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.

International Journal of Infectious Diseases 100 (2020) 421–424

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Short Communication

Low-dose subcutaneous tocilizumab to prevent disease progression in patients with moderate COVID-19 pneumonia and hyperinflammation

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ARTICLE INFO

Article history:
Received 23 June 2020
Received in revised form 4 July 2020
Accepted 23 July 2020

Keywords:
COVID-19
SARS-CoV-2
Inflammation
Cytokine release syndrome
IL-6
Tocilizumab

ABSTRACT

Aim: This study aimed to evaluate the safety and efficacy profile of low-dose tocilizumab (TCZ), to prevent disease progression, subcutaneously administered to patients with moderate COVID-19 pneumonia and hyperinflammation.

Methods: Clinical characteristics and outcomes were retrospectively analysed of patients – with laboratory-confirmed bilateral COVID-19 pneumonia, hyperinflammation (C-reactive protein (CRP) ≥20 mg/dL), no hypoxaemia (oxygen saturation >90%), and no contraindications to TCZ – who were treated with subcutaneous TCZ (324 mg) administered within 48 h from hospitalization on top of standard of care (SOC). They were compared with matched controls treated with SOC only before TCZ was available at the institution. Clinical data were available for all patients until death or until day 35 for those discharged from hospital.

Findings: Ten consecutive patients (six males, median age 55 years) treated with TCZ on top of SOC, and ten patients (six males, median age 56 years) treated with SOC only were included. TCZ was well-tolerated with no clinically relevant adverse events. TCZ was associated with a reduction in CRP at day 1 (−50%, IQR −28 to −80) and day 3 (−89%, IQR −79 to −96; $p = 0.005$ for within-group), whereas there was no significant change in CRP values in the SOC group ($p < 0.001$ for between-group comparisons at both time points). TCZ resulted in a parallel improvement in oxygenation, as assessed by the ratio of partial pressure of oxygen to fraction of inspired oxygen (P/F) ratio, which increased at day 1 (+11%, IQR +6 to +16; $p = 0.005$ for within-group and $p = 0.006$ for between-group comparisons), and day 3 (+23%, IQR +16 to +34; $p = 0.005$ for within-group and $p = 0.003$ for between-group comparisons). None of the TCZ-treated patients had disease progression, defined as requirement of oxygen therapy or mechanical ventilation, whereas progression occurred in five (50%) patients among the SOC group.

Conclusions: Low-dose subcutaneous TCZ may be a safe and promising therapeutic option administered on top of SOC to prevent disease progression in hospitalised patients with moderate COVID-19 and hyperinflammation.

Introduction

Many patients with coronavirus disease 2019 (COVID-19) present with pulmonary infiltrates and rapidly progress to severe disease characterised by refractory hypoxaemia requiring mechanical ventilation (Potere et al., 2020a). Elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6), reflecting an

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https://doi.org/10.1016/j.ijid.2020.07.078
1201-9712/

hyperinflammatory response, identify patients with progression to refractory hypoxaemia (Wu et al., 2020).

Subcutaneous tocilizumab (TCZ), a humanised anti-IL-6 receptor antibody, is approved for the treatment of rheumatoid arthritis, giant-cell arteritis and cytokine storm related to cancer therapeutics. Recent reports have suggested that high-dose intravenous TCZ (8 mg/kg) may be an effective treatment for severe-to-critical COVID-19 patients, due to its ability to rapidly reduce fever and pro-inflammatory markers and improve oxygenation (Xu et al., 2020; Toniati et al., 2020; Sciascia et al., 2020; Campochiaro et al., 2020). It is unknown whether TCZ can be subcutaneously administered to prevent progression to severe disease in patients with moderate COVID-19 pneumonia and hyperinflammation.

This study presents a retrospective analysis of clinical characteristics and outcomes of ten consecutive patients (six males, median age 55 years) with laboratory-confirmed COVID-19 bilateral pneumonia, hyperinflammation (CRP $\geq$ 20 mg/dL), no hypoxaemia (oxygen saturation >90% on room air), and no contraindications to TCZ (including bacterial or fungal infection, neutropoenia or liver injury) who were treated with TCZ 324 mg, administered subcutaneously in two simultaneous 162 mg injections within 48 h of admission, on top of standard of care (SOC) at Pescara General Hospital, Italy, between 28 March 28–21 April 2020. Patients signed informed consent for the off-label use of TCZ. Ten hospitalised COVID-19 patients matching for sex, age and the same treatment criteria, who received SOC in the same institution between 7–27 March 2020, served as controls (Table 1). Clinical data were available for all patients until death; for those discharged from hospital, additional clinical information was obtained by phone contact at 35 days. Data were presented as median and interquartile range (IQR). Within-group changes were compared using the Wilcoxon test for paired analysis, and between-groups differences were analysed using the Mann-Whitney test for unpaired test.

Table 1
Clinical characteristics at baseline.

	TCZ + SOC group (n = 10)	**SOC group** (n = 10)
Gender		
Male	6 (60%)	6 (60%)
Female	4 (40%)	4 (40%)
Age	55 (54–60)	56 (49–60)
Smoker	2 (20%)	1 (10%)
Chronic underlying comorbidities		
Arterial hypertension	4 (40%)	4 (40%)
Diabetes mellitus	2 (20%)	3 (30%)
Coronary heart disease	1 (10%)	0
Chronic kidney disease	1 (10%)	1 (10%)
Obesity	2 (20%)	0
Malignancy	1 (10%)	0
Signs and symptoms on admission		
Fever	10 (100%)	10 (100%)
Cough	8 (80%)	6 (60%)
Dyspnoea	1 (10%)	1 (10%)
Fatigue or myalgia	4 (40%)	1 (10%)
Nausea, vomiting or diarrhoea	2 (20%)	0
Headache or confusion	1 (10%)	0
Symptoms onset to hospitalisation	5 (4–8)	5 (3–6)
Vital signs on admission		
Systolic blood pressure, mmHg	135 (130–140)	120 (115–125)
Diastolic blood pressure, mmHg	80 (75–90)	75 (75–75)
Heart rate, beats per minute	87 (78–90)	86 (78–103)
Respiratory rate, breaths per minute	17 (15–18)	16 (15–20)
Oxygen saturation, %	96 (95–96)	96 (95–98)
Concomitant pharmacologic treatment during hospital stay		
Hydroxychloroquine	9 (90%)	10 (100%)
Darunavir/cobicistat	0	5 (50%)
Lopinavir/ritonavir	0	2 (20%)
Systemic corticosteroids	6 (60%)	5 (50%)
Oxygen therapy during hospital stay		
None	10 (100%)	6 (60%)
Nasal cannula or mask	0	3 (30%)
Non-invasive mechanical ventilation	0	2 (20%)
Invasive mechanical ventilation	0	2 (20%)

Treatment with TCZ was well-tolerated with no clinically relevant adverse events. In particular, none of the patients experienced neutropoenia (absolute neutrophil count <1000/mm3), bacterial infections or liver injury (elevation in alanine aminotransferase 5 times above normal value) (Supplementary Table 1). Treatment with TCZ was associated with a reduction in CRP at day 1 (–50%, IQR –28 to –80) and day 3 (–89%, IQR –79 to –96; p = 0.005 for within-group), whereas there was no significant change in CRP values in the SOC group (p < 0.001 for between-group comparisons at both time points (Figure 1A). In parallel, treatment with TCZ resulted in an improvement in oxygenation, as assessed by the ratio of partial pressure of oxygen to fraction of inspired oxygen (P/F) ratio, which significantly increased at day 1 (+11%, IQR + 6 to +16; p = 0.005 for within-group and p = 0.006 for between-group comparisons), and day 3 (+23%, IQR +16 to +34; p = 0.005 for within-group and p = 0.003 for between-group comparisons (Figure 1A).

None of the patients treated with TCZ had disease progression, defined as requirement of oxygen therapy or mechanical ventilation (Figure 1B). At day 14, eight patients had been discharged and two were still in hospital without need for oxygen therapy. At day 35, all patients had been discharged without supplemental oxygen (Supplementary Table 2). Among the SOC group, COVID-19 progressed in five (50%) patients: three (30%) required supplemental oxygen through nasal cannula or mask, and two (20%) needed non-invasive mechanical ventilation (NIV) first and invasive mechanical ventilation (IMV) afterwards, and one subsequently died (Figure 1B). At day 14, five patients had been discharged without supplemental oxygen and five were still in hospital (three without supplemental oxygen, one requiring NIV and one IMV). At day 35, eight patients were discharged without supplemental oxygen and two were still in hospital (one without supplemental oxygen and one requiring IMV) (Supplementary Table 2).

These findings suggest that early IL-6 receptor blockade with TCZ may reduce the risk of progression to severe disease in hospitalised patients with moderate COVID-19 pneumonia and hyperinflammation. SARS-CoV viruses trigger an inflammasome-mediated response characterised by high levels of interleukin-1β (IL-1β) (Siu et al., 2019), and IL-1β blockade with anakinra or canakinumab has been shown to be associated with more favourable outcomes (Cavalli et al., 2020; Ucciferri et al., 2020). Moreover, IL-1β derived from the inflammasome, as well as the IL-1α isoform, released from dying alveolar epithelial cells induce expression of IL-6, which plays a key role in lung injury and refractory hypoxaemia. Intravenous IL-6 blockers are often provided on a compassionate-use basis to severe-to-critical COVID-19, with reported beneficial effects (Xu et al., 2020; Toniati et al., 2020; Sciascia et al., 2020; Campochiaro et al., 2020), and are currently under investigation in randomised controlled trials. Recent studies have reported favourable outcomes with subcutaneous TCZ (324 mg) in patients with severe COVID-19 (Guaraldi et al., 2020; Potere et al., 2020b). However, many patients with COVID-19 have moderate disease not requiring supplemental oxygen. Hyperinflammation may promote disease progression, as indicated by higher levels of inflammatory biomarkers being associated with dire outcomes (Wu et al., 2020). Notably, dexamethasone was recently reported to reduce mortality in COVID-19 patients with respiratory failure, but not in those not requiring supplemental oxygen (World Health Organization, 2020).

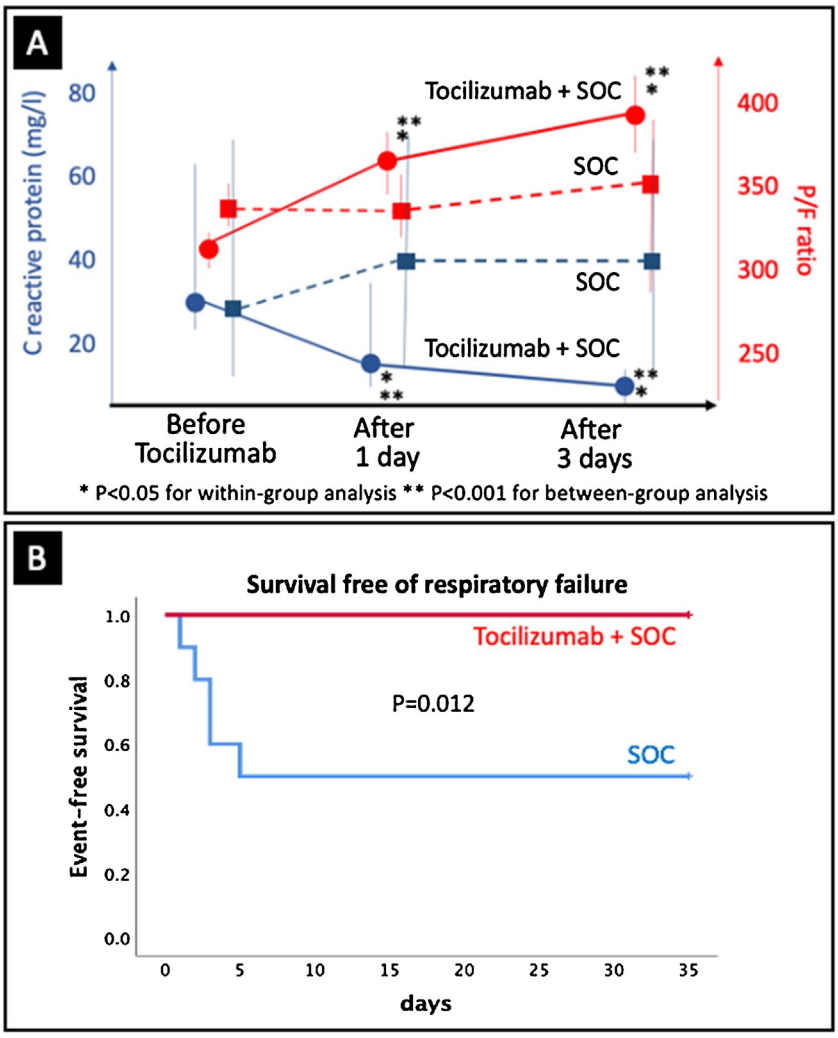

Figure 1. A) Changes in C-reactive protein and P/F ratio.
Interval changes are shown in C-reactive protein (CRP) and partial pressure of oxygen to fraction of inspired oxygen (P/F), a measure of hypoxaemia, in the patients who received tocilizumab on top of standard of care (SOC) ($n = 10$) as compared with patients who received standard of care only (SOC) ($n = 10$). Patients receiving tocilizumab had a significant improvement in CRP and P/F at 1 and 3 days ($p = 0.005$ for within-group changes at each timepoint). No significant changes were seen in the patients receiving SOC only (all $p > 0.05$). When compared with patients receiving SOC only, patients receiving tocilizumab on top of SOC had a significantly greater reduction in CRP and improvement in P/F ratio ($p < 0.001$ for between-groups differences at each timepoint). B) Survival free of respiratory failure.
Patients receiving tocilizumab (TCZ) on top of standard of care (SOC) were significantly less likely to need oxygen therapy (by means of nasal cannula, non-invasive mechanical ventilation or mechanical ventilation) than patients treated with SOC only matched for sex, age and severity of illness (Log-rank Mantel Cox Chi-square 6.367, $p = 0.012$).

This study had several limitations: primarily being the small number of patients included, the non-random nature of the comparisons, and the possible immortal time bias. It reported the innovative use of early subcutaneous TCZ in hospitalised patients with moderate COVID-19 who are at risk of progressive disease. Despite being preliminary, the data appear reassuring in terms of safety, and favourably compare with those of patients treated with SOC at the current centre and other published cohorts (Potere et al., 2020a).

Authors' contribution

The corresponding author had full access to all data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: NP, AAb, GP. Extraction and review of data: NP, GR, MLV. Statistical analysis: NP, EPol, AAb. Interpretation of the data: NP, AAb, GP. Drafting of the manuscript: NP, MDN, AAb. Supervision: GP. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the manuscript: All authors.

Conflict of interests

MDN has received personal fees from Bayer, Daiichi Sankyo, Sanofi, Pfizer, Leo Pharma, and Aspen, outside of the submitted work. AAb has received research support from Novartis, Olatec, and Swedish Orphan Biovitrum, outside of the submitted work. All other authors declare no competing interests.

Funding

There was no funding source for this study.

Acknowledgments

We thank all patients who agreed to participate to the study. We thank our colleagues (Pierluigi Cacciatore, Donatella Cibelli, Franco Colameco, Fabio Di Stefano, Alessandro Pieri, Valeria Pace Palitti, Federica Sozio, Rosa Scurti, Angelo Trovato, Raffaele Zicolella, and Giacomo Zuccarini) who incessantly worked to contain the COVID-19 pandemic and provided feedback on this report.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.07.078.

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