Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Compassionate use of tocilizumab in severe SARS-CoV2 pneumonia

Miguel Górgolas Hernández-Mora, Alfonso Cabello Úbeda, Laura Prieto-Pérez, Felipe Villar Álvarez, Beatriz Álvarez Álvarez, María Jesús Rodríguez Nieto, Irene Carrillo Acosta, Itziar Fernández Ormaechea, Aws Waled Mohammed Al-Hayani, Pilar Carballosa, Silvia Calpena Martínez, Farah Ezzine, Marina Castellanos González, Alba Naya, Marta López De Las Heras, Marcel José Rodríguez Guzmán, Ana Cordero Guijarro, Antonio Broncano Lavado, Alicia Maciás Valcayo, Marta Martín García, Javier Bécares Martínez, Ricardo Fernández Roblas, Miguel Ángel Piris Pinilla, José Fortes Alen, Olga Sánchez Pernaute, Fredeswinda Romero Bueno, Sarah Heili-Frades, Germán Peces-Barba Romero

Division of Infectious Diseases, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain
Department of Pneumology, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain
Department of Microbiology, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain
Department of Pharmacy, Fundación Jiménez Díaz, Spain
Department of Pathology, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain
Department of Rheumatology, Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Spain

Abstract

Introduction: Tocilizumab (TCZ) is an interleukin-6 receptor antagonist, which has been used for the treatment of severe SARS-CoV-2 pneumonia (SSP), which aims to ameliorate the cytokine release syndrome (CRS) induced acute respiratory distress syndrome (ARDS). However, there are no consistent data about who might benefit most from it.

Methods: We administered TCZ on a compassionate-use basis to patients with SSP who were hospitalized (excluding intensive care and intubated cases) and who required oxygen support to have a saturation >93%. The primary endpoint was intubation or death after 24 h of its administration. Patients received at least one dose of 400 mg intravenous TCZ from March 8, 2020 to April 20, 2020.

Results: A total of 207 patients were studied and 186 analyzed. The mean age was 65 years and 68% were male patients. A coexisting condition was present in 68% of cases. Prognostic factors of death were older age, higher IL-6, d-dimer and high-sensitivity C-reactive protein (HS-CRP), lower total lymphocytes, and severe disease that requires additional oxygen support. The primary endpoint (intubation or death) was significantly worst (37% vs 13%, p < 0.001) in those receiving the drug when the oxygen support was high (FiO2 >0.5%).

Conclusions: TCZ is well tolerated in patients with SSP, but it has a limited effect on the evolution of cases with high oxygen support needs.

© 2020 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Since December 2019, the SARS-CoV-2 pandemic has affected more than 12.5 million people worldwide and more than 560,000 fatalities have been recorded (Anon, 2020a) at the time of writing. Patients with severe SARS-CoV-2 pneumonia (SSP) die due to poor oxygenation despite ventilatory support and different...
treatments, including drugs with antiviral activity, such as remdesivir, lopinavir/ritonavir, interferon beta, hydroxychloroquine, and/or anti-inflammatory drugs, such as corticosteroids, azithromycin, and low molecular weight heparin amongst others (Cao et al., 2020; John et al., 2020; Colson et al., 2020; Arabi et al., 2018).

Pathological postmortem samples of lung and bone marrow of these patients show diffuse alveolar damage with alveolar edema, hyaline membranes, and microvascular thrombosis along with extensive hemophagocytosis in the bone marrow (Prieto-Pérez et al., 2020). Laboratory data show high levels of ferritin, interleukin-6, C-reactive protein, LDH, and D dimer, all indicative of a cytokine release syndrome (CRS)-induced acute respiratory distress syndrome (Guan et al., 2020; Chen et al., 2020; Li et al., 2020; Rodriguez-Morales et al., 2020) derived from the viral infection.

It is believed that the severity of SARS-CoV-2 pneumonia depends not only on the viral load in lung tissue but mainly on the inflammatory response of the host. Interleukin-6 is a key factor for the activation of the cis- and trans-signaling pathways leading to the CRS (Moore and June, 2020; Tejajo, 2017). Tocilizumab (TCZ) is an interleukin-6 receptor antagonist, which has been used for the treatment of rheumatoid arthritis (Navarro et al., 2014) and for the treatment of chimeric antigen receptor (CAR) T cell–induced CRS in cancer patients (Channappanavar and Perlman, 2017; Tanaka et al., 2016; Yildizhan and Kaynar, 2018). Information about its use for SARS-CoV-2 pneumonia is limited (Xu et al., 2020; Di Giambenedetto et al., 2020; Luo et al., 2020; Guaraldi et al., 2020), and the results of randomized clinical trials are still pending (Anon, 2020b; Anon, 2020c).

We present a cohort of 207 patients treated with TCZ at a single institution during the COVID-19 outbreak in Madrid with the aim to identify, which clinical or laboratory factors might influence the evolution of SSP in this group of patients and to evaluate the tolerance of this drug in this clinical entity.

**Methods**

**Patients**

From March 8 to April 19, 2020, a total of 207 patients with SSP admitted to the Fundación Jiménez Díaz University Hospital in Madrid received TCZ. SSP was defined as the presence of unilateral or bilateral lung infiltrates with basal oxygen saturation below 94% in patients with confirmed positive COVID-19 RT-PCR (Viasure® SARS-CoV-2 Real Time PCR detection kit) in nasopharyngeal or throat swabs or in the absence of microbiological confirmation, the existence of clinical (fever, cough, dyspnea, fatigue, etc.), radiological (lung infiltrates), epidemiological (close contact with documented patients), and laboratory data (lymphopenia, high levels of ferritin, high sensitivity C reactive protein (HSCRP), LDH, interleukin-6, and D-dimer) suggestive of COVID-19 infection.

Our standard treatment for SSP included lopinavir/ritonavir [200 mg/50 mg for 7 days] (if the disease started fewer than 7 days before admission), hydroxychloroquine [400 mg bid 1 day and 200 mg bid 4 days], doxycycline [100 mg bid for 7 days] or azithromycin [500 mg od for 5 days], low molecular weight heparin [Enoxaparin 20–40 mg od], cyclosporine [from 1.5 mg/kg/day], n-acetylcysteine [600 mg iv bid], pulse corticosteroids [methylprednisolone 250 mg iv od for 3 days] and, in some cases, interferon beta 1-b [0.25 mg/48 h subcutaneously for 14 days]. This treatment protocol was approved by the Drug Commission of the Fundación Jiménez Díaz University Hospital. The decision to use this combination of drugs despite not having the results of randomized clinical trials was based on the initial WHO and Spanish Ministry of Health recommendations plus the pathophysiological perception that intensive immunomodulation was required to ameliorate the disease severity.

TCZ was recommended as a rescue treatment for patients not improving after the initial three days of intensive therapy, including pulse steroids and low-dose cyclosporine (see above) and requiring a FiO2 greater than 0.35% to achieve an oxygen saturation above 93%. A single dose of TCZ [400 mg if weight <75 kg and 600 mg if >75 kg] was given intravenously. Seventeen patients with very severe disease (median FiO2 1% and IQR:0–4)–1 received one or two more consecutive doses if the drug was readily available. Twenty-nine patients received TCZ with FiO2 <0.35%, despite our protocol recommendation, because of their physician's decision. Ten patients received TCZ when they required high flow oxygen support (FiO2 >1) and were not included in the analysis as they were being attended at the intensive care respiratory unit, just before intubation at the intensive care unit. None of the patients included in the study were at the intensive care unit at the time of TCZ administration and none had any concomitant known acute or previous infection or contraindication for its use at the time of TCZ administration (less than 50 × 10^9 platelets or less than 500 neutrophils per μL, ALT or AST 5-fold elevations, or decreased renal function).

**Study assessments**

Data on patient's oxygen support at admission, before, and after TCZ administration were recorded according to the standard clinical practice. Laboratory values before TCZ administration, including absolute lymphocyte counts, serum ferritin, interleukin-6, high-sensitive C reactive protein, D-Dimer, serum creatinine, ALT, AST, LDH, and lipid profile were available for most cases. Laboratory data after TCZ administration were obtained later than 2–5 days, and were not available in all cases. The primary endpoint was the need for intubation or death. Eleven patients who required intubation or died within 24 h after TCZ administration were not included in the analysis (4 died and 7 were intubated) because we believed that there was not enough time to evaluate the effect of the drug, as most of them were in an extremely severe condition at the time of TCZ administration and these patients will be evaluated in another study of critical cases attended in intensive care.

**Program oversight**

All patients signed an informed consent for the compassionate use of TCZ before its administration. This study was approved by the Medical Ethics Committee of the Fundación Jiménez Díaz University Hospital. All data were collected by the investigators who performed the statistical analysis.

**Statistical analysis**

All patients who received at least one dose of TCZ between March 8, 2020 and April 20, 2020 were included in the study. Distribution normality was assessed using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean (SD), nonnormally distributed data as median (IQR), and categorical variables as frequency (%). Differences between groups were analyzed using the Chi–square test for categorical data or one-way ANOVA for continuous data. Kaplan–Meier's curves were used for survival studies. Results are reported as point estimates and 95 percent confidence intervals. The analysis was conducted with SPSS software version 24.0.
Results

Patients

In total, 207 hospitalized patients received at least one dose of 400 mg or 600 mg iv TCZ between March 8, 2020 and April 20, 2020, of whom 21 were excluded from the analysis because they required high oxygen flow before TCZ administration (10 cases) or were intubated or died within the first 24 h after TCZ administration (11 cases) leaving 186 patients for the analysis. Overall, 169 (91%) patients received one dose, 16 patients two doses, and 1 patient three doses.

Baseline characteristics of the patients

The main clinical characteristics of patients are summarized in Table 1. The mean age of patients was 65 years and 68% were male patients. In all, 68% of patients had a coexisting condition, high blood pressure being the most prevalent (51%). At the time of TCZ administration, 114 (61%) patients required FiO2 ≥0.5 and 72 (39%) required FiO2 <0.5. The main laboratory values before TCZ administration showed a marked elevation of ferritin, interleukin-6 and C-reactive protein, D-dimer, and a low absolute lymphocyte count.

Almost all patients (168 patients, 90.3%) had received antiretroviral drugs (lopinavir/ritonavir) for a median duration of 3 days (IQR: 1–5). Hydroxychloroquine or chloroquine sulphate had been administered to 97.8% of cases; ciclosporine to 89.2%, interferon beta-1b to 9.7%, and LMWH to 96.2%. Pulse methylprednisolone had been given to 95.7% of cases at a dose of 250 mg/day for one to three days before TCZ. Antimicrobial agents, either doxycycline or azithromycin, were given to all patients for a minimum duration of 5 days.

During a follow-up period of 15 days, 51 patients achieved the primary endpoint (intubation or death), 19 patients needed intubation (of whom 4 died), and 36 died (32 of whom were not intubated). The primary endpoint (intubation or death) was significantly different in the group receiving TCZ when the oxygen support was higher (FiO2 >0.5%) than those with FiO2 ≤0.5% (37% vs 13% and p < 0.001) (Figure 1, Table 2).

Changes in laboratory data 2–5 days after TCZ administration are shown in Table 3. A statistically significant decrease in the median serum ferritin and the median HSCRP was observed. Interleukin-6 and D-dimer median serum levels increased, and the median absolute lymphocyte count remained stable.

Thirty-six patients died despite TCZ treatment. The main demographical, clinical, and laboratory data of patients who died and survived are shown in Table 4. Patients who died were older (75±8 years versus 62±5 years and p < 0.001), had any coexisting condition (89% vs 63% and p = 0.003), specifically high blood pressure (69% vs 46% and p = 0.12); had a higher interleukin-6 before and after treatment (389 vs 116, p = 0.017, and 1168 vs 311, p < 0.001, respectively), a higher mean HSCRP after treatment (3.5 vs 2.0 and p < 0.009), a lower absolute lymphocyte count before and after treatment (633 vs 803, p = 0.052, and 527 vs 860, p = 0.001, respectively), and a higher median D-dimer before and after treatment (8288 vs 2045, p = 0.027, and 7832 vs 3190, p = 0.027, respectively). The global survival rate of those who received TCZ was 81% (150 patients), and it was 94% for those who received it when their oxygen support was with a FiO2 <0.5%, and 72% when it was >0.5% (p = 0.000).

Safety

A total of 11 (5.9%) patients had serious adverse reactions related to TCZ reported by their treating physicians, including increased hepatic enzymes (5 cases) or bilirubin (3 cases), increased creatinine (3 cases), hyperkalemia (1 case), and headache (1 case). Secondary acquired infections after TCZ administration were documented in 13 cases (63%), including fungal (Candida spp., 7 cases and Aspergillus spp., 2 cases) and bacterial (Pseudomonas aeruginosa 2 cases, Klebsiella pneumoniae 2 cases, and Enterococcus spp. 2 cases).
Table 2
Clinical characteristics of patients with early (FiO2 \(<0.5\)) and late (FiO2 >0.5) tocilizumab treatment.

| Characteristics                  | Early (n = 72) | Late (n = 114) | p     |
|----------------------------------|---------------|---------------|-------|
| Mean age (SD)-yr                 | 64 (11)       | 66 (12)       | 0.139 |
| Male sex-no. (%)                 | 49 (68)       | 77 (68)       | 0.942 |
| Ethnicity-no. (%)                |               |               |       |
| Caucasian                        | 68 (94)       | 109 (96)      | 0.717 |
| Latin American                   | 4 (6)         | 5 (4)         | 0.717 |
| Coexisting conditions-no. (%)    |               |               | 0.307 |
| None                             | 26 (36)       | 33 (29)       |       |
| Hypertension                     | 34 (47)       | 60 (53)       | 0.472 |
| Diabetes                         | 10 (14)       | 29 (25)       | 0.059 |
| Obesity                          | 15 (21)       | 42 (37)       | 0.021 |
| Vasculopathy                     | 16 (22)       | 13 (11)       | 0.048 |
| Chronic obstructive lung disease | 7 (10)        | 6 (5)         | 0.245 |
| Chronic renal failure (GFR <30 ml/min) | 4 (6)  | 2 (2)         | 0.153 |
| Immunosuppression                | 9 (13)        | 11 (10)       | 0.541 |
| Mean duration of symptoms prior to tocilizumab therapy (SD)-days | 10.7 (5) | 11.7 (6) | 0.237 |
| Mean duration of hospital admission prior to tocilizumab therapy (SD)-days | 3.8 (3) | 3.3 (3) | 0.298 |
| Concomitant treatment-no. (%)    |               |               |       |
| Steroids                         | 68 (94)       | 110 (97)      | 0.503 |
| Protease inhibitors              | 62 (86)       | 106 (93)      | 0.123 |
| Hydroxychloroquine               | 71 (99)       | 111 (97)      | 0.569 |
| Cyclosporine                     | 59 (82)       | 107 (94)      | 0.011 |
| Interferon                       | 5 (7)         | 13 (11)       | 0.316 |
| Heparin                          | 68 (94)       | 111 (97)      | 0.307 |
| Antibiotics                      | 72 (100)      | 114 (100)     |       |
| Median laboratory values (SD)    |               |               |       |
| Serum ferritin–μg/liter          | 1842 (1850)   | 1466 (1443)   | 0.139 |
| High-sensitivity C-reactive protein–mg/dl | 12 (11) | 12 (10) | 0.864 |
| Interleukin-6–pg/ml              | 156 (329)     | 176 (624)     | 0.830 |
| D-dimer–mg/liter                 | 2278 (4709)   | 3864 (13,302) | 0.345 |
| Absolute lymphocytes–per mm³     | 862 (630)     | 712 (323)     | 0.034 |
| Primary endpoint-no. (%)         |               |               |       |
| Global                           | 9 (13)        | 42 (37)       | <0.000 |
| Invasive ventilation             | 5 (7)         | 14 (12)       | 0.242 |
| Death                            | 4 (6)         | 32 (28)       | <0.000 |

Table 3
Clinical, laboratory, imaging data, and outcomes of patients with severe SARS-CoV-2 pneumonia treated with tocilizumab.

| Characteristics                  | Before | After | p     |
|----------------------------------|-------|-------|-------|
| Oxygen-support category-no. (%)  |       |       |       |
| - FiO2–0.21% (Ambient air)       | 2 (1-1)| 38 (20-4)|       |
| - FiO2–0.24%                     | 3 (1-6)| 8 (4-3) |       |
| - FiO2–0.28%                     | 6 (3-2)| 23 (12-3)|       |
| - FiO2–0.35%                     | 36 (19-4)| 22 (11-8)|       |
| - FiO2–0.4%                      | 23 (12-3)| 14 (7-5) |       |
| - FiO2–0.6%                      | 21 (11-3)| 6 (3-2)  |       |
| - FiO2–1%                        | 95 (51-1)| 24 (12-9)|       |
| - Intubated/dead                 | 51 (27-4)|       |       |
| Median laboratory values (IQR)   |       |       |       |
| - Serum ferritin–μg/liter        | 1211 | 1139 | 0.003 |
| - High-sensitivity C-reactive protein–mg/dl | 716–2,105 | 673–1,880 |       |
| - Interleukin-6–pg/ml            | 42   | 149  | <0.001 |
| - D-dimer–mg/liter               | 821  | 1197 | <0.001 |
| - Absolute lymphocytes–per mm³   | 700  | 700  |       |
| Clinical evolution-no. (%)       |       |       |       |
| - Endpoint (intubation or death) | 51 (27-4)|       |       |
| - Intubation                     | 19 (10-2)|       |       |
| - Death                          | 36 (19-4)|       |       |
| - Live hospital discharge        | 150 (80-6)|       |       |
| - Median days from 1st dose until discharge | 10 (7–15)|       |       |
| - Median days of hospitalization | 14 (7–19)|       |       |
| Radiological evolution-no. (%)   |       |       |       |
| - Improvement                    | 71 (38)|       |       |
| - Unchanged or deterioration     | 106 (57)|       |       |
| - Not available                  | 9 (5) |       |       |
| Tocilizumab-related serious adverse events-no. (%) |       |       |       |
| - Increase liver enzymes (AST, ALT) | 5 |       |       |
| - Increase bilirubin             | 3    |       |       |
| - Increase creatinine            | 3    |       |       |
| - Headache                       | 1    |       |       |
| - Hyperkalemia                   | 1    |       |       |
| Acute infection after tocilizumab-no. (%) |       |       |       |
| - Fungal                         | 9    |       |       |
| o Candida spp.                   | 2    |       |       |
| o Aspergillus spp.               | 2    |       |       |
| o Pseudomonas aeruginosa         | 2    |       |       |
| o Klebsiella pneumoniae         | 2*   |       |       |
| o Enterococcus spp.              | 2    |       |       |

* Combined with other pathogens.

Discussion

SARS-CoV-2 has infected more than 12.5 million people and killed more than 560,000 and, as yet, there is a lack of effective therapy for this novel disease (Fauci et al., 2020). Several antiviral drugs, such as remdesivir—an RNA polymerase nucleotide analog—and lopinavir/ritonavir—an HIV protease inhibitor—have been tested either in a limited number of cases or in small clinical trials showing some benefits (remdesivir) (John et al., 2020) or none at all (lopinavir/ritonavir) (Cao et al., 2020). However, clinical and pathological studies of SARS-CoV-2 disease indicate that a systemic cytokine storm due to macrophage activation may be the leading cause of death in the vast majority of patients, usually occurring two to four weeks after primary infection (Channappanavar and Perlman, 2017; Mehta et al., 2020; Karakike and Giamarellos-Bourboulis, 2019). Therefore, immunomodulatory drugs have been used empirically with the aim of regulating and suppressing the inflammatory reaction that leads to multi-organ failure and death (Moore and June, 2020; Teijaro, 2017), and, in a recent trial, the use of dexamethasone has been effective for those requiring invasive mechanical ventilation (Horby et al., 2020).

At present, there are more than 50 trials under way with TCZ (clinicaltrials.gov) that will give clear information on the efficacy of this drug for severe Covid-19 disease. In the meantime, cohort studies, as ours, and clinical reports, are the only source of available information.

An initial report of 21 patients treated in China by Xu et al showed clinical improvement in all cases without deaths or adverse effects (Xu et al., 2020). However, compared to our series,
their patients were a median of 7 years younger and also had a lower proportion of concomitant diseases, factors that might explain our higher fatality rate. In addition, the mean IL6 value of the patients in Xu’s series is similar to that of our group of survivors, but significantly lower than that of those who died in our study. It is possible that the blockage of the IL6R by TCZ might require higher doses in patients with higher serum IL6 levels. We could not evaluate this issue in our series as only a small proportion of our patients received two or more doses of TCZ.

A second cohort by Luo et al of 15 patients, 8 of them also treated with steroids as most of our patients, showed a higher mortality rate (3/15, 20%), particularly in those patients with higher C reactive protein levels before TCZ administration (Luo et al., 2020). Our data show similar results, demonstrating a worse prognosis for those with higher CRP before and after TCZ treatment. However, other biomarkers such as IL6 levels and total lymphocyte count, and the amount of oxygen support needed are also key factors for the prognosis of this infection.

One of the larger cohort studies published so far includes 179 subjects treated in different centers in Italy (Guaraldi et al., 2020) and they used the same composite endpoint as ours, that is the need for intubation or death. Of note, both cohorts studied are similar in terms of age, comorbidities, and severity of the disease, but not in the proportion of subjects treated with steroids, which is much higher in ours. Despite this, the proportion of patients who achieved the primary endpoint (intubation or death) is similar in both series, 25.7% in Guaraldi’s and 27.4% in ours. The proportion of new acute infections after TCZ was lower in our series (6.3%) as compared to theirs (13%), even with the use of steroids and cyclosporine in our group of patients. This might be related to a different and prolonged use of antibiotics in our series or perhaps to a lack of recorded information due to the retrospective nature of the study. Of note, we did not observe any herpesvirus reactivation. In another large cohort study carried out in Italy (Mikulska et al., 2020), with 196 subjects included, they observed an improvement in the results in nonintubated patients, treated early, in our cohort, with TCZ, methylprednisolone or both. Several studies have shown improvements in median hospital stay or in respiratory and laboratory parameters (Moreno-Pérez et al., 2020; Sciascia et al., 2020). Even in patients who required intensive care unit support and mechanical ventilation, other authors have reported significant benefits when TCZ was added to the treatment of patients (Biran et al., 2020; Somers et al., 2020; Kewen et al., 2020). Despite these findings in several studies, the first study designed by the pharmaceutical company, the COVACTA trial, failed to meet its primary endpoint (Furlow, 2020). However, the company had recently announced (Anon, 2020d) the efficacy of TCZ, with a reduction in the likelihood of needing mechanical ventilation in hospitalized patients with COVID-19-associated pneumonia, in the EMPACTA phase III clinical trial (Anon, 2020e). A detailed analysis of these data would be required after its publication.

The most significant result of our study, which should be evaluated in well-designed clinical trials, is that TCZ administration in severe but not critical cases is associated with a good prognosis, avoiding disease progression in 94% of cases, and only 6% requiring intubation because of progressive respiratory insufficiency. In contrast, we have observed that when the drug is given in more critical cases, with higher oxygen support needs, its value is less clear, at least in this group of cases treated with a single dose of TCZ and multiple drug combinations, including corticosteroids and cyclosporine. It is possible that higher or repeated TCZ doses might have added additional benefits. Mortality rates in hospitalized patients with SSP vary widely but it is approximately 15.1–28% in Spanish, Italian, and Chinese studies (Fernández Cruz et al., 2020; Grasselli et al., 2020; Zhou et al., 2020), significantly higher than that of our series of patients who received TCZ early in the course of the disease, when FiO2 requirement was below 0.5.

Surrogate markers of macrophage activation, such as serum ferritin levels, interleukin-6 levels, and high sensitivity C reactive protein, changed after TCZ therapy, which indicate a reduction of the inflammatory process. As expected, the median interleukin-6 levels increased 48 h after TCZ, as have been shown in previous reports (Luo et al., 2020; Guaraldi et al., 2020). Unfortunately, we do not have further data of these markers, days or weeks after TCZ treatment. As expected, elevated inflammatory markers are associated with poor prognosis, despite TCZ use.

Most patients received only one dose of 400 mg TCZ, mainly because of shortage of the drug during the peak of the epidemic. Seventeen patients received two or more doses of the drug showing similar outcomes than those who received a single dose. These data suggest that even 400 mg of TCZ might be adequate for the reduction of the acute inflammatory process in severe cases; however, critical cases might require higher or repeated doses, an issue that we could not evaluate in our cohort.

The safety and tolerance of TCZ were good in previous studies of non SARS-CoV-2 patients (Fernández Cruz et al., 2020; Burmester et al., 2016). In our series, a small number of serious adverse events were reported and attributed by physicians to the drug. The acquisition of secondary nosocomial infections was detected in 13 patients (6.9%), most of them being lung or urinary tract infections of fungal or bacterial etiology. However, all these cases had previously received systemic corticosteroids, cyclosporine, and antibiotics, and most of them were admitted in the intensive care unit at the time the secondary infection was detected. These infections are probably due to the combination of these treatments and risk factors. This is notable because patients with rheumatoid arthritis or those receiving CAR-T cell therapy for cancer who are treated with long term use of TCZ are prone to infectious
Acknowledgments

We would first like to express our deepest gratitude to the patients and their families, who in a time of grief have contributed to the understanding of this disease. We are also grateful to the whole team of physicians and health personnel for their tireless, altruistic dedication, strength and effort during the current pandemics. Finally, we would like to acknowledge Dr. Frances Williams, for her invaluable role as English editor, Laura Cereceda as data manager, and Drs. Sánchez-Verde and Rodríguez de Lema for their contribution to the graphical abstract.

Appendix.

The components’ full names and academics degrees of the COVID-FJD TEAM are as follows:

Belén Arroyo MD, Sonsoles Barrio MD, Marcela Valverde MD, Sheila Recuero MD, Elizabet Petkova MD, Belén Zamarro MD, Mariam Vélez MD, Clara Peiró MD, Soraya de la Fuente MD, Roberto Sierra MD, Javier López Botet MD, Antonio Herranz MD, Jorge Hernández MD, Silvia Rubio MD, Luis Nieto MD, Alicia Estrella MD, Laura Castañeda MD, Jorge Polo Sabau MD, Ana Lucía Rivero Montecagudo MD, Diego Meneses MD, Marta del Palacio Tamarit MD, Elisa Ruiz Arabi MD, Ana Venegas MD, Fernando Tornero Romero MD, Victoria Torrente MD, Pilar Barrio MD, Eduardo Alonso MD, Carolina Dassen MD, Blanca Rodríguez Alonso MD, Myriam Rodríguez Couso MD, Gabriela Rosello MD, Carmen Álvaro MD, Cici Feliz MD, María José Diez Medrano MD, Camila García MD, José Luis Larrea MD, Ana Pello MD, Beatriz González MD, Tatiana Hernández MD, Nancy Sánchez MD, Otto Oliva Oliva MD, Javier Vélez MD, Susana Fraile MD, Maite Ortega MD, Lara Cantero MD, Silvana Scaletti MD, Vanessa Pérez MD, Catalina Martín MD, Teresa Stock MD, Silvia Pérez MD, Andrés Silva MD, Alberto Andrés MD, Marta Oses MD, Miguel Morante MD, Lina Martínez MD, Juliana Botero MD, Diana Fresnedo MD, Yolanda Martínez MD, Aida Franganillo MD, Amelia Gil MD, Ana Belén Jiménez MD, Adrián Arapiles MD, María Cruz Aguilera MD, Rafael Rubio MD, Alicia Sánchez MD, Begoña Sánchez MD, Rocío Cardá MD, Jerys Cárdenas MD, Lina Martínez MD, Manuel de la Calle MD, Rafael Touriño MD, José Luis Larrea MD, Miguel Morante MD, Alicia Aurea MD, Marta Monsalvo MD, Iris Martínez MD, Catalina Martín MD, Andrés Silva MD, Blanca Barroso MD, Ana Salomé Pareja MD, Ángel Rodríguez Pérez MD, Raúl Fernández Prado MD, Miguel Ángel Navas MD, Alfonso Romero MD, Ana Nieto Ribeiro MD, Beatriz Giraldez MD, Carolina Gotera Rivera MD, Teresa Gómez García MD, Erwin Javier Pinillos Robles MD, Andrés Giménez Veloando MD, Herminia Ortiz Mayoral MD, Francisco José Los de Hierro MD, Marwan Mohamed Choukri MD, Ainhoa Izquierdo Pérez MD, Laura Núñez García MD, Pablo López Yeste MD, Laura de la Dueña Muñoz MD, Elena Heras Recuero MD, María de los Ángeles Zambrano Chacón MD, Fernanda Troncoso Acevedo MD, Carlos López Chang MD, Elena Cabezás Pastor MD, Abdulkader El Hachem Debek MD, María José Romero Valle MD, Esther Canovas Rodríguez MD, Ángel Miracle MD, Marta González Rodríguez MD, Diana Betancor MD, Nicolás González Mangado MD, Sergio Farrais Villalba MD, Gonzalo Díaz Cano MD, José Manuel Corredor Rodríguez MD, Marina Fernández Ochoa MD, Alicia Gómez-Lopez MD, José María Romero Otero MD, Laura Ortega Martín MD, Leyre Baptista Serna MD, José Antonio Esteban Chapel MD, Andrea Castro-Villacañas Farzamnia MD, Laura Esteban-Lucía MD, Ángel Martínez Pueyo MD, Hans Paul Gaebelt MD.

References

COVID-19 Map - Johns Hopkins Coronavirus Resource Center n.d. https://coronavirus.jhu.edu/map.html. [Accessed 11 July 2020].

308

complications (Burmester et al., 2016; Grøn et al., 2019; Le et al., 2018; Maschmeyer et al., 2019), but this does not seem to be the case with single or limited Tcz administration.

Our study has several limitations, basically due to the retrospective collection of data and the absence of a control group. First, the decision to administer Tcz was made by the medical team responsible for each patient, despite our treatment protocol. Therefore, the clinical status of patients and the timing of drug administration after the onset of Covid-19 symptoms were variable; initially it was indicated in extreme respiratory-compromised patients and later it was prescribed much earlier, with lower FiO2 support, allowing us to study its efficacy in this situation. Second, the total amount of drug and number of doses that patients received were not uniform, due, as previously mentioned, to a shortage of the drug in the country during the peak of the epidemic. Thirdly, most patients had received previous and/or concomitant drugs, including systemic corticosteroids and hydroxychloroquine, which have anti-inflammatory properties. Therefore, we could not properly assess the impact of these drugs on the overall response of patients treated with Tcz. Finally, survival rates would also have been influenced by the UCI committee decision whether a patient was eligible for intubation. Only large randomized clinical trials will be able to determine the impact of different immunomodulatory or anti-inflammatory drugs administered simultaneously.

In summary, our data support the use of Tcz in Ssp, in combination with corticosteroids and other immunomodulatory drugs such as cyclosporine. When the respiratory compromise is still not very severe, the survival rate is high (94%) and there are very limited side effects and secondary infections.

Funding

None declared.

Contributors

MG, AC, LP, OS, FR, SH, and GP conceived and designed the study. LP, IC, OS, and FR contributed to the literature research. FV, BA, MJR, IF, AW, PC, SC, FE, MC, AN, ML, MJR, ACG, AB, AM, MM, and JB contributed to the data collection. RF, MAP, JP, OS, FR, MG, and AC contributed to data interpretation. MG, and AC contributed to the tables elaboration. MG, LP, and GP contributed to the writing of the report.

Conflict of interest

MG reports grants and personal fees received from Viiv Healthcare, personal fees from Gilead, and personal fees from Janssen outside the submitted work.

AC reports grants and personal fees received from Viiv Healthcare, personal fees from Gilead, personal fees from Janssen, and personal fees from Merck outside the submitted work.

BA reports personal fees received from Gilead and Viiv Healthcare outside the submitted work. All other authors declared no conflict of interest.

Ethical approval

This study was approved by the Medical Ethics Committee of the Fundación Jiménez Díaz University Hospital. Reference approval number: EO069-020.
Tocilizumab in COVID-19 Pneumonia (TOCVID-19) - Full Text View - ClinicalTrials.gov n.d. https://clinicaltrials.gov/ct2/show/NCT04317092. [Accessed 21 April 2020].

A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia - Full Text View - ClinicalTrials.gov n.d. https://clinicaltrials.gov/ct2/show/NCT04320615. [Accessed 21 April 2020].

https://www.roche.com/media/releases/med-cor-2020-09-18.htm.

Grasselli G, Converti G, Notarangelo M, et al. Early use of corticosteroids or immunosuppressors in COVID-19: a single center experience. J Med Virol 2020;92(7):814–8. https://doi.org/10.1002/jmv.25801.

Le RQ, Li L, Yuan W, Shord SS, Nie L, Hambremar BA, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T-cell-induced severe or life-threatening cytokine release syndrome. Oncologist 2018;23:943–7. https://doi.org/10.1634/theoncologist.2018-0026.

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2020;382:1199–207. https://doi.org/10.1056/NEJMoa2001136.

Luo P, Liu Y, Qi L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol 2020;92(7):814–8. https://doi.org/10.1002/jmv.25801.

Maschmeyer G, De Greef J, Mellinghoff SC, Nosari A, Thiebaut-Bertrand A, Bergeron A, et al. Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology. A position paper by the European Conference on Infections in Leukemia (ECIL). Leukemia 2019;33:844–62. https://doi.org/10.1038/s41375-019-03388-x.

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall BS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.

Mikulska M, Nicolini LA, Signori A, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One 2020;15(8)(e0227831). doi:10.1371/journal.pone.0227831.

Moore BJ, June CH. Cytokine release syndrome in severe COVID-19. Science (80-) 2020; https://doi.org/10.1126/science.ABB8925.

Moreno-Pérez O, Andres M, Leon-Ramirez JM, et al. Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: a retrospective cohort study. J Autoimmun 2020;110:105253. https://doi.org/10.1016/j.jaut.2020.105253 (Epub ahead of print).

Navarro G, Taroumian S, Barroso N, Duan L, Furst D. Tocilizumab in rheumatoid arthritis: a meta-analysis of efficacy and selected conundrums. Semin Arthritis Rheum 2014;43:458–69. https://doi.org/10.1016/j.semarthrit.2013.08.001.

Prieto-Pérez L, Fortes J, Soto C, et al. Histiocytic hyperplasia with hemophagocytosis and acute alveolar damage in COVID-19 infection. Mod Pathol 2020; https://doi.org/10.1038/s41379-020-0613-1.

Rodríguez-Morales AJ, Cardona-Ospina FA, Garzón-Ócampo F, Villamizar-Peña R, Holguín-Rivera JA, et al. Investigating the cellular basis of the 2019 novel coronavirus pneumonia by real-time flow cytometry. J Immunol Methods 2020;555:105923. doi:10.1016/j.jim.2020.105923.

Di Giambenedetto S, Cicciullo A, Borghetti A, Gambassi G, Landi F, Visconti E, et al. Use of tocilizumab in patients with COVID-19 infection. J Med Virol 2020; 0:0–2. https://doi.org/10.1002/jmv.25897.

Fauci AS, Lane HC, Redfield RR. COVID-19:navigating the uncharted. N Engl J Med 2020; 382:1268–9. https://doi.org/10.1056/NEJM2020382126890.

Fernández Cruz A, Ruiz Antoran B, Muñoz Gómez A, et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: a retrospective controlled cohort study. Antimicrob Agents Chemother 2020;64(8)(e01618–002020). https://doi.org/10.1128/AAC.01618-20.

Furlow B. COVACTA trial raises questions about tocilizumab’s benefit in COVID-19. Lancet Rheumatol 2020;2(10):e592. https://doi.org/10.1016/S2665-9913(20)30313-1.

Graselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcome of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574–81.

Gran KL, Glnberg B, Nargaard M, Meinert F, Østergaard M, Dreyer L, et al. Initial infection risk in rheumatoid arthritis during treatment with abatacept, rituximab and tocilizumab; an observational cohort study. Rheumatology 2019; https://doi.org/10.1093/rheumatology/kez530.

Guarad S, Zi N, Hu Y, Li G, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;1–13. https://doi.org/10.1056/NEJMoa2002032.

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol 2020;2: https://doi.org/10.1016/S2665-9913(20)30317-9.

Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. https://doi.org/10.1016/j.tdisca.2020.06.22.21372733. John H, Tomashke Kay M, Dodd Lori E, et al. Remdesivir for the treatment of COVID-19—preliminary report. N Engl J Med 2020;2; https://doi.org/10.1056/NEJMoa2007764.