

Correspondence on 'Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry' by Gianfrancesco *et al*. Compassionate use of tocilizumab in severe COVID-19 with hyperinflammation prior to advent of clinical trials – a real-world district general hospital experience

The coronavirus disease 2019 (COVID-19) has resulted in a global pandemic with multiple casualties. Within the UK, specific groups of patients including those with rheumatic diseases requiring significant immunosuppression were advised to shield from the public to protect themselves from COVID-19 during the heart of the pandemic.¹ In their important paper, Gianfrancesco *et al* found lower rates of hospitalisation in patients with rheumatic diseases with COVID-19 who were taking traditional synthetic and biological disease modifying antirheumatic drugs (DMARDs).² With regard to biologic DMARDs, most of their registry patients were taking tumour necrosis factor inhibitors but did also include other therapies including interleukin-6 (IL-6) antagonists.

They also provide an interesting suggestion of the potential benefit of biologic DMARD therapy in COVID-19 patients particularly in cases associated with a hyperinflammatory response. Indeed, it has been recognised that subsets of COVID-19 patients can develop a cytokine storm involving the uncontrolled production of cytokines such as IL-6.^{3,4} Moreover, observational studies suggest the potential benefit of IL-6-antagonism using

tocilizumab (TOC).⁵⁻⁷ Internationally, TOC has been used in Italy, China and Ireland.⁸⁻¹⁰

Early during the UK pandemic, there was no access to clinical trials. Moreover, our Trust faced the second highest pressure index in the UK in relation to the number of admissions of COVID-19 patients.¹¹ Our intensive care unit and general medical inpatient wards had to expand within our hospital to meet the necessary demands of patient care. We also recognised that certain COVID-19 patients developed significant inflammatory responses. Based on this, published observational data elsewhere and the lack of early access to clinical trials, we proposed the compassionate use of TOC in a specific subset of COVID-19 patients.

In March 2020, we identified patients with severe COVID-19 and hyperinflammation. We defined severe COVID-19 as any patient with positive COVID-19 PCR swab and respiratory failure requiring a minimum of 40% oxygen therapy. Hyperinflammation was defined as a ferritin above 500 ng/mL with upgoing trend, and a C-reactive peptide (CRP) above 100 mg/L. The decision to initiate TOC necessitated multidisciplinary discussion between intensivists, pharmacists and both local and tertiary care rheumatologists. This was a novel approach to bedside therapeutic decision-making, reflecting the close collaboration between clinicians in secondary and tertiary care, thereby directly sharing specialist experience and knowledge at the clinical coalface. The TOC treatment regime consisted of two intravenous doses at 8 mg/kg 12 hours apart. We would consider a third dose after 24 hours if there was no significant improvement.

A total of eight patients (seven male, one female) received TOC with doses ranging between 400 and 700 mg. The mean age was 59.4 years (49–81 range) with seven belonging to the Black, Asian and Ethnic Minority (BAME) group. Three patients

Table 1 Clinical characteristics of COVID-19 patients treated with tocilizumab (TOC)

Patient	Comorbidities	Organ Failure	Pre-TOC Inflammation Parameters	Post-TOC Inflammation Parameters	Outcome
1	None	Respiratory Cardiovascular	Ferritin 1933 ng/mL CRP 360 mg/L	Ferritin 1759 ng/mL CRP 154 mg/L	Deceased
2*	Asthma Diabetes mellitus Hypertension Obesity	Respiratory Cardiovascular Renal	Ferritin 3504 ng/mL CRP 412 mg/L	N/A	Deceased
3	Splenectomy Hypertension	Respiratory	Ferritin 24, 203 ng/mL CRP 168 mg/L	Ferritin 3202 ng/mL CRP 40 mg/L	Alive
4	Diabetes Mellitus Hypertension Chronic Kidney Disease Obesity	Respiratory Renal	Ferritin 1730 ng/mL CRP 355 mg/L	Ferritin 356 ng/mL CRP 113 mg/L	Deceased
5	Hypertension	Respiratory Renal Cardiovascular	Ferritin 2006 ng/mL CRP 390 mg/L	Ferritin 933 ng/mL CRP 51 mg/L	Deceased
6	None	Respiratory Cardiovascular	Ferritin 1449 ng/mL CRP 376 mg/L	Ferritin 1353 ng/mL CRP 94 mg/L	Alive
7†	Hypertension	Respiratory Cardiovascular	Ferritin 1386 ng/mL CRP 233 mg/L	Ferritin 1317 ng/mL CRP 75 mg/L	Alive
8	None	Respiratory Renal Cardiovascular	Ferritin 17, 810 ng/mL CRP 442 mg/L	Ferritin 18, 777 ng/mL CRP 164 mg/L	Deceased

Organ failure listed is prior to TOC. Post-TOC inflammation parameters are after 72 hours unless otherwise stated.

*Patient only received one dose of tocilizumab as passed away prior to second dose.

†Patient received four doses of tocilizumab due to administrative error.

TOC, tocilizumab; I & V, intubation & ventilated; CRP, C-reactive peptide.

had no comorbidities. Seven patients required intensive care. Three patients improved following TOC administration and were discharged home. Two of these patients received TOC in intensive care within 24 hours of hospital presentation. The third patient avoided intensive care. The five deceased patients were all of BAME ethnicity and died of COVID-19-related complications. They were all in multiorgan failure at the time of TOC administration, receiving it 3–4 days following hospital presentation. All patients except one had improvements in CRP, and six had improvements in ferritin, triglycerides or D-dimer following TOC. Five patients had worsening transaminitis following TOC administration which was of no clinical significance. One patient was readmitted with pyelonephritis, acute kidney injury, ureteric stone and hydronephrosis requiring a ureteric stent and high-dependency care. This patient by administrative error received four doses of TOC at his initial admission. The patient made a full recovery. The clinical characteristics of the eight patients are summarised in [table 1](#).

In this unprecedented time, with limited treatment options available for rapidly deteriorating patients, we explored if IL-6 blockade with TOC may benefit a specific, defined subgroup of patients with evidence of hyperinflammation. One significant difference we note between our practice and published observational studies was the early administration of TOC in the latter. Therefore, we raise the question of whether TOC administration at an earlier disease course prior to the development of non-respiratory organ failure would be a more suitable therapeutic window.

The rapid evolution of conventional randomised controlled clinical trials meant that continuation of our compassionate approach could not be ethically justified or sustained. However, our real-world experience describes a clinical model of how newer therapeutic approaches can be rapidly implemented in the midst of a hitherto unprecedented pandemic. We also encourage clinicians to develop strong links with tertiary care experts so that patients can be channelled into appropriate trials at an earlier disease course. Furthermore, we encourage rheumatologists to continue to record characteristics of rheumatic patients with COVID-19 onto the Global Rheumatology Alliance registry as highlighted by Gianfrancesco *et al*.

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Dr TA were directly involved in patient care as well as data collection and analysis for the manuscript. Dr JJM was our tertiary care Rheumatologist who helped our local Rheumatology team with patient care. She also proof-read the manuscript and helped with draft rewrites. Finally, Dr JM-C was directly involved with patient care, helped with data collection and also proof-read the manuscript. Overall, each author meets the authorship criteria of the ICMJE.

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REFERENCES

- Public Health England. Guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19, 2020. Available: <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19>
- Gianfrancesco M, Hyrich KL, Al-Adely S, *et al*. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
- Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
- McGonagle D, Sharif K, O'Regan A, *et al*. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020;19:102537.
- Luo P, Qiu L, Liu X, *et al*. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol* 2020.
- Xu X, Han M, Li T, *et al*. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020:615.
- Sciascia S, Aprà F, Baffa A, *et al*. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* 2020;38:529–32.
- Nicastrì E, Petrosillo N, Ascoli Bartoli T, *et al*. National Institute for the Infectious Diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management. *Infect Dis Rep* 2020;12:8543.
- Health Service Executive. Interim guidance for the use of tocilizumab in the management of patients who have severe COVID-19 with suspected. *Hyperinflammation* 2020.
- National Health Commission of the People's Republic of China. Interpretation of "New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Version 7)", 2020. Available: <http://www.nhc.gov.cn/yzygj/s7652m/202003/a31191442e29474b98bfed5579d5af95.shtml>
- Batchelor G. Revealed: the hospitals facing most pressure to meet coronavirus demand. *Health Service Journal* 2020.