Anakinra After Corticosteroid and/or Tocilizumab Treatment in Patients with Severe COVID-19 Pneumonia and Moderate Hyperinflammation. A Retrospective Cohort Study.

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Abstract

Introduction: Little evidence appears to exist for the use of anakinra, a recombinant interleukin-1 receptor antagonist, after non-response to treatment with corticosteroids alone or combined with tocilizumab in patients with severe COVID-19 pneumonia and moderate hyperinflammatory state.

Patients and Methods: A retrospective observational cohort study was carried out involving 143 patients with severe COVID-19 pneumonia and moderate hyperinflammation. They received standard therapy along with pulses of methylprednisolone (group 1) or methylprednisolone plus tocilizumab (group 2), with the possibility of receiving anakinra (group 3) according to protocol. The aim of this study was to assess the role of anakinra in the clinical course (death, admission to the intensive care ward) during the first 60 days after the first corticosteroid pulse. Clinical, laboratory, and imaging characteristics as well as infectious complications were also analyzed.

Results: 74 patients (51.7%) in group 1, 59 (41.3%) patients in group 2, and 10 patients (7%) in group 3 were included. 8 patients (10.8%) in group 1 died, 6 (10.2%) in group 2, and 0 (0%) in group 3. After adjustment for age and clinical severity indices, treatment with anakinra was associated with a reduced risk of mortality (adjusted hazard ratio 0.518, 95% CI 0.265-0.910; $p=0.0437$). Patients in group 3 had a lower mean CD4 count after 3 days of treatment. No patients in this group presented infectious complications.

Conclusions: In patients with moderate hyperinflammatory state associated with severe COVID-19 pneumonia, treatment with anakinra after non-response to corticosteroids or corticosteroids plus tocilizumab therapy may be an option for the management of these patients, and may improve their prognosis.

Introduction

In December 2019, a severe respiratory syndrome associated with pneumonia caused by a new human coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified, and spread rapidly to become a global public health problem [1]. The syndrome associated with this infection presents several clinical manifestations with a direct correlation between the severity of pneumonia, systemic inflammation, progression to respiratory failure, and death [2].

The clinical course of COVID-19 is characterized by three different phases [3]. In the initial phase there is strong viral replication accompanied by influenza-like symptoms. The second phase is usually associated with high fever and pneumonia-like symptoms, despite a steady decrease in viremia. Subsequently, some patients develop a third hyperinflammatory phase with an increase in cytokine storm markers such as C-reactive protein, ferritin, and D-dimers [4] along with a significant decrease in T lymphocytes. Adult respiratory distress syndrome (ARDS) as a result of hyperinflammation is considered the leading cause of death in these patients [5,6]. Once the hyperinflammatory state develops, prompt, individualized treatment is essential to control it and avoid multiorgan failure and death.

In patients with severe SARS-CoV-2 infection, increased IL-1 alpha and beta expression has been demonstrated prior to the deterioration in respiratory function, which supports the involvement of IL-1 in the physiopathology of ARDS in these patients [7].

Anakinra is a recombinant IL-1 receptor antagonist that is commonly used to treat hyperinflammatory conditions such as macrophage activation syndrome (MAS). Anakinra was shown to increase the survival rate in patients with sepsis who meet the criteria for MAS, and who had liver dysfunction and disseminated intravascular coagulation [8]. This drug has also been used to treat several rare syndromes characterized by hyperinflammation mediated by the altered regulation of cytokine responses [9] [10]. Several studies have reported the benefits of anakinra as an initial treatment for patients with hyperinflammation associated with severe SARS CoV-2 infection [11] [12] [13] [14], although these studies did not focus on patients who failed to respond to corticosteroid pulses or tocilizumab therapy alone or in combination.

In the present study we aimed to analyze the usefulness of IL-1 blockade with anakinra in a series of patients with severe pneumonia and moderate hyperinflammation after failure to respond to corticosteroid pulses and/or tocilizumab therapy. We also aimed to identify laboratory and clinical factors predictive of the response to anakinra.

Materials And Methods

Patients and Study Design

This retrospective cohort study included 143 patients admitted consecutively to San Cecilio University Hospital of Granada, Spain between 15 March and 15 May, 2020 with severe SARS-CoV-2 pneumonia and hyperinflammation. The diagnosis was confirmed by PCR in a nasopharyngeal exudate, and all patients had fever $>38^{\circ}\text{C}$ and met two of the following laboratory criteria: PCR >90 mg/L, ferritin level >500 $\mu\text{g/L}$, D-dimer level >0.5 mg/L. Severe pneumonia was considered present when basal oxygen saturation was $<93\%$ or partial O_2 pressure was <65 mmHg, with radiological evidence (chest X-ray or chest CT scan) of unilobar or multilobar involvement compatible with COVID-19 influenza [15].

All patients received standard treatment according to our hospital protocol, except when there were contraindications for electrocardiographic studies. The protocol consisted of hydroxychloroquine (800 mg/day on the first day and 400 mg/day for another 4 days), azithromycin (500 mg on the first day and 250 mg/day for 5 days), lopinavir/ritonavir (800/200 mg daily for 14 days), and ceftriaxone (2 g per day for 7–10 days) together with thromboembolism prophylaxis with low-molecular-weight heparin.

The immunosuppressive treatment protocol our hospital recommended for patients with hyperinflammation associated with severe SARS-CoV-2 pneumonia consisted of three phases. 1) Intravenous methylprednisolone (MTP) 2 mg/kg/day was given for 3 days, with the possibility of 2 further days if necessary due to partial clinical improvement (group 1, corticosteroid treatment). 2) After evaluating quality of life and life expectancy for each patient prior to admission, the medical team could

opt to use tocilizumab for those patients who did not show clinical improvement or whose respiratory condition worsened within 48 hours (group 2, CTS+TCZ). Tocilizumab was administered as a single intravenous dose adjusted according to body weight: patients <75 kg received 400 mg iv; those >75 kg received 600 mg. 3) In patients whose respiratory condition did not improve or worsened within 48 hours after starting treatment with TCZ, subcutaneous anakinra was administered during 48 hours. According to our center's protocol, anakinra could be administered instead of tocilizumab in patients with serum levels of IL-6 <40 pg/mL if there was no respiratory improvement 48 hours after receiving MTP boluses (group 3). The dose of anakinra was adjusted according to body weight. On the first day, patients who weighed 50–60 kg received 100 mg/12 h, patients who weighted 60–75 kg received 100 mg/8 h, and patients who weighed >75 kg received 100 mg/6 h. On the second day, all patients received 100 mg/12 h.

On admission, demographic characteristics (age, gender) and comorbidities (hypertension, diabetes, ischemic heart disease, kidney failure, heart failure, obesity, chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea) were recorded, along with laboratory data, clinical severity indices (CURB-65 and Quick Sepsis-related Organ Failure Assessment [qSOFA]), use of antiaggregants, anticoagulants, and ACEI/ARA-2, and radiological severity. The CURB-65 score is a quantitative measure of pneumonia severity [16], and the qSOFA score identifies patients with infection who are at high risk of death [17].

The following laboratory parameters were recorded before and 72 hours after treatment: C-reactive protein, serum ferritin, total lymphocyte count with CD4 and CD8 subpopulations, and D-dimers. The levels of CRP and ferritin were also analyzed 1 month after the first MTP bolus.

The severity of unilobar or multilobar pulmonary involvement was evaluated by chest X-ray and CT scan. A semiquantitative scoring system developed by the British Thoracic Imaging Society [18] was used to estimate lung involvement based on the affected area, and involvement was classified as mild (<25%), moderate (25–50%), or severe (>51%).

The primary outcomes of interest were the numbers of deaths and ICU admissions within 60 days after receiving the first corticosteroid pulse. Data were obtained from the digital medical records managed by our regional healthcare service, and were analyzed with SPSS software (version 24.1 licensed to the University of Granada). The study protocol was implemented in accordance with the principles of the Declaration of Helsinki. Each patient or their legal representative or closest relative was informed about the use of off-label treatments, and written informed consent was obtained to use these treatments, and to analyze and process the data.

Results

A total of 143 patients admitted consecutively between 15 March and 15 May, 2020 with severe SARS-CoV-2 pneumonia who met predefined hyperinflammation criteria were included in this study. For analysis and comparison, the patients were divided into three groups: 74 (51.7%) in group 1 (CTS), 59 (41.3%) in group 2 (CTS+TCZ), and 10 (7%) in group 3 (anakinra). Table 1 shows the clinical and

demographic characteristics and laboratory abnormalities in all patients treated with CTS, CTS+TCZ or anakinra upon admission, and their clinical course.

In the entire cohort, 52% of the patients were older than 65 years. Regarding the frequencies of comorbidities, 52% had hypertension, 41% had obesity, 25% had respiratory diseases, 18% had diabetes, 11% had kidney failure, 9% had heart failure, and 6% had ischemic heart disease. More than 2 comorbidities were recorded for 49 (31%) patients. No differences were found in the percentage frequencies of comorbidities between the different treatment groups.

On admission, chest X-ray revealed multilobar infiltrates in 109 patients (76%) and chest CT scan showed moderate to severe involvement in 65 (46%) patients.

No differences on admission were found between the three treatment groups regarding demographic characteristics, comorbidities, CURB-65 or qSOFA score, or degree of radiological involvement (Table 2).

Fifty-two percent of the patients received treatment with corticosteroid pulses only (group 1), 41% received corticosteroids plus tocilizumab (group 2), and 7% received anakinra (group 3) after failure to respond to treatment with corticosteroids alone or with tocilizumab.

All 14 deaths (9.8%) observed during the 60 day follow-up period after admission occurred within the first 30 days: 8 (10.8%) in group 1, 6 (10.2%) in group 2, and no deaths during this period in group 3. Of the 10 patients who received anakinra, 4 (40%) had previously received only corticosteroid pulses, and 6 (60%) had received combined therapy with corticosteroids and tocilizumab. More patients in group 2 (7, 11.9%) and group 3 (2, 20%) were intubated in comparison to group 1 (2, 2.7%), with a mean duration of UCI stay of around 4 weeks. By day 60 after admission, none of the patients was in the ICU, and the 2 patients in group 3 who required intubation had been extubated and transferred to the regular inpatient ward.

Table 3 shows the laboratory data for the different treatment groups on admission, after 3 days, and after 1 month. On admission there were no differences between treatment groups in the values of CRP, D-dimers, total lymphocytes, CD4, or CD8, except for the lower CD4 value on day 3 after admission in group 3.

To determine whether anakinra therapy was related to a better prognosis, the chi-squared statistical test of independence was used. In addition, the contingency coefficient was significant for the association between anakinra therapy and the patients' clinical course.

The 95% confidence interval for the difference in the proportions of patients who died while on anakinra treatment and those who died in groups 1 and 2 indicated that the mortality rate was lowest in group 3.

The Kaplan–Meier survival curves indicated a higher likelihood of survival at different time points in patients treated with anakinra (Figures 1 and 2).

Cox regression models adjusted for the variables age, CURB-55 score and qSOFA score provided the risk ratio for anakinra treatment, which showed that the risk of death was reduced by almost 50% in patients who received this therapy. Anakinra was well tolerated in all patients, and no infectious complications were recorded.

Discussion

Our findings suggest that the use of anakinra in patients with moderate hyperinflammation associated with severe SARS-CoV-2 pneumonia after previous failure of corticosteroid and/or tocilizumab therapy may be an alternative in the management of these patients, and may prevent deaths.

Immunosuppressive therapies are being used in patients with severe COVID-19 who develop hyperinflammatory state because of the pathogenic role of pro-inflammatory cytokines such as IL-1, IL-6 and tumor necrosis factor alpha.

Corticosteroid therapy has been used initially, and appears to reduce the mortality rate [19] [20]. Preliminary data from the RECOVERY trial showed that in severe COVID-19 pneumonia requiring oxygen or mechanical ventilation, moderate doses of dexamethasone resulted in lower 28-day mortality [21]. Tocilizumab, a humanized monoclonal antibody against IL-6, has been proposed to reduce the risk of intubation and/or death [22] [23] [24] [25] in patients with COVID-19 pneumonia associated with hyperinflammatory state, although it should be noted that the follow-up period in these previous studies was less than 28 days. In the present study, the 60-day mortality rate was similar in the group of patients who received corticosteroids and the group that received corticosteroids plus tocilizumab. However, the percentage of patients who required intubation was higher in the latter group, a finding probably related to the fact that those patients with worse quality of life and lower life expectancy for whom tocilizumab was ruled out as an option were also not considered candidates for ICU admission. These observations suggest that in patients with hyperinflammatory state who do not respond to corticosteroids, the addition of tocilizumab may not reduce mortality. This is consistent with phase III results from the COVACTA trial [26], which did not meet its primary endpoint of improved clinical status in hospitalized patients with severe COVID-19-associated pneumonia or its secondary endpoint of patient mortality at week 4. Together, these findings suggest the importance of determining the specific inflammatory profile in patients who are candidates for tocilizumab [27].

Anakinra is an IL-1 receptor antagonist that may be an alternative biologic for patients suffering from severe COVID-19 pneumonia and hyperinflammation who fail previous treatment with corticosteroids and/or tocilizumab. This drug may also have an additional beneficial effect on the prothrombotic state in these patients, since IL-1 blockade has been shown to reduce mortality rates in patients with acute myocardial infarction, as well as in patients with severe sepsis, liver dysfunction, and disseminated intravascular coagulation [28] [29] [30].

In the present study, 95% of the patients presented associated comorbidities, although without differences between treatment groups on admission in their CURB-65 or qSOFA scores. The predictive

factors associated with higher mortality rate and worse prognosis were age, diabetes mellitus, ischemic heart disease, obesity, heart failure, hypertension, and kidney failure. Older age was the most important factor in patients with SARS-CoV-2 infection, and has been associated with the development of ARDS and subsequent death [31].

In the present study, the 30-day and 60-day mortality rate was lower in the group that received anakinra as rescue treatment after failure to respond to corticosteroids alone or with tocilizumab. This may have been a result of using an early treatment strategy with anakinra in patients who had not improved or who had worsened within 48 hours after receiving corticosteroid pulses and/or tocilizumab.

No differences were found in patients' clinical course (death or ICU admission) at 60 days between patients with multimorbidity or patients older than 65 years treated with corticosteroids (group 1) and those who received corticosteroids and tocilizumab (group 2).

Regarding the 10 patients who received anakinra (group 3) because their clinical status did not improve or worsened despite treatment with corticosteroids and/or tocilizumab, their clinical course at 60 days (death or ICU admission) showed no association with previous treatment with corticosteroids alone or combined with tocilizumab. It is therefore possible that IL-1 blockade acted synergistically with corticosteroids or IL-6 blockade, and thus led to additional beneficial effects in controlling hyperinflammatory state.

The usefulness of anakinra therapy in patients with SARS-CoV-2 pneumonia who develop secondary hemophagocytic lymphohistiocytosis was recently reported [32]. This result together with the present findings suggests that anakinra could be administered instead of tocilizumab in patients with hyperinflammation associated with severe COVID-19 who have low serum IL-6 levels (<40) after failed corticosteroid therapy. The different cytokine profiles in these patients may determine their clinical response to the blockade of specific cytokines, a consideration we believe is important in designing future studies.

The likely beneficial effects of anakinra on the common pattern of coagulopathy observed in patients with COVID-19 were not associated with differences between groups in serum D-dimer levels before or after 3 days of treatment. Although IL-1 blockade has been associated with increased tissue factor expression, it is likely that other mechanisms derived from IL-1 blockade, such as reduced venous thromboinflammation and reduced platelet activation [33] [34] [35], may be beneficial in improving prothrombotic state in patients with severe SARS-CoV2 infection.

No differences were found in serum ferritin levels at 1 month between the three groups, suggesting that hyperinflammatory state was controlled to a similar degree in all patients regardless of their immunosuppressive treatment [36]. Although elevated ferritin levels have been considered a clinical factor associated with a poor prognosis in patients with cytokine storm [37], we observed no between-group differences in the association between serum ferritin levels and mortality – a finding probably related in part to the fact that the elevation in ferritin was moderate in all patients in the present cohort.

Other laboratory factors associated with a worse prognosis, e.g. lymphopenia [38], were not associated with an increased mortality rate in any treatment group. The analysis of lymphocyte subpopulations showed that CD4 count was significantly lower on day 3 in the group treated with anakinra, although there were no significant differences between groups in CD8 count. Patients with severe respiratory failure associated with SARS-CoV-2 infection present CD4 depletion, so it is likely that IL-1 blockade contributes to an increase in circulating CD4 and thus helps to restore immune balance, with a better prognosis [39].

The dose of anakinra used in the present cohort was established based on pharmacokinetic criteria and was adjusted to body weight in an effort to minimize the risk of infection, given that our patients had previously received corticosteroids and/or tocilizumab. In one recently published study [40] the dose of anakinra associated with clinical improvement in patients with ARDS, hyperinflammation, and COVID-19 was higher (10 mg/kg/d); however, these patients had not been previously treated with corticosteroids and/or tocilizumab. This higher dose of anakinra was associated with a 24% rate of severe adverse effects and a 14% rate of infectious complications. In the present study, no patients had infectious complications, probably because of the lower dose of anakinra; this finding was also reported in a recent study [13] that used similar doses of anakinra.

The limitations of the present study are its retrospective observational design and the small sample size of the group that received anakinra. In addition, all the patients rescued with anakinra were male, a factor associated with greater severity, and this does not allow us to extrapolate our observations to women. In addition, we note that the sample size in group 3 (anakinra treatment) was small, and that a larger sample size would likely influence the significance level. However, the patients were recruited consecutively, and the treatment protocol was the same for all patients. In addition, patients in all groups had similar clinical severity indexes and similar age distributions, making them a more or less homogeneous sample.

In conclusion, the use of anakinra in patients with moderate hyperinflammation associated with severe COVID-19 pneumonia after previous failure of corticosteroid and/or tocilizumab therapy may be an alternative for the management of these patients, and may reduce mortality. However, randomized clinical trials are needed to confirm the possible benefits of this therapeutic strategy.

Declarations

Ethics

Our study was approved by the ethics committee named "Comité Etico de Investigación Provincial de Granada".

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DECLARATION OF COMPETING INTERESTS

None.

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Abbreviations

COVID-19, human coronavirus disease caused by SARS-CoV-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ICU, intensive care unit; ARDS, adult respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; Quick Sepsis-related Organ Failure Assessment, qSOFA; CT, computed tomography; MAS, macrophage activation syndrome; CTS, corticosteroids; TCZ, tocilizumab

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Tables

Table 1. Clinical and demographic characteristics on admission, laboratory abnormalities, and clinical course in patients treated with CTS, CTS+TCZ or anakinra.

	CTS (Group 1)	CTS + TCZ (Group 2)	Anakinra (Group 3)	p-value*
mean (SD), years	68.18 (13.68)	62.17 (11.45)	60.80 (11.43)	0.950
sex, n (%)	39 (52.7)	40 (67.8)	10 (100)	0.011
-65 score , mean (SD)	1.81 (0.84)	1.80 (0.69)	1.50 (0.53)	0.828
A score , mean (SD)	0.55 (0.67)	0.80 (0.78)	0.40 (0.52)	0.680
rbidities n (%):				
ial hypertension	37 (50)	32 (54.2)	4 (40)	0.469
, asthma	16 (21.6)	18 (30.5)	2 (20)	0.696
ty	32 (43.2)	24 (40.7)	3 (30)	0.453
nic heart disease	4 (5.4)	4 (6.8)	0 (0)	0.425
; insufficiency	8 (10.8)	5 (8.5)	0 (0)	0.300
tes	12 (16.2)	12 (20.3)	2 (20)	0.877
insufficiency	11 (14.9)	4 (6.8)	0 (0)	0.262
.ted , n (%)	2 (2.7)	7 (11.9)	2 (20)	0.130
.tion duration , median days	29.50 (13)	29 (31.5)	24.50 (25)	0.272
lmission	36 (4)	14.5 (24)	30.50 (25)	0.374
on median (IQR),				
, n (%)	8 (10,8)	6 (10,2%)	0 (0%)	0.280
ng/L), mean (median;	99.38 (78.00;	136.69	118.54	0.501
	78.45)	(112.60; 72.60)	(94.10; 90.25)	
lcitonin , mean	0.19	0.28	0.17	0.933
an; SD)	(0.08; 0.32)	(0.16; 0.42)	(0.11; 0.16)	
loponia (<600	62 (83.8)	46 (78.0)	8 (80)	0.925
lL) n (%)				
nean (median; SD)	418.26	440.54 (429.50;	360.00 (343.50;	0.237
	(392.00;	210.85)	265.02)	
	212.59)			
nean (median; SD)	216.46	256.47 (206.00;	395.50 (424.00;	0.589
	(183.00;	207.24)	229.70)	
	147.75)			
in , mean (median;	846.86	1184.30	1032.88	0.497
	(676.00;	(915.20	(1129.20;	
	637.26)	;768.62)	517.59)	
l0 , n (%)	73 (98.6)	22 (37.3)	9 (90)	0.203
er , mean (median	6.42 (0.99;	5.31 (1.21;	1.11 (0.47; 2.06)	0.669
	38.59)	16.08)		
gregants,				
agulants				
blockers , n (%):				
ggregants	15 (20.3)	7 (11.9)	0 (0)	0.162
agulants	6 (8,1)	3 (5.1)	0 (0)	0.395
/ ARA-2	33 (44.6)	27 (45.8)	4 (40)	0.754

*For comparisons of group 1 and group 2 versus group 3.

Abbreviations: CTS, corticosteroids; TCZ, tocilizumab; IQR, interquartile range; SD, standard deviation; qSOFA, Quick Sepsis-related Organ Failure Assessment; AARS, angiotensin aldosterone renin system; ACEI, angiotensin-converting enzyme inhibitors;

ARA-2, angiotensin receptor antagonist 2; CRP, C-reactive protein; COPD: chronic obstructive pulmonary disease

Table 2. Analysis of the association between treatment and patient characteristics. Values of $p > 0.05$ indicate no association between treatment and a given characteristic or factor.

Factors	Variables	Chi-squared test	Degrees of freedom	p-value
Comorbidities	Arterial hypertension	1.654	2	0.437
	COPD, asthma	1.529	2	0.466
	Obesity	0.651	2	0.722
	Ischemic heart disease	0.755	2	0.686
	Heart failure	1.292	2	0.524
	Diabetes	0.399	2	0.819
	Kidney failure	3.546	2	0.170
Score				
	CURB-65	4.878	10	0.899
	qSOFA	6.991	6	0.322
Plain chest X-ray	Plain chest X-ray	3.112	4	0.539
CT involvement	CT involvement	5.645	4	0.227

Abbreviations: qSOFA, Quick Sepsis-related Organ Failure Assessment; CT, computed tomography

Table 3. Laboratory findings on admission, 3 days after admission, and 1 month after admission in different treatment groups.

Ferritin						
	Admission		Day 3		1 month	
Treatment	Mean (SD)		Mean (SD)		Mean (SD)	
Anakinra	1033.0	(517.676)	869.5	(390.068)	551.7	(467.396)
Corticosteroids alone	846.851	(637.269)	902.189	(718.175)	302.684	(242.688)
CTS + TCZ	1184.39	(768.602)	1207.63	(803.918)	416.868	(310.275)
D-dimer						
	Admission		Day 3			
Treatment	Mean (SD)		Mean (SD)			
Anakinra	1.0	(2.16025)	1.5	(2.36878)		
Corticosteroids alone	6.43243	(38.5899)	3.97297	(13.8069)		
CTS + TCZ	5.35593	(16.0546)	4.62712	(9.43745)		
Lymphocytes						
	Admission		Day 3			
Treatment	Mean (SD)		Mean (SD)			
Anakinra	1181.0	(640.129)	1069.0	(1289.91)		
Corticosteroids alone	1058.24	(585.087)	1028.93	(699.309)		
CTS + TCZ	978.305	(586.395)	981.525	(590.794)		
CD4						
	Admission		Day 3			
Treatment	Mean (SD)		Mean (SD)			
Anakinra	360.0	(265.019)	356.5	(294.864)		
Corticosteroids alone	418.262	(212.593)	876.643	(286.335)		
CTS + TCZ	440.542	(210.848)	815.875	(364.798)		
CD8						
	Admission		Day 3			
Treatment	Mean (SD)		Mean (SD)			
Anakinra	395.5	(229.702)	335.0	(265.872)		
Corticosteroids alone	216.462	(147.75)	592.786	(434.339)		
CTS + TCZ	256.479	(207.237)	627.063	(484.869)		
CRP						

	Admission		Day 3		1 month	
Treatment	Mean (SD)		Mean (SD)		Mean (SD)	
Anakinra	118.6	(90.2554)	29.1	(30.3844)	11.6	(16.3041)
Corticosteroids alone	99.3649	(78.4254)	49.3243	(68.9048)	9.84483	(35.5023)
CTS + TCZ	136.729	(72.6282)	57.322	(66.4873)	12.2963	(40.0272)

Abbreviations: SD, standard deviation; CTS, corticosteroids; TCZ, tocilizumab; CRP, C-reactive protein

Figures

Figure 1

Figure 2

Kaplan–Meier cumulative hazard curve