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Tocilizumab Rescue Therapy in Severe COVID-19 Pneumonia

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Abstract

Aim

COVID-19 refers to a spectrum of disease caused by the severe acute respiratory coronavirus type 2 (SARS-CoV-2), an RNA virus first reported in December 2019 which has since resulted in a global pandemic. Multiple reports suggest that a hyper-inflammatory immune response contributes to multi-organ failure and death in a subset of patients. This is triggered by a cytokine cascade, in which interleukin-6 (IL-6) plays a key role.

Methods

We describe our experience with the anti-IL-6 monoclonal antibody tocilizumab. Retrospective data from 8 patients in ICU with severe COVID-19 was collected.

Results

8 patients were included. Tocilizumab was associated with a statistically significant defervescence of fever in the at day 2 and day 4 post administration (paired t-test, p=0.029, p = 0.009 respectively) and marked reduction in CRP levels (mean decrease 277mg/l day 0 to 3). One patient was managed with non-invasive ventilation and was discharged 11 days later. 7 patients had a prolonged period of IMV (median duration 21 days +/- 23). 3 patients subsequently died and 5 were discharged alive after a median hospital admission duration of 48 days (+/- 23.5).

Conclusion

Overall, clinical outcomes were mixed, but positive biomarker response and an absence of severe side-effects attributed to this treatment is encouraging.

Introduction

Severe acute respiratory coronavirus 2 (SARS-CoV-2), a novel coronavirus first described in Wuhan, China[1] in December 2019 has since resulted in a pandemic with over 12.5 million cases in 212 countries worldwide. In Ireland, there were 68,356 confirmed cases and 1984 deaths from the virus at the time of writing[2]. SARS-CoV-2 binds to the alveolar epithelial cell via the angiotensin converting enzyme-2 (ACE2) receptor, resulting in activation of the innate and adaptive immune systems[3]. This triggers a cascade of pro-inflammatory cytokines, including IL-6 which plays an important role in immune activation[4]. Although rapid viral replication is implicated in severe disease, a notable feature of severe COVID-19 is a hyper-inflammatory response or 'cytokine-release storm', leading to acute respiratory distress syndrome (ARDS), multi-organ failure and death[5]. This syndrome shares clinical and biochemical features with haemophagocytic lymphohistiocytosis (HLH), a rare hyper-inflammatory syndrome with varying aetiology that presents with blood cytopenias, exuberant cytokine release and resultant multi-organ failure[6]. The H score was developed in 2014 by Fardet et al, as a means of measuring diagnostic probability of HLH and validated in patients with infection as the causative factor[7].

Tocilizumab is a recombinant human monoclonal antibody against the IL-6 receptor[6]. It is currently approved for immune modulation in rheumatoid arthritis and juvenile idiopathic arthritis[8]. Tocilizumab has been used successfully in the treatment of HLH, particularly in the setting of cytokine storm secondary to chimeric antigen receptor T cell therapy[9]. A 15 patient retrospective case series from Wuhan, China suggested there may be a benefit from tocilizumab in severe COVID-19[10]. Randomised control trials are currently underway, but this case series data and the absence of proven effective treatments for severe COVID-19 (aside from standard evidence-based supportive care) led to off-label use of tocilizumab in this setting. Several European countries established criteria for tocilizumab administration, based on serum d-dimer and presence of features of hyper-inflammation[11,12].

Given the ongoing exponential worldwide growth of this pandemic, there is an urgency to identify treatments that may be effective in reducing the severity of illness and mortality. The RECOVERY trial is currently ongoing, with patients randomised to various treatments including dexamethasone, tocilizumab, or ritonavir/lopinavir. Dexamethasone has been shown to improve 28-day mortality in patients receiving invasive ventilation or oxygen. There is ongoing randomisation of patients to receive tocilizumab with results pending, with patients recruited in early disease and also eligible for second randomisation to tocilizumab in the event of deterioration with O2 saturation <92% and CRP >75. We report here a cohort of patients with more severe COVID-19 pneumonia who received tocilizumab in an ICU setting as rescue therapy.

Methods

All patients with severe COVID-19 who received intravenous Tocilizumab at Naas General Hospital (n=5) and St James' Hospital, Dublin (n=3) were recruited into the study. A retrospective chart review was performed with demographics, medical comorbidities, laboratory results, imaging findings, treatments received, and clinical outcomes recorded.

Real time polymerase chain reaction (PCR) on nasopharyngeal swab confirmed SARS-CoV-2 infection in all patients. The study was conducted in accordance with the Declaration of Helsinki and ethical approval was granted by the National Research Ethics Committee.

All patients in this study were critically unwell and receiving care in ICU at time of drug administration. In the absence of an approved clinical trial, decision to treat was made following multi-disciplinary discussion involving the primary treating Consultant, Clinical Lead for Critical Care, treating ICU Consultant, a Consultant Microbiologist and a Consultant in Infectious Disease where appropriate. Patient selection criteria for tocilizumab was in line with current Health Service Executive Ireland recommended guidelines[11]. All patients had confirmed COVID-19 pneumonia, hypoxia (defined as peripheral arterial oxygen saturation (SpO_2) of <93% or ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) <300mg) and established signs of hyper-inflammation (temperature >38^oC, d-dimer >1000mg/ml and/or elevated CRP or serum ferritin). Tocilizumab was avoided in patients with evidence of active uncontrolled bacterial infection. All patients received a single loading dose of tocilizumab at 8mg/kg. Data was collected from the day prior to tocilizumab (defined as D-1), prior to infusion on day of treatment (D0) and on days 1 - 5 post-treatment.

Tocilizumab was given in addition to standard medical care which included non-invasive or invasive ventilatory support, enteral nutrition and broad-spectrum antibiotic therapy where indicated. Clinical management was at the discretion of the treating consultant physician. All patients received venous thromboembolism prophylaxis with low molecular weight heparin. All patients were initially treated with hydroxychloroquine in conjunction with a macrolide and one patient received lopinavir/ritonavir. Glucocorticoids were administered in 6 individuals; two for concomitant asthma exacerbation and in four cases for severe ARDS.

Results

Eight patients were included, of whom two were female. Median age was 56 (+/- 7.75). Seven of eight patients were receiving invasive mechanical ventilatory support at time of tocilizumab treatment, and 6 were receiving vasopressors for shock. All patients met criteria for at least moderate ARDS (presence of bilateral infiltrates and PaO_2:FiO_2 ratio of <200mmHg), with 3 meeting criteria for severe ARDS (PaO_2:FiO_2 ratio of <100mmHg). All patients demonstrated persistent pyrexia despite broad spectrum antimicrobial therapy and had negative sputum and blood cultures. The median duration of symptom onset prior to receiving tocilizumab was 13.5 days (+/-5 days).

The majority of patients demonstrated defervescence in the 48 hours following tocilizumab administration. There was a significant reduction in maximum recorded body temperature at day 2 compared to day 0 (paired t-test, p=0.029) and at day 4 compared to day 0 (p= 0.009) (figure 1). Changes in PaO_2:FiO_2 ratio (figure 4) and in vasopressor requirement were variable and not statistically significant over the following 5 days. 4 of 8 patients demonstrated reduction in WHO clinical severity score over the following 5 days (figure 2).

Serum C-reactive protein levels demonstrated marked reduction following tocilizumab (figure 3) with a mean decrease of 277mg/L between day 0 and day 3 (95% CI -406 to -148, p=0.0014, paired t-test). There was no significant change in d-dimer or ferritin post treatment. At day 5 post-treatment compared to day 0 serum fibrinogen was decreased (p= 0.012, paired t-test) and serum lymphocyte count increased (p=0.035, paired t-test). H score did not demonstrate significant change at day 0 as compared to day 5 (mean day 0 69 +/- 53 vs 74 +/- 30).

Three patients subsequently developed sepsis with bacteraemia (2 cases with MRSA) at > 1 week following tocilizumab administration, one of whom subsequently died from multi-organ failure. No patients developed deranged liver function tests or gastrointestinal perforation. Of those who received tocilizumab, 1 individual was managed with non-invasive ventilation and was discharged 11 days later. The remaining 7 patients all had prolonged period of IMV (median duration 21 days +/- 23). 3 patients subsequently died and 5 were discharged alive after a median hospital admission duration of 48 days (+/- 23.5).

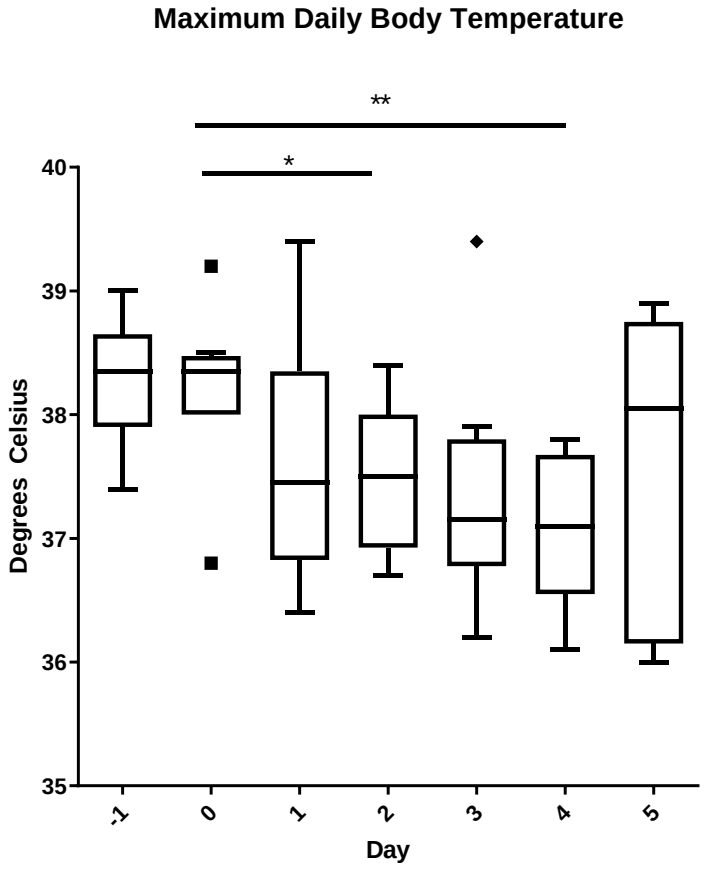

Figure 1: *Maximum recorded temperature following tocilizumab therapy. Tukey method with mean and honest significant difference displayed, n=8. Paired t-test, p<0.05 considered significant.*

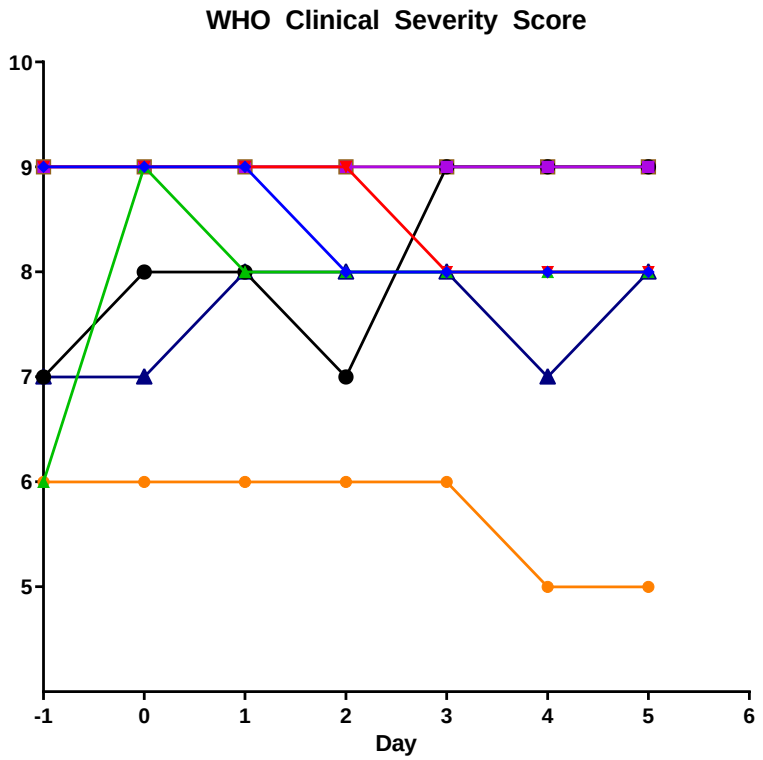

Figure 2: *WHO Clinical severity Score following tocilizumab therapy, n=8*

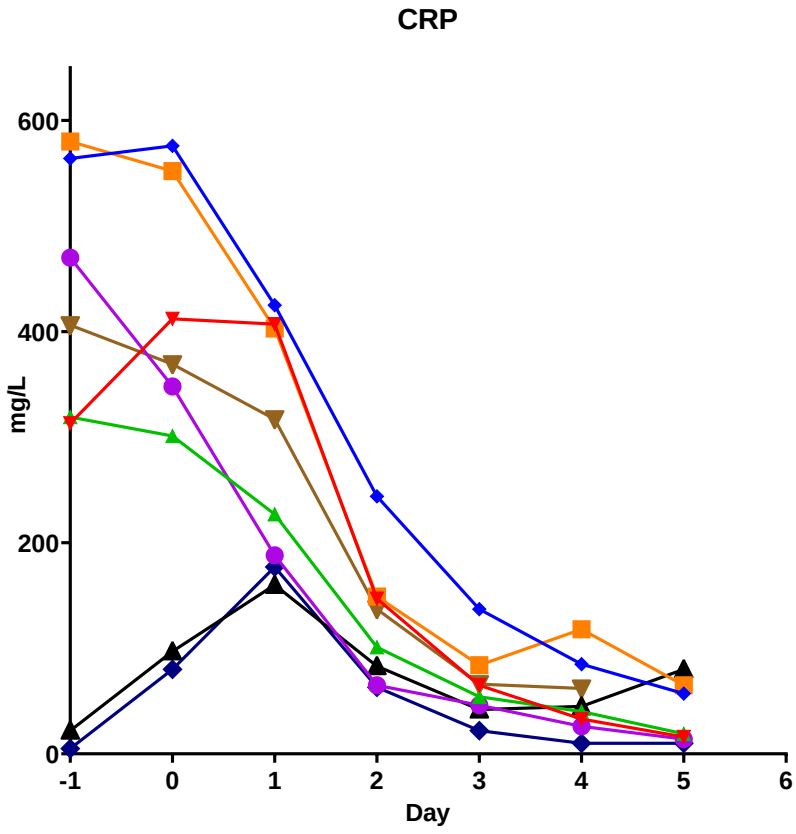

Figure 3: *Serum C-reactive protein following tocilizumab therapy, n=8*

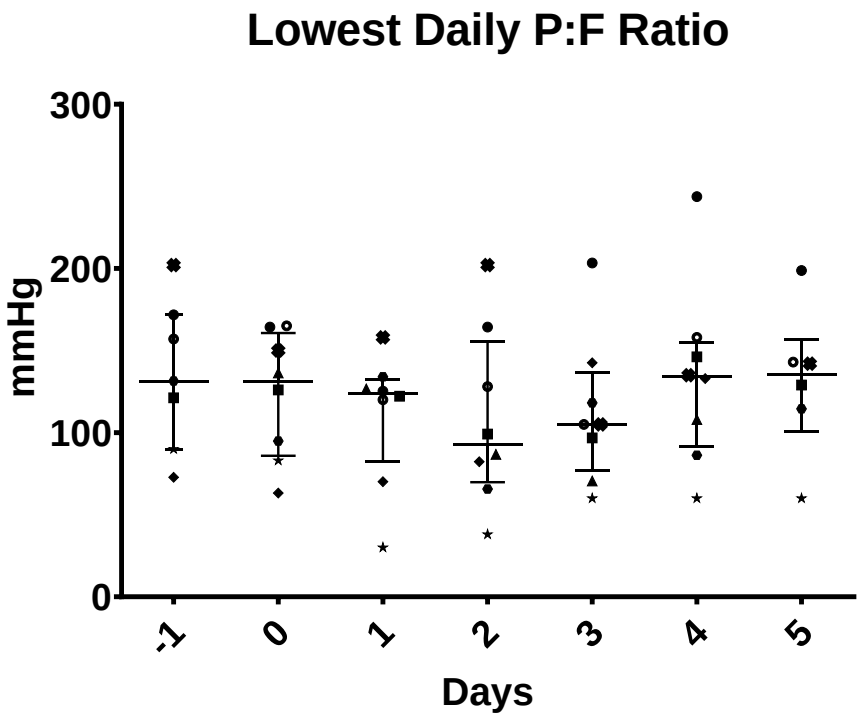

Figure 4*: Lowest recorded P:F ratio, mmHg. Individual patients represented by symbol, mean and SD indicated by error bars. N=8, 7 receiving IMV and 1 non-invasive ventilation.*

Discussion

The aim of this study was to report clinical and biomarker data from patients with severe COVID-19 pneumonia receiving tocilizumab as rescue therapy in the ICU. All patients had severe COVID-19 with WHO Clinical Progression Scale score of 6 or higher[14]. Guidance from other European countries suggests consideration of anti-IL6 therapy in selected patients with IL-6 level >40pg/nl OR d-dimer >1000ng/ml after exclusion of alternative causes. All our patients had d-dimers greater than this value (in many cases considerably higher). IL-6 was of limited clinical utility in our centre due to lag time between sampling and results of 1 week. All our patients were discussed at daily consultant-led microbiology rounds, were culture negative and were receiving broad spectrum antimicrobial therapy at time of tocilizumab therapy.

Tocilizumab was associated with a striking defervescence of fever in the 48 hours following administration and a marked reduction in CRP levels. Other parameters including d-dimer and ferritin demonstrated little change, though there was a reduction in fibrinogen and an increase in lymphocytes. Vasopressor requirement, P:F ratio (figure 4) and WHO severity index were variable and demonstrated no clear improvement following tocilizumab.

One patient who received therapy during milder phase of illness (prior to mechanical ventilation) was successfully managed with non-invasive ventilation and the trajectory of illness improved over the coming days.

Another patient who had been referred for extra-corporeal membrane oxygenation (ECMO) at time of drug administration demonstrated stabilisation of clinical trajectory, but still required a prolonged period of IMV (2 weeks) prior to successful extubation. Whether clinical improvement can be ascribed to Tocilizumab is unknown in the absence of a control, but our experience suggests that administration of therapy at an earlier phase of disease may have greater clinical impact.

Our study has important limitations. The lack of a control group makes comment on efficacy or otherwise of tocilizumab impossible. Differences in patient treatments and in particular in use of glucocorticoids may confound results. Glucocorticoid administration in our centre was not protocolised and was based on individual physician decision. There were no immediate drug-related adverse events in any patients, though the subsequent development of gram negative and MRSA sepsis reinforces the need for caution with immune modulating therapies in this cohort.

More research is required to characterise the hyper-immune response precipitated by COVID-19, and results from randomised control trials of anti-IL6 therapy are eagerly awaited. As noted in trials of the anti-viral therapy remdesivir, timing of treatment administration is a key consideration[15]. Data from observational cohorts can help to guide adequately powered RCTs to establish potential benefits and safety profile of tocilizumab in COVID-19. Our experience suggests that tocilizumab may have a role as rescue therapy in the ICU in selected patients receiving mechanical ventilation and that this warrants further investigation with RCT.

In conclusion, our study suggests tocilizumab may have a role in COVID 19 pneumonia characterised by hyperinflammatory response, given the positive shift in inflammatory biomarkers observed. Clinical outcomes observed were variable and it is difficult to conclude clinical benefit attributable to tocilizumab. Of note, three patients developed bacteraemia, a potential serious adverse effect of tocilizumab therapy. Randomised controlled trials are currently underway, evaluating the efficacy of tocilizumab in patients with varible severity of COVID 19[13].

Declaration of Conflicts of Interest:
The authors declare no relevant conflicts of interest.

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References:

1. H Lu, CW Stratton, YW Tang, Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle, [published January 16, 2020], J Med Virol. 2020. Apr 92(4):401-402.

2. European Centre for Disease Prevention and Control, COVID-19 situation update worldwide, as of 12 July 2020, ECDC, updated 12 July 2020, Available from https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases
3. J Amiral, AM Vissac, J Seghatchian, Covid-19, induced activation of hemostasis, and immune reactions: Can an auto-immune reaction contribute to the delayed severe complications observed in some patients?. Transfus Apher Sci. 2020;59(3):102804. doi:10.1016/j.transci.2020.102804
4. Chi Zhang, Zhao Wu, Jia-Wen Li, Hong Zhao, Gui-Qiang Wanga, Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality, Int J Antimicrob Agents. 2020 May; 55(5): 105954.
5. SH Nile, A Nile, J Qiu, L Li, X Jia, G Kai, COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine Growth Factor Rev. 2020;53:66-70. doi:10.1016/j.cytogfr.2020.05.002
6. P Mehta, D F McAuley, M Brown, E Sanchez, R S Tattersall, J J Manson et al. COVID-19: consider cytokine storm syndromes and immunosuppression, The Lancet, VOLUME 395, ISSUE 10229, P1033-1034, MARCH 28, 2020
7. L Fardet, L Galicier, O Lambotte, C Marzac, C Aumont, D Chahwan, et al, Development and Validation of the HScore, a Score for the Diagnosis of Reactive Hemophagocytic Syndrome, Arthritis and Rheumatology, 2014;66(9):2613-2620. doi:10.1002/art.38690
8. H I Brunner, N Ruperto, Z Zuber, C Keane, O Harari, A Kenwright, Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial, BMJ, Annals of Rheumatic diseases, 2015;74(6):1110-1117. doi:10.1136/annrheumdis-2014-20535
9. M Hutchinson, R S Tattersall, J J Manson, Haemophagocytic lymphohisticytosis—an underrecognized hyperinflammatory syndrome, Rheumatology, Volume 58, Issue Supplement 6, November 2019, Pages vi23–vi30
10. P Luo, Y Liu, L Qiu, X Liu, D Liu, J Li, Tocilizumab treatment in COVID-19: A single center experience, Journal of Medical Virology, 2020;92(7):814-818. doi:10.1002/jmv.25801
11. C Bergin, P Browne, P Murray, M O'Dwyer, N Conlon, D Kane, et al, Interim Recommendations for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation, V2 20 Mar 2020, available at https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/interim-recommendations-for-the-use-of-tocilizumab-in-the-management-of-patients-who-have-severe-covid-19-with-suspected-hyperinflammation.pdf Accessed 04/03/21
12. Italian National Society of Infectious Diseases, Guidelines for the managment of COVID-19 infection. Available at https://www.eahp.eu/sites/default/files/covid19_vademecum_2.0_13_marzo_2020.03_11.pdf, date accessed 23/07/20
13. Recovery Trial, Protocol available at https://www.recoverytrial.net/files/recovery-protocol-v8-0-2020-07-08.pdf Accessed 05/08/21
14. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection, A minimal common outcome measure set for COVID-19 clinical research, The Lancet Infectious Diseases, 12 June 2020.
15. J Grein, N Ohmagari, D Shin, G Diaz, E Asperges, A Castagna, Compassionate Use of Remdesivir for Patients with Severe Covid-19, The New England Journal of Medicine, June 11 2020, 2020; 382:2327-2336