Real-life experience of tocilizumab use in COVID-19 patients

Rheumatology key message

- The current preliminary evidence of use of tocilizumab in COVID-19 patients is promising.

Dear Editor, Coronavirus disease 2019 (COVID-19) has been confirmed in 2,878,196 people worldwide with case fatality rate 6.9% as per WHO Situation Report of 27 April 2020. Accumulating evidence suggests that a subgroup of patients with COVID-19 might have a hyper-inflammation response (aka cytokine storm syndrome) evidenced by elevated circulating levels of several cytokines including IL-6. Tocilizumab, an anti-IL-6 receptor antibody used for rheumatoid arthritis and temporal arthritis and approved by the FDA for cytokine release syndrome, has been used in many countries as an experimental treatment for these patients.

Our objective was to summarize the current evidence of tocilizumab use in COVID-19 patients. We searched Medline, Embase, Cochrane Database of Systematic Reviews, the reference lists of relevant articles, the preprint servers medRxiv and ChinaXiv and the ResearchGate website. The last search was carried out on 25 April 2020. We included all original studies, including case reports, in human adult patients (aged >18) with confirmed COVID-19 treated with tocilizumab regardless of publication status.

Our researches yielded a total of 13 eligible articles (n=92 patients), four retrospective studies [1–4], two case series [5, 6] and seven case reports [7–13]. Three articles were from China [1, 4, 12], France [3, 8, 13], Italy [5, 7, 10] and the USA [2, 6, 9], respectively and one from South Africa [11] with the largest one from France (n=30 patients) [3]. A total of 66 (72%) of the patients were male. The median age was 58.8 years (interquartile range, 56.8–61 years). There was a broad range of comorbidities, including hypertension and diabetes, and 20/92 (21.7%) patients were on immunosuppression [2, 3, 10, 12].

The main indication of tocilizumab use was worsening hypoxia. CRP was 189 mg/l (interquartile range, 126–189 mg/l) and based on 41 patients, IL6 levels were 132.4 pg/ml (interquartile range, 46.8–132.4 pg/ml). Median ferritin levels were 2,682 ng/ml based on 32 patients. The imaging (chest X-ray or CT chest) before tocilizumab initiation demonstrated worsening findings including ground-glass opacities in comparison with the one on admission [4, 9, 11]. Tocilizumab was commenced from day 8–22 from the onset of symptoms and the majority of patients (42.4%) had one dose of 8 mg/kg or 400 mg intravenously. Patients also received other experimental treatments, such as antiviral therapy [4–6, 11–13] and hydroxychloroquine [3, 5, 6, 8–10]. Thirty-one (34%) patients also received methylprednisolone [1, 4, 10, 12].

Outcome measures, laboratory parameters and adverse events after tocilizumab treatment are presented in Table 1. The patient progress results are available for 76 out of 92 patients. A total of 44/76 (57.9%) patients improved and 31/76 (40.8%) were discharged from the hospital. Furthermore, 13/76 (17.1%) patients remained stable or with moderate disease. Nine out of 76 (11.8%) patients died, eight (10.5%) patients remain in critical condition [2, 3, 9] and two (2.6%) patients got worse. Initial improvement was noticed in 25/76 (32.9%) patients within the first 24 h with reduction or even normalization of temperature [4, 7, 8, 10, 11]. CRP decreased in accordance with the clinical improvement and even normalized after a median of 5 days [1, 4, 5, 11, 12]. Based on the IL-6 levels of 17/92 (18.5%) patients, IL-6 spiked shortly after the tocilizumab administration and then decreased, but continued to increase in four patients that died or deteriorated [1, 10, 12]. The temporary increase in IL-6 serum levels is probably explained by the unavailability of IL-6 receptor which is blocked by the tocilizumab. A total of 3/44 (6.8%) patients with clinical improvement also had repeat CT chest that demonstrated reduction in ground-glass opacities [7, 12, 13]. Tocilizumab was well tolerated, except for six (6.5%) patients [3, 6, 10].

The results are encouraging (75% improved, remained stable or with moderate disease with Tocilizumab), but should be evaluated with caution due to the low quality of studies (retrospective nature, small sample size, missing data, no clear outcome measures). Future studies should focus on patient-centred outcome measures, such as death and prevention of ventilation. Randomization should also be considered in any future work. Additionally, the above positive findings could be misleading because of publication bias and the underreporting of negative studies. However, this preliminary evidence supports the consideration of tocilizumab in the research efforts in the fight against the COVID-19 hyper-inflammation response.

In line with the above findings, on 27 April, the results of a French open-label randomized controlled trial (n=129) were announced by the Assistance Publique-Hôpitaux de Paris. A total of 129 patients with COVID-19, not requiring intensive care upon admission, were randomized equally to standard of care with tocilizumab and standard of care alone. According to the press release, a significantly lower proportion of patients reached the primary outcome (need for ventilation or
### Table 1: Outcome measures, laboratory parameters and adverse events after tocilizumab treatment

| Author, year | Study type | Country | Sample size, n | When Improvement noticed | CRP (mg/l) | Progress | Adverse events |
|--------------|------------|---------|----------------|--------------------------|------------|----------|----------------|
| Cellina, 2020 | Case report | Italy | 1 | Improvement in his blood tests 1 day after | 96 mg/l 1 day after administration | Clinical condition progressively improved and ventilatory support was gradually weaned | Not reported |
| De Luna, 2020 | Case report | France | 1 | SPo2 at 97% with oxygen at a rate of 3 l/min and no fever 1 day after | 13 mg/l 4 days after | Discharge 3 days after tocilizumab | Not reported |
| Di Giambenedetto, 2020 | Case series | Italy | 1 | Not reported | 92 mg/l 2 days after and normal levels 10 days after | Progressive resolution of dyspnoea and oxygen saturation at 98% with FiO2 0.31 6 days after | No adverse events |
| Ferrer, 2020 | Case report | USA | 1 | Vasopressor requirement and PaO2/FiO2 ratio remain variable | Not reported | Vasopressor requirement and PaO2/FiO2 ratio remain variable | Not reported |
| Fontana, 2020 | Case report | Italy | 1 | Apyrexial since tocilizumab administration | Not reported | PaO2 showed progressive improvement and oxygen treatment was stopped. Discharge on day 22 after admission with SO2 95% on room air | Suspected leucopenia with neutropaenia resolved with IVIG, urinary culture positive for multi-resistant Pseudomonas aeruginosa treated with meropenem |
| Luo, 2020 | Retrospective study (27 January to 5 March 2020) | China | 15 | Not reported | Normal levels by day 7 in patients with clinical improvement or stabilization | Eight patients (53.3%) clinical stabilization, 2 (13.3%) clinical improvement, 3 (20%) died (critically ill patients), 2 (13.3%) disease aggravation (one critically and other seriously II) | Not reported |
| Michot, 2020 | Case report | France | 1 | Rapidly afebrile | 33 mg/l 4 days after | Clinical improvement and oxygen was fully discontinued on day 7 of admission, patient ultimately clinically fully recovered | No |
| Morrison, 2020 | Case series | USA | 1 | Not reported | Not reported | Not reported | Not reported |
| Pereira, 2020 | Retrospective study (13 March to 4 April 2020) | USA | 14 | Not reported | Not reported | Three patients (21.4%) died, 4 (28.6%) remain in ICU, 5 (35.7%) remain with moderate disease on the general medical floor and 2 (14.3%) have been discharged | No adverse events |
| Roumier, 2020 | Retrospective study (21 March to 2 April 2020), median follow-up: 8 days | France | 30 | Not reported | Not reported | Three patients (10%) had died, while 4 (7.1%) and 6 (30%) were discharged from the ICU and from hospital respectively | 2 patients (6.7%) developed mild hepatic cytolysis and one patient (3.3%) ventilator-acquired pneumonia |
| Xu, 2020 | Retrospective study (5 to 14 February 2020) | China | 21 | Apyrexial on the first day after tocilizumab and remained stable after | Normal values in 16 patients (84.2%) 5 days after | Nineteen patients (90.5%) have been discharged including two critically and the rest remained under hospital observation with remarkable clinical improvement and no fever. The mean hospitalization time was 13.5 days after the treatment | No adverse events |
| Zhang, 2020 | Case report | China | 1 | Not reported | Normal levels 2 weeks after | Chest tightness disappeared in 3 days, discharge 19 days after | Not reported |
| Schleicher, 2020 | Case report | South Africa | 1 | Improvement in his fever, biomarkers and hypoxaemia within 24 hours | Normal levels 7 days after | Discharged 3 days after | Not reported |
death at day 14) in the tocilizumab arm. Results of this study will be submitted for publication in a peer-reviewed journal. There are still 32 ongoing clinical and observational trials registered on clinicaltrials.gov (accessed on 29 April 2020). However, these studies vary in participant and intervention criteria with several diverse primary and secondary outcomes. This may make future attempts of synthesizing the results across clinical trials difficult, leading to different policies in different countries. This heterogeneity highlights the global need to identify which is the right time and dosing scheme of tocilizumab for patients with COVID-19.

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Anastasia-Vasiliki Madenidou1 and Marwan Bukhari1

1Rheumatology Department, University Hospitals of Morecambe Bay NHS Foundation Trust, Barrow-in-Furness, Lancaster, UK

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Correspondence to: Marwan Bukhari, Rheumatology Department, University Hospitals of Morecambe Bay NHS Foundation Trust, Royal Lancaster Infirmary, Ashton Road, Lancaster LA1 4RP, UK.

E-mail: marwan.bukhari@mbht.nhs.uk

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