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Clinical Immunology 223 (2021) 108631

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Full Length Article

Effectiveness and safety of intravenous tocilizumab to treat COVID-19-associated hyperinflammatory syndrome: Covizumab-6 observational cohort☆

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Tocilizumab
IL-6R antagonist
Treatment
Cytokine release syndrome

ABSTRACT

Although the starting event in COVID-19 is a viral infection some patients present with an over-exuberant inflammatory response, leading to acute lung injury (ALI) and adult respiratory distress syndrome (ARDS). Since IL-6 plays a critical role in the inflammatory response, we assessed the efficacy and safety of tocilizumab (TCZ) in this single-centre, observational study in all Covid-19 in-patient with a proven SARS-CoV-2 rapidly progressing infection to prevent ALI and ARDS. 104 patients with COVID-19 treated with TCZ had a lower mortality rate (5·8%) compared with the regional mortality rate (11%), hospitalized patient's mortality (10%), and slightly lower than hospitalized patients treated with our standard of care alone (6%). We found that TCZ rapidly decreased acute phase reactants, ferritin and liver release of proteins. D-Dimer decreased slowly. We did not observe specific safety concerns. Early administration of IL6-R antagonists in COVID-19 patients with impending hyperinflammatory response, may be safe and effective treatment to prevent, ICU admission and further complications.

1. Introduction

As of December 2019, SARS-CoV2 outbreak that causes COVID-19 has rapidly spread from Wuhan, China all over, to almost every country in the world, leading to the World Health Organization (WHO) to describe COVID-19 as a pandemic on 11 March 2020 [1–6].

Accumulating evidence suggests that a subset of patients with severe COVID-19 develop an acute and fast release of different cytokines as a severe immune activation response ("cytokine release syndrome" CRS), leading to acute respiratory distress syndrome (ARDS). This sepsis-like storm may lead to a life-threatening multi-organ failure. CRS, firstly described in previous epidemic processes in patients with Severe Acute Respiratory Syndrome (SARS) [7,8] and Middle East Respiratory Syndrome (MERS-CoV) diseases, both caused by coronaviruses, can be triggered by infections, trauma or therapeutic interventions, such as chimeric antigen receptor (CAR)-T cell therapy. Dysregulation of

☆ This study was part of a fully supported research grant (COV20/00070) from ISCIII Spain.
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https://doi.org/10.1016/j.clim.2020.108631
Received 10 September 2020; Received in revised form 4 November 2020; Accepted 9 November 2020
Available online 12 November 2020

immune response has also been reported in COVID-19. Interestingly, IL-2, IL-7, IL-10, IL-12, interferon-γ, macrophage inflammatory protein 1-α, and tumor necrosis factor-α, play a role in this cytokine comprehensive storm, meanwhile it seems that the outstanding cytokine is IL-6 [9]. IL-6 is a cytokine with pleiotropic activity. When produced mainly by macrophages, fibroblasts, and dendritic cells in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), performs a protective function against the virus healing damaged tissue through induction of this acute phase and immune responses. Beside higher plasma levels of those inflammatory cytokines, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), has been found in most severe COVID-19 cases [2,3,7], suggesting that presence of CRS. Ending up, among the inflammatory cytokines, IL-6 may enter the pulmonary circulation in large numbers, triggering lung functional disability and death [9].

Nowadays, it is widely accepted that after the initial viral acute replication phase, there is a hyper-inflammatory process that might be targeted for the treatment of the severe disease phase. This opened the window of opportunity for the possible recommendations of biological disease modifying antirheumatic drugs (bDMARD's) such as IL-6R antagonists (tocilizumab, sarilumab) and IL-6 blocker (siltuximab) and targeted synthetic (ts) DMARDs (the Janus kinase (JAK) inhibitors tofacitinib, baricitinib) to be used to stop the CRS. Different guidelines from all over suggested various drugs and strategies according to their availability, stock and self-experience with those therapies [10,11].

Intravenous (*iv*) Tocilizumab (TCZ), a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that blocks IL-6 from binding to the soluble and membrane-bound IL-6R emerged as an available option to use in the present outbreak. Based on methodologically weak, but positive results of tocilizumab in the treatment of severe COVID-19 patients from observational studies [12,13], case reports [14,15] and the experience of tocilizumab in inducing rapid reversal of CAR T cell-induced CRS [16], several clinical trials are being conducted (NCT04317092, NCT04320615, NCT04322773) to assess the efficacy and safety of tocilizumab in severe COVID-19 patients. TCZ was included in the 7th updated diagnosis and treatment plan for COVID-19 by the China National Health Commission and it is considered as a potential therapeutic strategy by the Spanish Agency for Medicinal Products and Medical Devices (AEMPS). For all these reasons, we included TCZ in an internal protocol for patients with moderate to severe COVID-19 progressing to CRS, in an attempt to prevent the need for transfer to the ICU, mechanical ventilation or death. The need for the management of severe COVID-19 disease is imperative, and every effort needs to be made to collect relevant real-life clinical outcomes.

Table 1
Main epidemiological characteristics and comorbidities of 104 TCZ treated patients.

	N	Mean	%	SD
Age	104	59·7		9·6
Gender	104			
Men	72	69·3 (%)		
Women	32	30·7 (%)		
Ethnicity	104			
Caucasian,	87	83·6 (%)		
Latin-European	16	15·3 (%)		
Asian-European.	1	0·96 (%)		
Age adjusted Charlson[a]	104	1		(0–2)
IL-6 level before TCZ	47	171·6 (pg/mL)		40–210·7 (pg/mL)
Comorbidities	104			
DM		15·3 (%)	16	
Hypertension		38·4 (%)	40	
Dyslipidemia		38·4 (%)	40	
Obesity		13·4 (%)	14	
Chronic lung disease		25 (%)	26	
Days of hospitalization[a]	104	12		(9–15)
ICU[b]				
Yes	104	22·1 (%)	23	
No		77·9 (%)	81	

ICU: intensive care unit, TCZ: tocilizumab, DM: diabetes mellitus.
[a] Median (P25/P75).
[b] Percent (Frequency).

2. Participants and methods

We did a single-centre, observational cohort analysis of patients who received iv TCZ treatment and were admitted while the pandemic in Barcelona, Spain at the university Hospital de la Santa Creu i Sant Pau. All patients aged 18 years or older with at least a real-time reverse transcription polymerase chain reaction (RT-PCR) positive test for SARS CoV2, and suspicion of CRS were initially included in this study.

We reviewed electronic medical charts of all patients admitted to hospital due of Covid-19. We collected demographics, baseline comorbidities predisposing factors, ICU admission and mortality rates. Laboratory results including hemoglobin, liver function tests, ferritin, D-dimer, white blood cell count, platelets, CRP, LDH and respiratory lung function parameters such as PaO2/FiO2 and SpO2/FiO a) at baseline, b) before the first infusion of TCZ and c) before discharge were also evaluated. All data collected on paper forms were entered into an electronic database using double entry for quality control.

All patients with SARS-CoV-2 infection were treated as a first step with hydroxychloroquine 400 mg/12 h (1d) followed by 200 mg/12 h (4 more days) plus azithromycin 500 mg/d (3 days). Selected patients who presented fast radiological progression, increased oxygen needs, and progressive increase of CRP, D-dimer, ferritin, AST, ALT levels and marked lymphopenia were labeled as candidates for bad prognosis and suitable to receive iv TCZ to prevent severe CRS. An expert committee evaluated the suitability of iv TCZ considering risk/benefit ratio and prescribed the therapy short early in the course of clinical onset of CRS, according to more than one of the following criteria: 1) Age-adjusted Charlson Comorbidity Index scores<4 [17], 2) Interstitial pneumonia with severe respiratory failure (score = 2 on the COVID respiratory severity scale), 3) rapid respiratory worsening requiring non-invasive or invasive ventilation (score ≥ 3 on the COVID respiratory severity scale). The presence of severe systemic inflammatory response criteria was confirmed by: high levels of D-dimer (>1500 ng/ mL) or progressively increasing D-dimer or alternatively high levels of IL-6 (>40 pg/mL). If so, patients were treated with TCZ (if ≥75 kg: a single dose of 600 mg, less than <75 kg: a single dose of 400 mg). Treatment regimens with a single dose were according to AEMPS recommendations. Exclusion criteria for IL-6R antagonist therapy were: AST/ALT values greater than 10 times the upper limit of normality, neutrophils <500 cells/ mm3, platelets <50,000 cells/ mm3, sepsis documented by other pathogens other than SARS-CoV-2, presence of comorbidity that can lead, according to clinical judgment, to a poor prognosis, complicated diverticulitis or intestinal perforation, or ongoing skin infection (uncontrolled pyodermitis with antibiotic treatment).

This observational study (code: Covizumab-6 IRS-TOC-2020-01) was based on clinical practice and review of the medical records, in strict compliance with the Hospital Ethics Committee. The study was also registered in the European network of centres for Pharmacoepidemiology and Pharmacovigilance with the register number (EUPAS34985). Patients confidentiality was protected by assigning an anonymous identification code, and the electronic data were stored in a locked, password-protected computer. The primary outcome was mortality rate, and the secondary outcome was days of admission to ICU.

Categorical variables were described as percentage and number of cases; for ordinal ones, median and interquartile range; for continuous variables mean and standard deviation. The progression in cohort of cases was evaluated by means of a Linear-Mixed model. The Akaike Information Criteria (AIC) was applied to choose the variance-covariance structure. Multiple time comparison used Sidak correction.

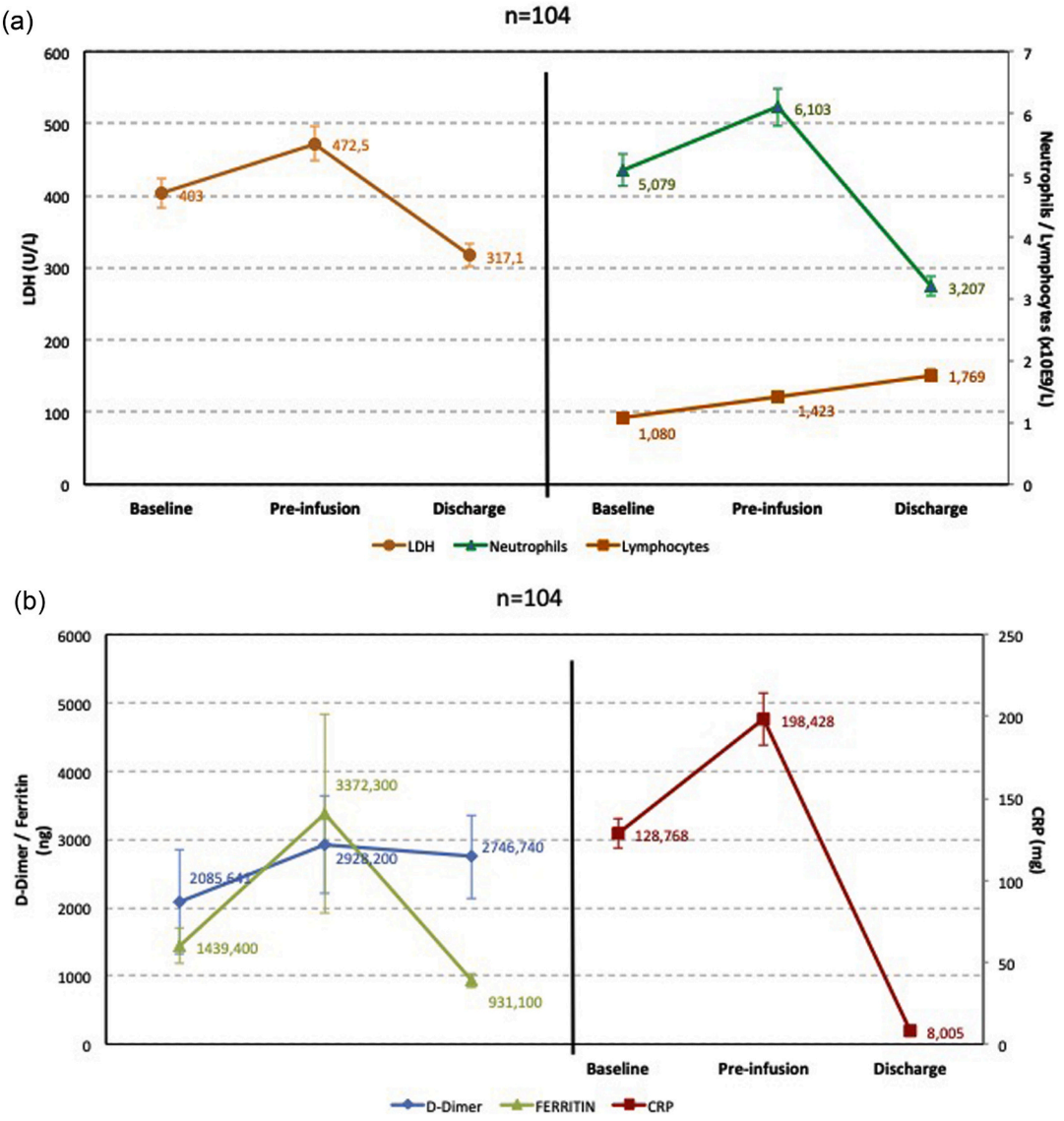

Fig. 1. Changes observed in LDH, Neutrophils, Lymphocytes as well as D-Dimer, Ferritin, CRP at baseline, before TCZ administration and before discharge.

The level of significance was set at 5% (alpha 0.05). All statistical analysis was performed with IBM-SPSS package (V 26).

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. This study was part of a fully supported research grant (COV20/00070) from ISCIII Spain.

3. Results

During the first wave of the Covid-19 outbreak, between March 9th to April 15th 2020, 2093 patients tested positive for SARS-CoV-2 by RT-PCR in our laboratory. Among them, 1383 needed hospitalization. Patients directly admitted to ICU ($N = 150$) were not included in the present analysis. TCZ was administered to 104 patients who clinically worsened and were included in the present analysis. The mean age was 59·7 years (SD 9·6), 72 (69·3%) were men and 32 (30·7%) were women with an aged-adjusted median Charlson index of 1. Eighty-seven (83·6%), were white Caucasian, 16 (15·3%) Latin-European and 1 (0·96%) Asian-European. Main comorbidities were DM (16 [15·3%]), hypertension (40 [38·4%]), dyslipidemia (40 [38·4%]), obesity (14 [13·4%] and previous chronic lung disease (26 [25%]). Median days of hospitalization were: 12 days (IQR: 9–15) (Table 1). Patients presented a baseline elevation of D-dimer, CRP, LDH, AST, ALT, GGT levels, with normal neutrophil count, but marked lymphopenia. Our patients got worse at day 7 (SD 2) on average. According to our clinical and serological guidelines, we also requested IL-6 plasma levels, which presented a mean value of 171·6 (SD 210·7), to support the clinical decision previous to start TCZ. At that acute phase they showed elevation of ferritin, D-dimer, CRP, LDH, AST, ALT, GGT levels, normal neutrophil count and lymphopenia. When those patients received a single dose of iv TCZ, we observed a general improvement of those inflammatory parameters before discharge. A non-significant decrease of ferritin (p0·054), D-dimer (p0·697), a significant improvement of LDH ($p < 0.001$) but light increase of AST, ALT ($p < 0·001$) and GGT (p0·003) levels. Patients also presented decrease in neutrophil count (p0·001) expectedly, as a side effect of TCZ, and lymphopenia improved significantly ($p < 0·001$) (Fig. 1). Interestingly, CRP before discharge showed the fastest decrease almost back to normal due to the effect of the blockade of IL6-R and the progressive effect on liver protein synthesis function (p ⟨0,001). Details of main serological changes observed at baseline, before infusion and after the treatment are shown in Table 2.

The main objective respiratory function parameters determined were oxygen saturation to fraction of inspired oxygen ratio (SpO2/FiO2) and ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional

Table 2
Changes in blood test parameters from baseline, previous to the infusion of Tocilizumab and control before discharge.

		Mean	SD	n	p
Ferritin (ng/mL)	Baseline	1439,4	1431,8	32	
	Pre-infusion	3372,3	13,680,2	89	0,054
	Discharge	931,1	760,3	56	
AST (U/L)	Baseline	44,02	23,88	104	
	Pre-infusion	52,03	30,84	98	0,091
	Discharge	50,71	39,16	82	
ALT (U/L)	Baseline	40,04	27,41	104	
	Pre-infusion	49,60	40,77	91	< 0.001
	Discharge	90,85	71,28	62	
GGT (U/L)	Baseline	87,50	89,95	66	
	Pre-infusion	132,39	127,94	56	0,003
	Discharge	161,76	127,94	41	
D-Dimer (μg/mL)	Baseline	2085,6	7728,9	103	
	Pre-infusion	2928,2	6724,9	88	0,697
	Discharge	2746,7	5225,3	73	
Hb (g/L)	Baseline	139,5	14,3	104	
	Pre-infusion	114,5	44,1	103	< 0.001
	Discharge	134,8	12,2	92	
LDH (U/L)	Baseline	403,0	168,2	96	
	Pre-infusion	472,5	398,8	90	< 0.001
	Discharge	317,1	134,8	76	
Lymphocytes (10^9/L)	Baseline	1080	1247	104	
	Pre-infusion	1423	3360	104	< 0.001
	Discharge	1765	0,654	86	
Neutrophils (10^9/L)	Baseline	5079	2865	104	
	Pre-infusion	6103	2443	103	< 0.001
	Discharge	3207	2004	87	
CRP (mg/L)	Baseline	128,8	91,7	102	
	Pre-infusion	198,4	161,5	103	< 0.001
	Discharge	8,0	14,2	91	
SpO2/FiO2	Baseline	392,3	91,8	104	
	Pre-infusion	231,7	80,8	103	< 0.001
	Discharge	407,5	67,0	81	
PaO2/FiO2	Baseline	278,2	71,9	94	
	Pre-infusion	201,3	78,1	61	< 0.001

AST (U/L): aspartate aminotransferase, ALT (U/L): alanine aminotransferase, GGT (U/L): Gamma-glutamyltransferase, Hb (g/L): hemoglobin, CRP (mg/L): C-reactive protein, SpO2/FiO2: Oxygen saturation to fraction of inspired oxygen ratio. PaO2/FiO2: ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen.

inspired oxygen (PaO2/FiO2). Our patients at baseline presented a moderate mean rate of SpO2/FiO2: 392·3 (SD 91·8) and PaO2/FiO2: 278·1 (SD 71·9). When the disease progressed from moderate to severe impairment parallel with the demand of oxygen, at day 7 (SD 2) presented a crude decrease in blood saturation that brought to a SpO2/FiO: 231·7 (SD 80·8) ($p < 0{\cdot}001$) and a PaO2/FiO2: 201·3 (SD 78·1). From that point, those selected patients according to Age-adjusted Charlson<4, and IL-6 levels, received iv TCZ leading to a progressive change and improvement of both lung function test parameters, which measured just before discharge showed a SpO2/FiO2: 407·5 (SD 67·0), with a PaO2/FiO2: 231 (SD 207) (when available) ($p < 0{\cdot}001$) Table 2. The majority of COVID-19 patients presented improvement of lung function and slight amelioration of chest X-ray opacities and diffuse infiltrates (Fig. 2).

Our cohort shows 12 (+/− 4·7 SD) days of hospitalization. ICU admission was needed in 22 patients (21·1%). The overall mortality rate was (5·8%) 6 patients. Mortality in hospitalized non-TCZ treated patients was 10%. The regional (Barcelona area) mortality rate of was 11%. We had no safety issues with a single dose of TCZ after two weeks. Patients were also followed-up whether in smaller satellite hospital or by a call center survey.

4. Discussion

Fighting the SARS-CoV-2 outbreak in Europe has been highly challenging. Since March we suffered the worst pandemic ever and the main hospitals in Barcelona were overwhelmed, specially from March 9th to April 15th 2020. The overload hospitals and the lack of consistent data, forced us to work in an emergency context. In November 2020, more than 47.423.447 people worldwide are infected and mortality rates undoubtedly will raise concern about the future effect of the pandemic on health systems and economic contraction.

Much has been commented about the lack of randomized trials (RCT) that hindered the design of appropriate guidelines. At the beginning of March, few clinical reports described the clinical behaviour of COVID-19 [18] and the pathogenic mechanisms of the virus to infect several organs, preferably, lungs and skin.

COVID-19 is somehow a disease split into two. The clinical picture shows a disease with a vast majority of infected cases with a mild to moderate disease. Accumulating evidence suggests that another small subset of patients may have, otherwise, a severe COVID- 19 disease with a second phase response with an immune activation and CRS in response to viral replication causing acute respiratory distress syndrome (ARDS) [4]. The infection induces lymphocytopenia that mostly affects the CD4+ T cell subset, including effector, memory and regulatory T cells. Secondly, the acute hyper-inflammation triggers an immunological response with the activation and maybe collaboration of several cytokines, leading to a CRS that may fatally end-up with organ damage, failure and in a short period of time, if not treated correctly, death [19]. The framework of the disease holds a hyperactivation overall of IL-6 with release and activation of liver proteins as acute phase reactants leading to the exaggerated immune response. The cytokine storm is reminiscent of secondary macrophage activation syndrome (MAS), observed scarcely in autoimmune diseases triggered by drug interactions, impairment of clearance metabolism and viral infection, mainly induced by IL-6 as well [20,21].

The World Health Organization (WHO), based on data from previous pandemics by SARS and MERS, did not support the use of steroids, acknowledging they might exacerbate COVID-19-associated lung injury [22–24]. Our standard of care (SOC) included hydroxychloroquine plus azithromycin to tackle the viral replication phase, and under clinical judgment deemed it necessary TCZ therapy to target the exuberant inflammatory response [25–27]. Antiretroviral therapy regimens such as Lopinavir, Darunavir, cobicistat, emtricitabina and tenofovir alafenamid, were suggested to be effective, but were withdrawn due to side effect [28]. Posteriorly, compassionate-use Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in a cohort of patients hospitalized for severe Covid-19 clinical improvement in 36 of 53 patients (68%) [29].

Seeking for new alternatives of treatment meanwhile the pandemic moved from East to West, targeted synthetic (ts) DMARDs JAKinhibitors (tofacitinib, baricitinib) and targeting pro-inflammatory cytokines with antibodies and bDMARDs have been proposed as potential treatments against COVID-19. Only randomized controlled trials, case control studies and single-center observational experiences may provide in the next few months shelter for the information about this issue [10,11].

Since IL-6 plays a key immune damaging role in CRS, IL-6 driven pathway is suggested as a potentially effective target for the second phase of the disease (hyperinflammation), blocking IL-6 dependent severe CRS [16].

Two retrospective observational studies have been conducted in China in clusters of severe or critical COVID-19 patients treated with tocilizumab in combination with SOC, with findings supporting the effectiveness of this therapeutic approach [12,13]. The first study included 21 patients and showed an improvement of fever and other symptoms and signs. Lung lesion opacity vanished in the majority of patients (90·5%), oxygen intake lowered in 75% of patients and one patient no longer needed oxygen therapy. In terms of laboratory parameters, lymphocytes level returned to normal in 52·6% patients, and abnormally elevated CRP decreased significantly in 84·2% patients. No deaths, adverse events (AEs) or subsequent respiratory infections were reported and most patients (90·5%) were discharged on average 13.5 ±

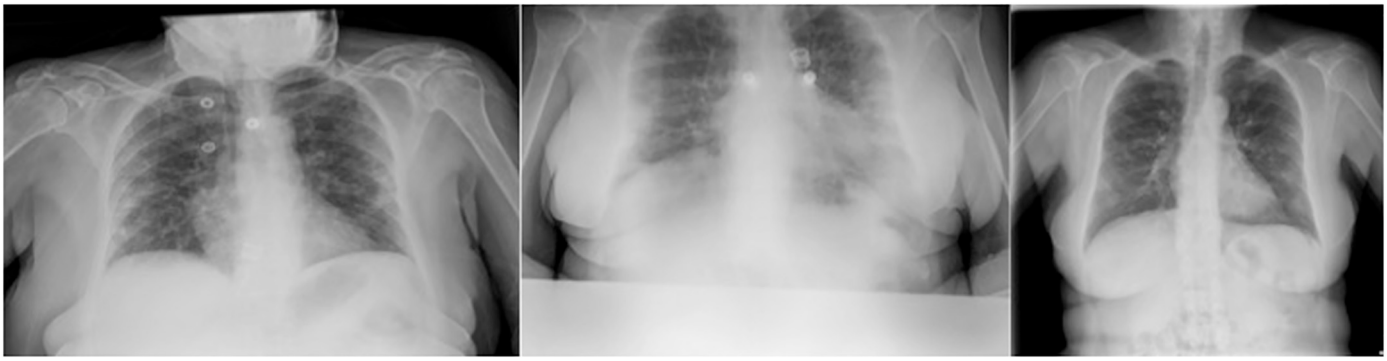

Fig. 2. Chest X-ray from a patient treated with iv tocilizumab a) baseline changes with few pleural bilateral infiltrates and few diffuse opacities b) progression of infiltrates, worsening of SpO2/FiO2 and PaO2/FiO2, together with positive clinical criteria of progression and increase of D-Dimer and IL-6 level. The patient received a single dose of 600 mg/iv TCZ, c) radiological improvement of lung infiltrates before discharge.

3.1 days after tocilizumab treatment [12]. Compared to Xu et al., our observational study shows the results of the treatment with TCZ in a number of patients 5 times larger (104), the biggest cohort described to date of patients treated with TCZ in the context of health emergency. Our patients presented clinical and radiological improvement as well, and 91 (87·5%) were discharged home presenting a FiO2%: 21%. Only 5 patients (4·8%) are still under hospitalization. Of those 104 critically ill patients 23 (22,1%) had to be admitted to the ICU at some point, but solely 6 patients (5·8%) died. We do not report any adverse events (AEs) or subsequent respiratory infections related to TCZ. As reported by Xu et al., AST, ALT, ferritin, CRP, and lymphocytes count returned to normal in the majority of cases. Consistently with the direct effect of TCZ in liver protein synthesis function, CRP decreased before discharge to 8 mg/dL, showing the effect of TCZ on the blockade of the IL-6 driven loop confirming the stop of the CRS.

The second study, that included 15 patients, has reported that CRP levels ameliorated and, in most patients, (66·7%) IL-6 levels showed an initial spike followed by a gradual decrease [13]. As mentioned above the clinical picture of the disease show a marked increase of liver function tests, and LDH, meaning organ disfunction. Increase of ferritin and CRP confirming the hyperinflammation status of the IL-6 dependent, second phase of the disease. The erratic elevation of D-Dimer describes a subset of patients with a higher probability of thrombosis, mainly in lung, that runs independent from TCZ treatment and could persist or even increase for a short period of time after the infusion, to later normalize. Similarly, as observed in systemic lupus erythematosus when they are active, patients with Covid-19 present with a decrease of lymphocyte count, that improved when they present a positive response to IL-6R antagonists such as TCZ or when the disease heals when viral load clears. We knew beforehand that using an antagonist of IL-6R, IL-6 levels would increase after infusion as observed in RA treated patients, thus we did not request IL-6 levels after treatment, while is not efficient and does not lead to changes in the management and treatment.

Our study has limitations. First of all, in the context of a world health emergency, we did not design the study as RCT, neither a case control study. And on the other hand, we have some few missing data in the final analysis. It has to be taken into account that we were more than a hundred different specialists (dermatologists, cardiologist, rehabilitation, gynecologists etc.), attending COVID-19 patients in hospital units lead by internists, infectious disease specialists and rheumatologists.

Our tertiary hospital has diagnosed to date with RT-PCR or serology 2093 patients with Covid-19 with a mean age of 61 years. Of these, 1343 (68%) with a mean age of 67 years needed hospitalization in one of the 12 hospital units we organized to face the peak. During the outbreak we had a general in-hospital population-based death rate of 11%, taking into account that 150 were directly admitted in ICU. This brings us to reinforce the rationale that our critically ill patients were on jeopardy. Thus, in the absence of globally accepted guidelines and recommendations, we decided to use iv TCZ. Even though within TCZ treated patients we had 22 patients admitted to ICU, we solely had a 5·8% of mortality (6 patients) surprisingly low considering the emergency context and the severity of the cases.

5. Conclusion

TCZ has demonstrated to be effective and safe for the treatment of CRS in SARS CoV-2 infected patients in a context of global emergency. This observational study might help to place TCZ as an alternative treatment until RCT (like ours *COV20/00070*) or further case control studies still ongoing give the answer of which are the first, and second line treatments among the two different phases of the Covid-19 infection.

Declaration of Competing Interest

The study received no funding. The authors declare no conflict of interest for this manuscript.

All researchers played a role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgements

We thank Cristina Anglès for her fast work managing patient database. We also thank all medical services and departments of Hospital de Santa Creu i Sant Pau, who helped to fight against the SARS-CoV-2 (Covid-19) outbreak in Barcelona.

References

[1] P. Zhou, X.-L. Yang, X.-G. Wang, Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin, bioRxiv 20 (2020).
[2] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062.
[3] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
[4] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069.
[5] J.J. Zhang, X. Dong, Y.Y. Cao, et al., Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy (2020), https://doi.org/10.1111/all.14238.
[6] D. Baud, X. Qi, K. Nielsen-Saines, D. Musso, L. Pomar, G. Favre, Real estimates of mortality following COVID-19 infection, Lancet Infect. Dis. (2020), https://doi.org/10.1016/S1473-3099(20)30195-X. S1473-3099(20)30195-X.
[7] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, the Northwell COVID-19 Research Consortium, D.P. Barnaby, L. B. Becker, J.D. Chelico, S.L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A. J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D. A. Hirschwerk, E.J. Kim, Z.M. Kozel, L.M. Marrast, J.N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area, JAMA 323 (20) (2020 May 26) 2052–2059, https://doi.org/10.1001/jama.2020.6775.
[8] P. Domingo, I. Mur, V. Pomar, H. Corominas, J. Casademont, N. de Benito, The four horsemen of a viral apocalypse: the pathogenesis of SARS-CoV-2 infection (COVID-19), EBioMedicine 58 (2020 Aug) 102887, https://doi.org/10.1016/j.ebiom.2020.102887.
[9] Y. Zhou, B. Fu, X. Zheng, et al., Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus, bioRxiv (2020), 2002.2012.945576.
[10] C.C. Lu, M.Y. Chen, W.S. Lee, Y.L. Chang, Potential therapeutic agents against COVID-19: what we know so far, J. Chin. Med. Assoc. 83 (6) (2020 Jun) 534–536, https://doi.org/10.1097/JCMA.0000000000000318.
[11] P. Richardson, I. Griffin, C. Tucker, et al., Baricitinib as potential treatment for 2019-nCoV acute respiratory disease, Lancet 395 (10223) (2020) e30–e31.
[12] X. Xu, M. Han, T. Li, et al., Effective treatment of severe COVID-19 patients with tocilizumab, Proc. Natl. Acad. Sci. U. S. A. (2020), https://doi.org/10.1073/pnas.2005615117, 202005615.
[13] P. Luo, Y. Liu, L. Qiu, X. Liu, D. Liu, J. Li, Tocilizumab treatment in COVID-19: a single center experience, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25801.
[14] J.M. Michot, L. Albiges, N. Chaput, et al., Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report, Ann. Oncol. (2020), https://doi.org/10.1016/j.annonc.2020.03.300.
[15] X. Zhang, K. Song, F. Tong, et al., First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab, Blood Adv. 4 (7) (2020) 1307–1310, https://doi.org/10.1182/bloodadvances.2020001907.
[16] R.Q. Le, L. Li, W. Yuan, et al., FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome, Oncologist 23 (8) (2018) 943–947, https://doi.org/10.1634/theoncologist.2018-0028.
[17] S. Dessai, R. Fasal, J. Dipin, D. Adarsh, S. Balasubramanian, Age-adjusted charlson comorbidity index and 30-day morbidity in pelvic surgeries, South Asian J. Cancer 7 (2018) 240.
[18] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, Intens. Care Med. (2020), https://doi.org/10.1007/s00134-020-05991-x.
[19] G. Schett, M. Sticherling, M.F. Neurath, COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nat. Rev. Immunol. 20 (2020).
[20] E.H. Choy, F. De Benedetti, T. Takeuchi, M. Hashizume, M.R. John, T. Kishimoto, Translating IL-6 biology into effective treatments, published online ahead of print, 2020 Apr 23, Nat. Rev. Rheumatol. (2020) 1–11, https://doi.org/10.1038/s41584-020-0419-z.

[21] C. Zhang, Z. Wu, J.W. Li, H. Zhao, G.Q. Wang, The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality, Int. J. Antimicrob. Agents (2020), https://doi.org/10.1016/j.ijantimicag.2020.105954.
[22] Y.M. Arabi, Y. Mandourah, F. Al-Hameed, et al., Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome, Am. J. Respir. Crit. Care Med. 197 (6) (2018) 757–767, https://doi.org/10.1164/rccm.201706-1172OC.
[23] C.D. Russell, J.E. Millar, J.K. Baillie, Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury, Lancet 395 (2020) 473–475.
[24] World Health Organization, Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (2019-nCoV) Infection is Suspected: Interim Guidance, WHO/nCoV/Clinical/2020.3, 28 January 2020.
[25] A. Savarino, L. Di Trani, I. Donatelli, R. Cauda, A. Cassone, New insights into the antiviral effects of chloroquine, Lancet Infect. Dis. 6 (2006) 67–69.
[26] X. Yao, F. Ye, M. Zhang, et al., In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa237 ciaa237.
[27] H. Corominas, I. Castellví, P. Domingo, J. Casademont, Facing the SARS-CoV-2 (COVID-19) outbreak with IL-6R antagonists, Eur. J. Rheumatol. (2020), https://doi.org/10.5152/eurjrheum.2020.20061.
[28] Y.M. Arabi, A.Y. Asiri, A.M. Assiri, et al., Treatment of Middle East Respiratory Syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial, Trials 21 (1) (2020) 8, https://doi.org/10.1186/s13063-019-3846-x.
[29] J. Grein, N. Ohmagari, D. Shin, et al., Compassionate use of remdesivir for patients with severe Covid-19, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2007016. NEJMoa2007016.