the six-category ordinal scale according to baseline PaO_2/FiO_2 ratio (B), and total volume of lung consolidation (C).

consolidated lung <17% (median 10 (7–17) days vs 24 (15–27) days; HR 0.28; 95% CI 0.06 to 0.61; p=0.01) as well as a volume of lung consolidation <600 cc (median 10 (7–17) days vs 24 (15–27) days; HR 0.32; 95% CI 0.07 to 0.58; p=0.01; figure 2C and online supplementary figure 2)

DISCUSSION

In this open-label observational study, we report on the first experience with high-dose intravenous sarilumab in patients with severe COVID-19 in addition to local standard of care. Sarilumab was used off label on a compassionate indication in a clinical setting overwhelmed by the COVID-19 pandemic. The 400 mg intravenous dose was decided based on pharmacokinetic and safety profiles similar to tocilizumab, another IL-6R antibody approved for rheumatoid arthritis, recently used in series of patients affected by COVID-19 with encouraging results.[15 26 27] Indeed, in light of the presumed central role of IL-6 in COVID-19 pathogenesis, tocilizumab was rapidly approved by the China National Health Commission for the treatment of critical patients with COVID-19 and is currently being tested in several of clinical trials (clinicaltrials.gov).[28] Patient enrolment in our study was, therefore, not only based on the presence of severe pneumonia but also tailored on a hyperinflammatory phenotype presumably driven by increased serum IL-6 characterised by fever, elevation of CRP and ferritin levels.[5–7]

IL-6 blockade with sarilumab was generally safe and associated with a low mortality rate, which however did not reach statistical significance when compared with what observed in a concomitant group of patients treated with standard of care alone. Similarly, sarilumab treatment was not associated to statistically significant improvements in the MV-free survival and in the duration of hospitalisation. These results might be at least partially explained by the limited number of subjects enrolled and by the relatively young age of the patient population (median 56 years), both being potential reasons that could have not allowed to record meaningful effects of sarilumab over standard of care. Indeed, age >65 years represents an independent predictor of COVID-19 mortality according to the majority of published international cohorts.[1–3 29] Accordingly, the young age of the study cohort might have been associated with a better outcome even when receiving standard of care alone, thus requiring a larger number of recruited patients to show a statistically significant advantage for the treatment.

In the present study, we also observed that baseline serum IL-6 level was apparently not associated with clinical improvement or overall survival, a finding that contrasts with the accepted notion of IL-6 being a predictor of dismal prognosis in patients with COVID-19.[1–3] Indeed, IL-6 serum level did not emerge as an independent predictor of clinical outcome in patients hospitalised at our institution during COVID-19 outbreak in northern

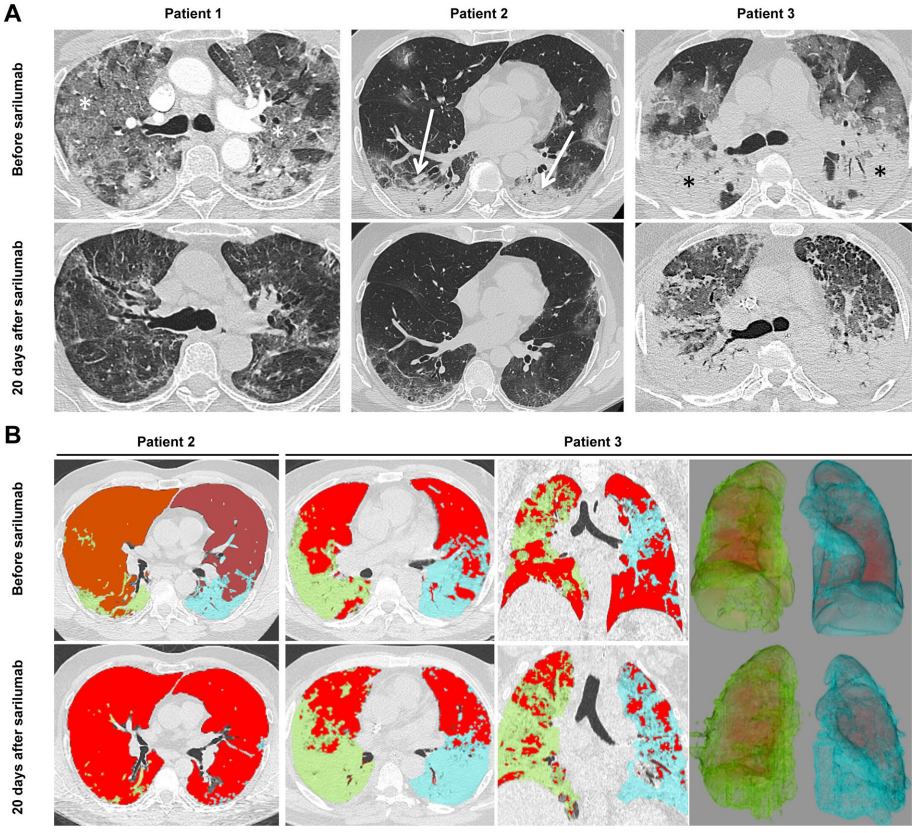

Figure 3 Imaging findings before and after sarilumab. (A) CT scan showing radiological improvement of bilateral 'ground-glass' opacities (asterisk) and lung consolidations (arrows) 20 days after enrolment in a patient treated with standard of care (patient 1) and in one treated with sarilumab (patient 2) having a volume of lung consolidation <17% at baseline. CT scan showing worsening of lung consolidations (asterisks) 20 days after sarilumab in a patient with a volume of lung consolidation >17% before infusion (patient 3). (B) Semiautomatic segmentation and quantification analysis of CT scans of patient 2 (axial) and patient 3 (axial, coronal and volume rendering) before and after sarilumab. Lung consolidations are shown in green (right lung) and blue (left lung).

Italy either, suggesting that pathophysiological mechanisms inherent to IL-6 pathway are likely not the only drivers of lung consolidation and respiratory failure in these patients.[29 30]

Still, our pioneering experience with sarilumab in severe COVID-19 provides three comforting suggestions. First, although not statistically significant, patients dying after sarilumab were numerically half of the patients treated with standard of care alone and time to death was significantly longer in the sarilumab group. While waiting for definitive confirmation of sarilumab efficacy in patients with severe COVID-19 from ongoing randomised trials, this last finding may acquire particular relevance in settings overwhelmed by COVID-19 outbreak and in shortage of ICU resources whereby prolonging survival may allow buying time to grant critical patients access to life-saving ICU or experimental treatments. Second, the rate of severe secondary infections—a possible major safety concern which might be expected during IL-6-blocking treatments—was not increased in sarilumab-treated patients as compared with those receiving standard of care. Third, the time to clinical improvement in patients with <17% of consolidated lung was significantly shorter after sarilumab infusion than after standard treatment. This last observation suggests that IL-6 blockade might be more effective if administered at a determinate radiological stage of COVID-19 pneumonia, possibly corresponding to an early phase of lung damage. Finally, our experience advocates considering the use of CT scan for early stratification of hospitalised patients and for enrolment in clinical trials, since the quantification of lung consolidation was among the strongest predictors of clinical progression and response to sarilumab treatment.[31]

The results of ongoing randomised placebo-controlled trials on larger number of patients are eagerly awaited to possibly substantiate our findings. In addition, in view of similar pharmacokinetic and safety profiles, useful information from parallel studies with tocilizumab will also be of extreme value to assess the possible efficacy of higher sarilumab doses.[27 32 33] In this sense, while we cannot exclude that higher doses of sarilumab might result in better outcomes, we can anticipate that safety concerns would represent a major issue. Our experience with tocilizumab, in fact, suggests that patients treated with two 400 mg infusions 24 hours apart show an increased incidence of adverse infectious events with no better outcomes compared with patients treated with a single infusion, supporting the notion that disease burden rather than cumulative drug dose represents a major determinant of COVID-19 response to anti-inflammatory therapies.[15] Indeed, early administration of colchicine, a known anti-inflammatory compound approved for autoinflammatory conditions, was recently associated to clinical improvement in domiciliary patients with COVID-19 at risk of clinical deterioration as well as in hospitalised patients with moderate respiratory impairment.[34 35]

Our study has both limitations and strengths. On one hand, the non-randomised retrospective design and the limited number of patients preclude definitive conclusions on the efficacy of sarilumab in severe COVID-19. On the other hand, because lethality of COVID-19 is higher in elderly individuals,[1–3] the young age of the study population raises the possibility that a larger cohort would have been needed in order to demonstrate a statistically

significant benefit over a small number of expected worsening events. Nonetheless, the study cohort was homogeneous and enriched in equally severe cases with a highly inflamed phenotype and comparable serum IL-6 concentration. Patients' characteristics at baseline were also rigorously matched and age-related mortality was in line with our hospitalised population.[29] Additional strengths include strict inclusion criteria, a clear and consistent treatment scheme, an informative 28-day follow-up, the absence of concomitant corticosteroid therapy and the presence of a comparison group. Finally, we first describe unique radiological insights in a homogeneous populations of patients treated with sarilumab, providing a cornerstone experience for designing further tailored therapeutic approaches and clinical trials.

In conclusion, we herein describe the first experience with intravenous sarilumab in patients with severe COVID-19 with hyperinflammatory phenotype. This pioneering experience should inform future studies to assess this and other biological agents in the treatment of SARS-CoV-2 infection.

Author affiliations
[1]Unit of Immunology, Rheumatology, Allergy, and Rare Diseases, San Raffaele Hospital, Milano, Lombardia, Italy
[2]Università Vita-Salute San Raffaele, Milan, Italy
[3]Clinical and Experimental Radiology Unit, Experimental Imaging Center, San Raffaele Hospital, Milan, Italy
[4]General Medicine and Advanced Care Unit, San Raffaele Hospital, Milan, Italy
[5]Internal Medicine, Diabetes & Endocrinology Unit, San Raffaele Hospital, Milan, Italy
[6]Hematology and Bone Marrow Transplant Unit, San Raffaele Hospital, Milan, Italy
[7]Department of Anesthesia and Intensive Care, San Raffaele Hospital, Milan, Italy

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Collaborators SARI-RAF Study Group members: Piera Angelillo; Andrea Assanelli; Elena Baldissera; Nicola Boffini; Enrica Paola Bozzolo; Stefania Calvisi; Corrado Campochiaro; Valentina Da Prat; Diana Canetti; Adriana Cariddi; Antonella Castagna; Giulio Cavalli; Maria Pia Cicalese; Fabio Ciceri; Lorenzo Dagna; Francesco De Cobelli; Giacomo De Luca; Emanuel Della-Torre; Giuseppe Di Lucca; Gaetano di Terlizzi; Nicola Farina; Maria Fazio; Salvatore La Marca; Giovanni Landoni; Marco Lanzillotta; Gaia Mancuso; Giacomo Monti; Luca Moroni; Angela Napolitano; Chiara Oltolini; Diego Palumbo; Marco Ripa; Patrizia Rovere-Querini; Annalisa Ruggeri; Silvia Sartorelli; Paolo Scarpellini; Marzia Spessot; Alessandro Tomelleri; Moreno Tresoldi; Alberto Zangrillo.

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ORCID iDs
Emanuel Della-Torre http://orcid.org/0000-0002-9192-4270
Corrado Campochiaro http://orcid.org/0000-0001-6806-3794
Lorenzo Dagna http://orcid.org/0000-0002-7428-315X

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