

Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support

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Abstract

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), resulting in symptoms, such as fever, cough, and shortness of breath. The SARS-CoV-2 virus has also been suggested to initiate a cytokine storm in patients with COVID-19 evidenced by elevated cytokines, such as interleukin-6 (IL-6) and C-reactive protein (CRP).

We report preliminary data from 21 patients with COVID-19 who developed pneumonia/acute respiratory distress syndrome (ARDS) and participated in a compassionate-use program at Papa Giovanni XXIII hospital in Bergamo, Italy.

All 21 patients received intravenous siltuximab – a chimeric mAb that binds to and blocks the effect of IL-6 – at a dose ranging between 700 to 1,200 mg (median 900 mg). The median age of patients treated was 64 years, and all patients were followed for a median of eight days. Serum CRP levels reduced in all 16 patients with available

data following treatment. An improvement in the clinical condition was observed in 33% (7/21) of patients, 43% (9/21) of patients stabilized as evidenced by no clinically relevant change in their condition, and 24% (5/21) experienced a worsening in their condition. Of those patients who experienced a worsening in their condition, one patient died, and one patient experienced a cerebrovascular event.

This analysis is presented to inform the medical community of the potential role of siltuximab in treating patients with ARDS secondary to SARS-CoV-2 infection, and a cohort study with patients treated with standard therapy in our hospital is ongoing, and will report the 30-day mortality rates upon completion.

Introduction

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), resulting in symptoms, such as fever, cough, and shortness of breath.

SARS-CoV and the Middle East respiratory syndrome CoV (MERS-CoV) are highly pathogenic coronaviruses that infect the lower respiratory tract causing severe pneumonia that results in rapid viral replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine levels including Interleukin-6 (IL-6) and C-reactive protein (CRP) that lead to severe respiratory failure, which can be described as acute respiratory distress syndrome (ARDS) (Channappanavar R and Perlman S. 2017). The SARS-CoV-2 virus has also been suggested to initiate a cytokine storm in patients with COVID-19 (Mehta P et al. 2020). IL-6 blockade has been identified as a potential strategy to mitigate the complications associated with COVID-19 infection. Tocilizumab, an IL-6R targeted monoclonal antibody (mAb), received rapid approval in China for treatment of patients with severe COVID-19 and extensive lung damage (National Health Commission of China, 2020; Xu X et al. 2020). We report preliminary data from 21 patients with COVID-19 who developed serious respiratory complications and were treated with siltuximab, a chimeric mAb that binds to and blocks the effect of IL-6 (NCT04322188). Siltuximab is approved by the European Medicines Agency and the Food and Drug Administration of the USA for treatment of adults with multicentric Castleman's disease who are human immunodeficiency virus and human herpes virus-8 negative (EUSA 2019).

Methods

This investigator-led study retrospectively analysed data collected on patients with pulmonary infection by SARS-CoV-2 (confirmed by clinical and radiological assessment) and ARDS (in accordance with the Berlin 2012 criteria) (Definition Task Force ARDS, 2012) who were admitted to the Papa Giovanni XXIII Hospital in Bergamo, Italy. Patients were treated according to the hospital standard of care, and received treatment with siltuximab administered intravenously at a dose of 11 mg/kg/day over 1 hour. A second dose could be administered at the physician's discretion, as part of a compassionate-use program approved by the Hospital Ethics Board. Data analysis was completed on 27 March 2020, when all patients had at least 7 days of follow-up after siltuximab administration.

All patients, or their legal representative, provided consent to participate in the study.

Results

Baseline patient and disease characteristics

Between 11 March 2020 and 24 March 2020, 21 patients with confirmed COVID-19 were admitted to the hospital. The median age of patients was 64 years (range 48-75 years), and more men than women were treated: 85.7% of (18/21) patients were male. Fever was a presenting symptom in 90.4% (19/21) of patients, 61.9% (13/21) of patients had a dry cough, and 71.4% (15/21) of patients had dyspnea (Table 1). The most prevalent comorbidities in this group of patients were: hypertension in 42.8% (9/21), cardiovascular disease in 19.0% (4/21), diabetes in 23.8% (5/21) of patients, respectively. In addition, one patient had a malignancy, one patient had cerebrovascular disease, and one patient had chronic kidney disease.

At baseline, serum CRP results were elevated in all patients (median 23.4 mg/dL; range 9.5 to 43.1 mg/dL). The IL-6 levels were available for 19/21 patients and were outside of the normal range: median 139.5 pg/mL; range 113, 239 pg/mL (Table 2). The PaO₂/FiO₂ (partial pressure of arterial oxygen over the fraction of inspired oxygen) ratio was available for 20/21 patients, and the baseline median value was 127 (range 69.0 to 291.0). All the 21 patients in the study, required ventilation by either continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV).

Siltuximab administration

All 21 patients received siltuximab at a median dose of 900 mg, ranging from 700 to 1,200 mg (Table 3). Five patients received a second dose of siltuximab; for three of these five patients the infusions were two days apart, and for two of these patients the infusions were three days apart. Patients were treated with siltuximab within two days after initiating ventilation with either CPAP or NIV. The median follow-up for all patients was eight days.

Patient response to treatment with siltuximab

Following treatment with siltuximab, serum CRP levels reduced to within the normal range by Day 5 and remained stable in all 16 patients with available data throughout the follow-up period (Figure 1).

In addition, 33% (7/21) of patients experienced an improvement in their condition with a reduced need for ventilation (i.e. patients were removed from CPAP and NIV), 43% (9/21) of patients experienced a stabilizing of their condition, and 24% (5/21) of patients experienced a worsening of their condition and required intubation (Table 4). One patient developed a cerebrovascular event.

Discussion

This compassionate-use program was initiated to understand the feasibility of suppressing CRP production with siltuximab and improving the outcomes in patients with COVID-19 requiring CPAP or NIV for pneumonia/ARDS treatment. Initial evidence from China where the first cases of COVID-19 emerged, indicate that excessive production inflammatory markers, such as IL-6 and CRP, correlate with severity of disease (Chen X et al. 2020; Conti P et al. 2020; Diao B et al. 2020; Gong J et al. 2020; Liu et al. 2020; Yang et al. 2020), and many more studies report a significant increase in IL-6 or CRP levels in patients with severe or critical COVID-19 compared with those patients with mild disease (Cai et al. 2020; Chen J et al. 2020; Feng C et al. 2020; Huang Y et al. 2020; Liu J et al. 2020; Qin C et al. 2020; Ruan Q et al. 2020; Shi Y et al. 2020; Wang Y et al 2020; Wang Z et al. 2020; Wu C et al.2020; Xu W et al. 2020; Xu X et al. 2020; Zeng Q et al. 2020; Zhao Z et al. 2020; Zhang B et al. 2020; Zhou F et al. 2020; Zhou Y et al. 2020).

Similarly, data from our retrospective analysis also show that baseline IL-6 levels and serum CRP levels were elevated beyond the normal range in all of the patients with available data, indicating the presence of inflammation, and suggesting that these patients were experiencing a virus-driven cytokine storm in response to SARS-CoV-2 infection (Channappanavar R and Perlman S. 2017;Mehta P et al. 2020; Xu X et al. 2020). The siltuximab antibody IL-6 complex neutralizes the activity of IL-6 to prevent acute-phase expression of CRP. Therefore, serum CRP levels provide an indirect measure of siltuximab efficacy in neutralizing IL-6 (Bloomfield et al. 2019; EUSA 2019), which is a recognised component of the cytokine storm associated with COVID-19 (Mehta P et al. 2020; Xu X et al. 2020). Five days following treatment with siltuximab, serum CRP was reduced to within the normal range in all patients with available data, and levels stabilized through to Day 7 of follow-up suggesting that inflammation levels were reduced in response to treatment. Furthermore, the clinical outcome was improved in seven patients and stabilized in nine patients as evidenced by a decrease in the numbers of patients requiring ventilation. Of note, there were a high number of middle aged and overweight men treated, which may not be representative of a typical population (Guan P et al. 2020).

The limitations of this report include that the compassionate-use program was set-up in a short period of time, to determine the effectiveness of siltuximab to reduce serum CRP levels, and understand whether IL-6 and CRP levels can be controlled to improve the outcomes for patients with pneumonia/ARDS associated with COVID-19. In addition, the report includes a short follow-up period with a limited number of patients.

This analysis is presented to inform the medical community of the potential role of siltuximab in treating patients with SARS-CoV-2 infection who develop pneumonia/ARDS requiring CPAP/NIV. A cohort study matching patients treated with siltuximab to those treated with standard therapy at our hospital is ongoing and will report full clinical outcome upon completion. With extended follow-up, we anticipate that the natural history of the disease shall be better described.

References

Bloomfield M et al. Anti-IL-6 autoantibodies in an infant with CRP-less septic shock. *Front Immunol* 2019; doi: 10.3389/fimmu.2019.02629

Cai Q et al. COVID-19 in a designated infectious diseases hospital outside Hubei province, China. *MedRxiv* submitted for publication, 2020:doi.org/10.1101/2020.02.17.20024018

Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). <https://www.cdc.gov/coronavirus/2019-ncov/index.html>

Channappanavar R and Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopath* 2017; 39:529–539

Chen J et al. Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19. *MedRxiv* submitted for publication, 2020:doi.org/10.1101/2020.03.09.20033068

Chen X et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *MedRxiv* submitted for publication, 2020: doi.org/10.1101/2020.02.29.20029520

Conti P et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-29 (COVI-19 or SARS-CoV2): anti-inflammatory strategies. *J Biol Regul Homeostat Agents* 2020;33(2):doi:10.23812/CONTI-E.

EUSA Pharmaceuticals. SYLVANT summary of product characteristics. 2019.

Diao B et al. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). *MedRxiv* submitted for publication, 2020: doi.org/10.1101/2020.02.18.20024364

Definition Task Force ARDS. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526-33

Gong J et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.02.25.20025643

Feng C et al. A novel triage tool for suspected COVID-19. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.19.20039099

Guan W et al. Clinical characteristics of coronavirus disease 2019 in China. N Eng J Med 2020; DOI: [10.1056/NEJMoa2002032](https://doi.org/10.1056/NEJMoa2002032)

Huang Y et al. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.02.27.20029009

Liu J et al. Epidemiological, clinical characteristics and outcome of medical staff infected with COVID-19 in Wuhan, China: a retrospective case-series analysis. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.09.20033118

Liu T et al. The potential role in IL-6 monitoring coronavirus disease 2019. MedRxiv submitted for publication, 2020: doi.org/10.1101/2020.03.01.20029769

Mehta P et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020:[doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)

National Health Commission of China Treatment Guidelines for COVID-19, v7. Available at: <http://www.nhc.gov.cn/zycqj/s7652m/202003/a31191442e29474b98bfed5579d5af95.shtml> accessed Mar 2020 [Translated by Googletranslate]

Qin C et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020. <https://doi.org/10.1093/cid/ciaa248>

Ruan Q et al. Clinical predictors mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Inten Care Med 2020:doi.org/10.1007/s00134-020-05991-x

Shi Y et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.12.20034736v1

Xu W et al. Clinical characteristics of SARS-CoV-2 pneumonia compared to controls in Chinese Han population. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.08.20031658v1

Xu X et al. Effective treatment of severe COVID-19 patients with tocilizumab. China Xiv submitted for publication 2020; chinaXiv:202003.00026v1

Wang Y et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.06.20032342

Wang Z et al. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis 2020:doi.org/10.1093/cid/ciaa272

Yang P et al. Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.02.28.20028068

Zeng, Q et al. Mortality of COVID-19 is associated with cellular immune function compared to immune function in Chinese Han population. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.08.20031229

Zhao Z et al. Clinical and Laboratory Profiles of 75 Hospitalized Patients with Novel 2 Coronavirus Disease 2019 in Hefei, China. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.01.20029785

Zhang B et al. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. MedRxiv submitted for publication, 2020:doi.org/10.1101/2020.03.12.20035048

Zhou F et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020:doi.org/10.1016/S0140-6736(20)30566-3

Zhou Y et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. Biorxiv submitted for publication
2020:<https://www.biorxiv.org/content/10.1101/2020.02.12.945576v1>

Tables and Figures

Table 1: Demographics and baseline characteristics of patients infected with SARS-CoV-2 (*N=21 unless specified)

| Characteristics | All Patients N=21* |
|---|-------------------------------|
| Gender, N (%) | |
| Male | 18 (85.71) |
| Female | 3 (14.29) |
| Age (years) | |
| Median (range) | 64.0 (48-75) |
| Min, Max | 48, 75 |
| Height (cm), N=10 | |
| Median | 178.0 |
| Min, Max | 168, 195 |
| Weight (kg), N=20 | |
| Median | 85.0 |
| Min, Max | 60, 110 |
| Comorbidities, N (%) | |
| Hypertension | 9 (42.86) |
| Diabetes | 5 (23.81) |
| Cardiovascular disease | 4 (19.05) |
| Malignancies | 1 (4.76) |
| Cerebrovascular disease | 1 (4.76) |
| Chronic kidney disease | 1 (4.76) |
| Signs and symptoms, N (%) | |
| Fever | 19 (90.48) |
| Dyspnea | 15 (71.43) |
| Dry cough | 13 (61.90) |
| Diarrhea | 5 (23.81) |
| Fatigue | 4 (19.05) |
| Myalgia | 3 (14.29) |
| Anorexia | 2 (9.52) |
| Time from hospitalization to start of treatment (days) | |
| Median | 3.0 |
| Min, Max | 0, 8 |

| | |
|---|--|
| Bilateral involvement of chest radiograph (N, %), N=21 | |
| Yes | 21 (100) |
| No | 0 |
| Interstitial vs parenchymal involvement (N %), N=21 | |
| Interstitial | 18 (85.71) |
| Parenchymal | 3 (14.29) |
| Ventilation status, N (%) | All Patients N=21 n (%) |
| Non-Invasive ventilation | 21 (100) |
| Mechanical ventilation | 0 |

Table 2: Laboratory findings of interest in patients infected with SARS-CoV-2 on admission to hospital

| | All Patients N= 21 |
|--|-------------------------------|
| IL-6 (pg/mL), N=19 | |
| Median | 139.5 |
| Min, Max | 113, 239 |
| C-reactive protein (mg/dL) N=21 | |
| Median | 23.40 |
| Min, Max | 9.5, 43.1 |
| PaO₂/FiO₂ (ratio), N=18 | |
| Median | 127.0 |
| Min, Max | 69.0, 291.0 |

Table 3: Treatment parameters

| | All Patients N=21 |
|---|------------------------------|
| Treatment within 24 hours vs 48 hours from CPAP/NIV (N, %), N=21 | |
| Within 24 hours | 18 (85.71) |
| Within 48 hours | 3 (14.29) |
| Siltuximab Dose (mg), N=15 | |
| Median | 900.0 |
| Min, Max | 700, 1200 |
| Patients receiving second infusion of siltuximab (N, %), N=21* | |
| Patients receiving second dose | 5 (23.81) |
| Patients not receiving second dose | 16 (76.19) |

*One patient who was moved to the intensive care unit and subsequently died

**For 3 patients, the two infusions were 2 days apart, and for 2 patients, they were 3 days apart

Table 4: Clinical outcomes following treatment with siltuximab in patients infected with SAR-CoV-2 experiencing ARDS

| Clinical Outcome | All Patients N=21 N (%) |
|--|--|
| Improvement (released from CPAP/NIV) | 7 (33) |
| No clinically relevant change (continuous use of CPAP/NIV) | 9 (43) |
| Worsening of condition (intubation or death) | 5 (24) |

