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Experience with the use of siltuximab in patients with SARS-CoV-2 infection

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ABSTRACT

Objectives. The study aims to describe characteristics and clinical outcome of patients with SARS-CoV-2 infection that received siltuximab according to a protocol that aimed to early block the activity of IL-6 to avoid the progression of the inflammatory flare.

Patients and methods. Retrospective review of the first 31 patients with SARS-CoV-2 treated with siltuximab, in Hospital Clinic of Barcelona or Hospital Universitario Salamanca, from March to April 2020 with positive polymerase-chain reaction (PCR) from a nasopharyngeal swab.

Results. The cohort included 31 cases that received siltuximab with a median (IQR) age of 62 (56-71) and 71% were males. The most frequent comorbidity was hypertension (48%). The median dose of siltuximab was 800 mg ranging between 785 and 900 mg. 7 patients received siltuximab as a salvage therapy after one dose of tocilizumab. At the end of the study, a total of 26 (83.9) patients had been discharged alive and the mortality rate was 16.1% but only 1 out of 24 that received siltuximab as a first line option (4%).

Conclusions. Siltuximab is a well-tolerated alternative to tocilizumab when administered as a first line option in patients with COVID-19 pneumonia within the first 10 days from symptoms onset and high C-reactive protein.

Keywords: IL-6; siltuximab; COVID-19 mortality.

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Experiencia con el uso de siltuximab en pacientes con infección por SARS-CoV-2

RESUMEN

Objetivo. Nuestro estudio tiene como objetivo describir las características clínicas y evolución de los pacientes infectados por SARS-CoV-2 tratados con siltuximab, de acuerdo con el protocolo local, con objetivo de bloquear precozmente la actividad de la Interleukina-6 evitando la progresión de la cascada inflamatoria.

Pacientes y métodos. Estudio retrospectivo de los primeros 31 pacientes con COVID-19 tratados con siltuximab en el Hospital Clínic de Barcelona y en el Hospital Universitario de Salamanca, en el periodo de marzo a abril, que tenían una PCR en frotis nasal positiva para SARS-CoV-2.

Resultados. Fueron incluidos 31 pacientes tratados con siltuximab, con una mediana (RIC) de edad de 62 años (56-71) y una prevalencia de varones del 71%. La comorbilidad más frecuente fue la hipertensión arterial (48%). La mediana de dosis administrada de siltuximab fue 800 mg con un rango de 785 mg a 900 mg. Siete pacientes recibieron siltuximab como terapia de rescate después de una dosis de tocilizumab. Al final del estudio, un total de 26 (83.9) pacientes recibieron alta hospitalaria vivos. La tasa de mortalidad fue de 16.1%, sin embargo, solo 1 de los 24 pacientes que recibieron siltuximab como primera línea de tratamiento falleció (4%).

Conclusiones. Siltuximab es una alternativa bien tolerada al uso de tocilizumab como primera línea de tratamiento para pacientes con neumonía por COVID-19 dentro de los primeros 10 días de síntomas y con proteína C-reactiva elevada.

Palabras clave: IL-6; siltuximab; COVID-19, mortalidad.

INTRODUCTION

Infection by Coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan and rapidly spread around the world. SARS-CoV-2 is characterized by a high viral replication during the first days associated to a range of clinical manifestations from asymptomatic or mild to classical symptoms including fever, bad general status, myalgia, and cough. More than 80% of the infected patients have a self-limited infection but 15-20% develop a severe pneumonia and require hospital admission. In contrast to other respiratory virus bacterial co-infection is not a major cause of hospitalization, but it is characterized by a progressive respiratory failure, and bilateral infiltrates in the X-ray that resembles an adult distress respiratory syndrome (ARDS) [1]. This clinical pattern associated with severe lymphopenia and high C-reactive protein (CRP) and other raised inflammatory parameters suggests that this corresponds with the cytokine release syndrome (CRS) [2].

Interleukin-6 (IL-6) plays an important role in CRS, therefore, the inhibition of this cytokine has been proposed as potential alternative for severe pneumonia due to SARS-CoV-2 [3]. The first description included 21 patients that were admitted in a Chinese hospital and received tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody. In few days, symptoms improved remarkably, in 75.0% of patients lowering of their oxygen intake was possible and no patient died. Currently, there is experience with tocilizumab in randomized trials [4,5]. No one of these studies have demonstrated a reduction in the mortality rate among those receiving the anti-IL-6 therapy but they were not powered enough to detect differences in mortality and at least in one of them there was a significant reduction in the intensive care unit (ICU) admission among those receiving tocilizumab [6]. Siltuximab is a chimeric monoclonal antibody that binds to and neutralizes the effect of IL-6 [7] instead of blocking the IL-6 receptor. A study from Italy evaluated siltuximab in 30 patients that were matched to 30 control patients using the propensity score analysis of baseline covariates. The 30-day mortality rate was significantly lower in the siltuximab-treated than the matched-control cohort patients (HR 0·462, 95% CI 0·221– 0·965); p=0·0399). Sixteen siltuximab-treated patients were discharged from hospital, four remained on mechanical ventilation, and 10 patients died. However, this article is included in a repository and it is not yet peer reviewed.

The main objective of the present article is to describe the characteristics and clinical outcome of the first 31 patients in two hospitals with a SARS-CoV-2 infection that received treatment with siltuximab according to a protocol that aimed to early block the activity of IL-6 to avoid the progression of the inflammatory flare.

PATIENTS AND METHODS

Both Hospitals ethical committees approved the study. The Institutional Ethics Committee of the Hospital Clinic of Barcelona approved the study and due to the nature of retrospective chart review, waived the need for inform consent from individual patients (HCB/2020/0273).

Patients admitted to Hospital Clinic of Barcelona or Hospital Universitario Salamanca, from March to April 2020 with a positive polymerase-chain reaction (PCR) from a nasopharyngeal swab or fulfilling the clinical diagnostic criteria for SARS-CoV-2 and treated with siltuximab were retrospectively reviewed.

The criteria for hospital admission were similar in both hospitals, including patients with respiratory symptoms and pneumonia (uni- or bilateral interstitial infiltrates) as indicated by the chest X-ray. For ARDS, the Berlin definition [8] was applied. When arterial blood oxygen pressure (PaO_2) was not available, the ratio between the percentage of oxygen saturation by fraction of oxygen inspired (SpO_2/FiO_2) ≤ 315 suggested ARDS in non-ventilated patients [9]. The antiviral treatment was initiated to all patients and consisted of lopinavir/ritonavir 400/100 mg twice a day for 7-14 days plus hydroxychloroquine 400 mg/12h on the first day, followed by 200 mg/12h for

Table 1 Baseline characteristics.

Study population	N (%)
Nº of patients	31
Age, median (IQR), years	62 (56-71)
Male sex (%)	22 (71)
Median follow-up, days (IQR)	14 (9-20)
Comorbidities	
Hypertension	15 (48.4)
Dyslipidaemia	11 (35.5)
Cardiomyopathy	4 (12.9)
Chronic respiratory disease	4 (12.9)
Diabetes mellitus	3 (9.7)
Chronic kidney disease	4 (12.9)
Initial symptoms	
Fever	30 (96.8)
Cough	23 (74.2)
Dyspnoea	14 (45.2)
Median days from symptom onset until admission (IQR)	7 (5-10)
Median days from admission to siltuximab administration (IQR)	2 (1-4)
Siltuximab administration in the regular ward (%)	25 (80.6)
Siltuximab administration in the ICU (%)	6 (19.4)
ARDS at hospital admission (%)	12 (38.7)
In hospital complications	
Acute renal failure without dialysis	5 (16)
Thrombosis	2 (6.5)
ARDS during hospitalization	13 (41.9)
Nosocomial infections	7 (22.6)
Urinary tract infection	3 (9.7)
Catheter associated infection	3 (9.7)
Not identified	1 (3.2)
Clinical outcomes (%)	
ICU admission in global cohort	11 (35.5)
ICU admission in 25 patients receiving siltuximab at general ward	5 (16.1)
Mechanical ventilation	
Non-invasive	9 (29)
Invasive	6 (19.4)
ICU discharge (%)	9 (81.8)
In-hospital mortality (%)	5 (16.1)

ICU, intensive care unit. ADRS, acute distress respiratory syndrome.

the next 4 days. From 18th of March, azithromycin 500 mg the first day and 250 mg/24h for 4 additional days was added to the regimen. The indication of an IL-6 inhibitor was the presence of pneumonia and progressive respiratory failure defined as the need of increasing the FiO_2 and a CRP ≥ 7 mg/dL or ferritin ≥800 ng/mL or lymphocyte count < 800 cells/mm^3. The first line option was tocilizumab but during the pandemic period the availability was limited and the alternative we chose was siltuximab. The dose was 11 mg/kg and a second dose could be administered at the physician's discretion. Siltuximab, in the majority of the cases presented in this report, was the first-line option but in some of them it was administered 24-48h after the first dose of tocilizumab due to non-adequate response (salvage therapy). The outcomes of the present study include intensive care unit (ICU) admission (for those patients that received siltuximab at the general ward), need of mechanical ventilation, in-hospital mortality rate and other complications including pulmonary embolisms and nosocomial infections.

Categorical variables were described using the absolute number and percentage and continuous variables using the median and interquartile range (IQR). The analysis was performed in SPSS version 23 (SPSS Inc., Chicago, IL).

RESULTS

The cohort included 31 cases that received siltuximab with a median (IQR) age of 62 (56-71) and 71% were males. The most frequent comorbidities were hypertension (48%), dyslipidaemia (35.5%), cardiomyopathy (12.9%), chronic respiratory disease (12.9%), chronic kidney disease (12.9%), and diabetes (9.7%). The median days from symptoms onset to hospital admission were 7 ranging from 5 to 10 days. Fever was a presenting symptom in 96.8% of patients, 74% also reported dry cough and 45.2% reported dyspnoea at hospital admission (table 1). Twenty-five (80.6%) patients had ARDS, 12 at hospital admission and 13 during hospital admission. ARDS was mild in 13 (41.9%) patients, moderate in 11 (35.5%), and severe in 1 (3.2%). All patients had a positive PCR from a nasopharyngeal swab and unilateral or bilateral interstitial infiltrate in the chest-X ray. Main laboratory findings at hospital admission are shown in table 2.

The median dose was siltuximab was 800 mg ranging between 785 and 900 mg. All patients received as antiviral treatment lopinavir/ritonavir plus hydroxychloroquine. Azithromycin was administered for 26 (83.9%) patients and 5 patients received remdesivir. As for other interleukin inhibitors, 8 patients also received tocilizumab and 6 anakinra. Eighteen

Table 2 Laboratory findings at hospital admission.

Laboratory findings, Median (IQR)	N (%)
D-dimer (ng/mL)[a]	800 (425-1,025)
Lymphocytes count (cell/mm^3)	900 (700-1,100)
C-reactive protein (mg/dL)	9.78 (5.09-24.64)
Ferritin (ng/mL)[b]	1,772 (971-2,204)
Lactate dehydrogenase (U/L)	346 (287-427)

[a] Measured in 30 cases; [b] Measured in 19 cases

Table 3 Additional antiviral and anti-inflammatory treatments.

Treatments received (%)	N (%)
Hydroxychloroquine	31 (100)
Lopinavir/ritonavir	31 (100)
Azithromycin	26 (83.9)
Remdesivir	5 (16.1)
Interferon	1 (3.2)
Steroid therapy	18 (58.1)
Steroid therapy prior to siltuximab	11 (35.5)
Tocilizumab	8 (25.8)
Tocilizumab prior to siltuximab	7 (22.58)
Days from tocilizumab administration to siltuximab (IQR)	2 (1-3)
Anakinra	7 (22.6)
Anakinra after siltuximab administration	6 (19.4)

patients (58.1%) received steroid therapy, 11 before siltuximab, 6 after, and 1 the same day (table 3).

Of the 25 patients that received siltuximab at a regular ward, 5 (16%) required intensive care unit (ICU) admission while 6 patients received siltuximab already in the ICU. Out of these 11 patients that required ICU admission, 6 required invasive mechanical ventilation (table 1). At the moment of the last revision, 26 (83.9) patients had been discharged alive and the mortality rate was 16.1% (5 patients). The mortality rate among the 7 patients that received siltuximab as a salvage therapy after tocilizumab was 43% (3 out of 7). On the other hand, only one patient out of 24 that received siltuximab as a first line option died (4%). Other clinical complications during admission included: thrombosis in 2 patients (one had a pulmonary embolism), 5 presented acute renal failure without need for dialysis, and 7 (22.6%) developed nosocomial infections during hospital admission, 3 a urinary tract infection and 3 a catheter-related bacteraemia (table 1).

DISCUSSION

Monoclonal antibodies directed against key inflammatory cytokines represent a class of adjunctive therapies for SARS-CoV-2 infected patients. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs is caused by a cytokine storm being IL-6 one of the key drivers. Therefore, monoclonal antibodies against IL-6 could theoretically improve clinical outcome. Many observational studies have demonstrated a potential efficacy of blocking the IL-6 pathway mainly using tocilizumab [10,11], in contrast, randomized trials have shown negative results in terms of reduction of mortality, but one has demonstrated a reduction in the risk of ICU admission [6]. Siltuximab was administrated to 31 patients with severe COVID-19 and the results when it is administered as a first line option are similar to those reported in our cohort using tocilizumab in the same indication [12]. As it would be expected, those patients that received siltuximab as a salvage therapy had a significantly worse outcome. Considering the mechanism of action of monoclonal antibodies, now it seems not reasonable to use it as a salvage therapy and when the patient is not responding to the IL-6 inhibition, probably these patients are not responding to IL-6 inhibition due to a different pathogenic mechanism that requires further investigation including co-bacterial infection, thrombosis or macrophage activation syndrome that require different treatment approaches.

In conclusion, siltuximab is a well-tolerated alternative to tocilizumab when administered as a first line option in patients with COVID-19 pneumonia within the first 10 days from symptoms onset and high C-reactive protein. In the future, it is necessary to better define the characteristics of patients that benefit from IL-6 inhibition as well as the precise timing of its administration.

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CONFLICTS OF INTEREST

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