**Cover Letter:**

Dear Editor,

We wish to submit an article of case report entitled “The dilemma of Tocilizumab treatment for a patient with critical COVID-19 disease and neutropenia: Case report and review of the literature” for your reputable journal (Clinical Case Reports – Wiley)

During the Covid-19 pandemic, there were limited treatment options. Tocilizumab is one of few therapeutic options that showed mortality benefit particularly in patients whom clinical course has been complicated by COVID-19 related cytokine storm. Neutropenia is one of the precautionary measures that limits its use while viral infections such as COVID-19 itself can cause profound leukopenia. What to do with patients presenting with COVID-19 infection complicated by cytokine storm while having clinical severe neutropenia?

In this case report, we present such dilemma which was managed through risk benefits assessment augmented by treatment Granulocyte- Colony Stimulating Factor G-CSF(Filgrastim) leading to full recovery.

Since the pandemic still evolving, we believe the scientific community deserved to collect evidence of different management strategies including treatment of such an important patients’ cohorts to aid towards safe outcomes.

We believe the manuscript is appropriate for publication by at Clinical Case Reports because it is within the spectrum and it provide new knowledge to the scientific community.

We confirm that this work is original and has not been published elsewhere, nor it is currently under consideration for publication elsewhere.

Thank you for your consideration for the manuscript.

Sincerely,

Ahmad Al Bishawi.

**The dilemma of Tocilizumab therapy for a patient with critical COVID-19 disease and neutropenia: Case report and review of the literature**

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**MeSH Keywords:**

COVID 19, Cytokine Storm, Tocilizumab, Interleukin 6, neutropenia, Filgrastim.

**Abbreviation:**

WBC: White Blood count

IL6: Interleukin 6

CSS: cytokine storm syndrome

PCR: Polymerase chain reaction

G- CSF: Granulocyte colony stimulating factor

ANC: Absolute neutrophilic count

CT Value: cyclic threshold value

CTPA: CT Pulmonary Angiography.

Abstract:

**Background:**

Infection following SARS-Co V-2 leading to COVID-19 disease is associated with significant morbidity and mortality. The clinical entity, COVID-19 Cytokine Storm Syndrome (CSS) is a severe immunological manifestation of the disease associated with ominous consequences.

Tocilizumab is Interleukin-6 inhibitors that has been shown to hamper the catastrophic outcomes of CCS including the need for mechanical ventilation as well as reduce mortality, but usage is limited by warnings of reactivation of potential latent infections or immune dysfunctions including severe neutropenia.

**Case Report:** We describe a case of 39-year- old Nepalese male patient with a background of scleritis maintained on azathioprine and rituximab therapy with normal baseline parameters including complete blood count who presented with acute COVID-19 infection including associated leukopenia as well as severe neutropenia (absolute neutrophil count of 300 cells/µL), then progressed to critical disease culminating into CSS. Based on risks and benefits evaluation, the patient was treated with Tocilizumab reinforced with Granulocytes -Colony Stimulating Factor (G-CSF, Filgrastim) to full recovery and safe outcome including reversal of neutropenia.

**Clinical Key Message:** for patients with COVID-19 disease progressing towards Cytokine Storm syndrome (CSS) in the presence of significant neutropenia, combined Tocilizumab and G-CSF therapy circumvent potential therapeutic limitations leading to safe outcomes.

**Introduction:**

The global pandemic of SARS-CoV-2 infection and COVID-19 disease engulfed the medical and scientific community around the world with evolving experience in the clinical evaluation and management of the disease spectrum. One of the intriguing phenomena observed during the pandemic is the variations in the clinical presentations of the disease, ranging from asymptomatic infection to severe disease necessitating critical care. It was recognized early during the pandemic that the pneumotropic virus is capable of causing severe lower respiratory tract infections culminating towards severe sepsis, multiorgan dysfunctions, multitude of pulmonary diseases including Acute Respiratory Distress Syndrome (ARDS) [1]. Besides, it has been established that respiratory failure and ARDS is one of the commonest causes of prolonged intubation and mechanical ventilation leading to reported significant mortality [2]. The full picture of the underlying mechanisms leading to severe sepsis and ARDS is not fully understood but frequently linked to the development of an intense hyperimmune response coined COVID-19 Cytokine Storm Syndrome (CSS) , characterized by simultaneous surge in immune activation , production of substantial inflammatory responses and cytokines leading to cascades of systemic manifestations , end organs damage and subsequent organs failure [3].

During the pandemic it was noticed that the majority of the worst outcomes including the worrying mortality is observed in patients with severe and critical disease who progress towards mechanical ventilation as well in patients with ARDS [2,4]. For such instances, it imperative to try to avoid early complications that might lead to such progressive complications. Furthermore, while studying inflammatory mediators during the pandemic , the cytokine interleukin -6 (IL-6) was found to play a pivotal role in early immune activation so it was plausible to examine the role of related inhibitors such as Tocilizumab to explore potential halting of the harmful pathological consequences. Tocilizumab is a recombinant humanized monoclonal antibody of the IgG1 class, that binds to soluble and membrane-bound IL-6 receptors inhibits signaling pathways. Before the pandemic, it has been licensed to treatment severe rheumatoid arthritis, juvenile idiopathic arthritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T cell therapy [5].

Basic research during the COVID-19 pandemic, led to repurposed therapeutic benefits established by the efficacy of the drug to degrade immune activation including systemic inflammation which is supported by evidence from randomized clinical trials in reducing associated mechanical ventilation as well as mortality outcomes [6]. However, emergency licensing authorization warned of precautionary measure to limit usage in case of significant active diseases such as TB, infectious hepatitis, or invasive fungal infections in addition to severe neutropenia with ANC < 1000 cells /uL [7]. This warning stems from the background history of biological treatment including Tocilizumab which has been around for the past two decades to treat rheumatological and inflammatory condition such as connective tissues and inflammatory bowel diseases. Their efficacy was balanced against highlighted precautions of reactivations or propagation of infections or enhanced susceptibility for secondary opportunistic infections. These tangible risks of compromising the immune system leading to secondary opportunistic infection has been highlighted in many observational studies being variable with the different biological agents [8,9].

While balancing the effective benefits of Tocilizumab therapy during COVID-19 disease specially CSS, its potential risks including precautions in patients with profound neutropenia must be carefully weighed. Moreover, such conditions have been highlighted as an indication to withheld or discontinue Tocilizumab therapy. Nevertheless, experience during the pandemic circumvented many restrictions and precautions in favor of safe patients’ outcomes.

Therefore, we outlay the clinical dilemma of using Tocilizumab therapy in a patient with severe COVID-19 and active CSS with potential fears of disease progression, in the context of profound clinical neutropenia. On risk benefits evaluation the patient was treated with the effective therapy but covered with G-CSF (Filgrastim) to safe outcome.

**Case Report:**

A 39-year-old male patient with a background history of probable autoimmune disease leading to undifferentiated scleritis was maintained by his ophthalmologist on azathioprine and rituximab therapy with stable disease for six years. The patient presented with typical respiratory and systemic symptoms of COVID-19 disease including fever, dry cough, headache, tiredness associated with nausea of one-week duration.

Prescribed medications included azathioprine 150 mg daily and parenteral Rituximab 1000 mg injections last given 4 months prior to presentation. From follow up notes prior to current presentation, complete blood counts including leukocytes parameter were within normal limits.

Initial evaluation demonstrated fever of 39.5° C, blood pressure of 103/64 mmHg, pulse rate of 95 per minute, respiratory rate of 22 per minute and oxygen saturation of 98 % on room air with no signs of respiratory distress. Chest examination revealed evidence of bilateral basal crackles while the rest of the physical examination was unremarkable. Initial blood investigations showed: leucopenia with WBC count of 1.1 x10 3 uL, neutropenia with absolute neutrophils count (ANC) of 0.3 x10 3/uL and lymphopenia of 0.6 x10 3uL while peripheral blood smear revealed markedly decreased WBC with severe neutropenia and lymphopenia with reactive changes (table 1 ). To assess for disease severity, severity biological markers were elevated: C-reactive protein (CRP) 124 mg/L, ferritin 1185 ug/L, lactate dehydrogenase (LDH) 459 U/L and D-dimer 4.18 mg/L.

Chest X-ray revealed bilateral infiltrates with visible hazy opacities (Figure 1). The clinical suspicion of moderate COVID-19 disease was confirmed through COVID-19 PCR with Cycle Threshold value (CT value) of 24 denoting early clinical disease.

The patient was admitted under airborne and contact precautions and started on the local protocol of Favipiravir, ampicillin/sulbactam therapy together with venous thromboembolism prophylaxis in form of low molecular weight heparin in addition to symptomatic treatment.

Because of the acute infection and fears of immune dysfunctions, prescribed immunosuppressive therapy was withheld. Over the following days, the patient condition deteriorated with high grade fever, worsening respiratory symptoms and laboratory parameters including progressive neutropenia with a remarkable rise in D-dimer to >35 mg/L as well as IL-6 of 115 pg/mL (Table 2). Searching for septic foci with repeated blood and urine cultures all returned negative. Associated pulmonary embolism was excluded with CT pulmonary angiogram (CTPA) but confirmed bilateral infiltrative changes. Despite these measures, the patient continued to deteriorate with respiratory compromise requiring higher oxygen supplementation. Escalation of management with broadening of the antibiotic coverage with piperacillin-tazobactam, together with COVID-19 specific therapy in form of 200 mg of parenteral Remdesivir therapy for the first day followed by daily 100 mg daily for the following 4 days as well as augmented management with 8 mg of parenteral dexamethasone therapy .

The clinical assessment of an evolving COVID-19 cytokine storm Syndrome (CSS) was considered and the decisions of administering Tocilizumab therapy was evaluated balanced between known benefits in pending CSS against the patient clinical condition of severe COVID-19 infection with profound neutropenia. Eventually 400 mg of parenteral tocilizumab was administered while closely monitoring clinical and laboratory parameters. Over the following days, there was gradual but remarkable improvement in clinical condition supported by falling of inflammatory parameters however the profound neutropenia was persistent. To curtail for that, the patient was started on GCSF in the form of Filgrastim 300 mcg twice daily with evident neutrophils rise within few days to ANC more than 1000 (Table 1) (figure 2).

During subsequent observation and hospital stay, the patient did not develop any active or opportunistic infections. Following recovery and consultation with managing ophthalmologist, the decision was made to continue withholding immune suppressive therapy pending progress and the patient was discharged to a safe outcome. Follow up revealed full recovery and no subsequent complications.

**Discussion**

The spectrum of COVID-19 disease manifest with variable clinical presentations ranging from asymptomatic to severe and critical disease encompassing the immunologically mediated condition Cytokine Storm Syndrome (CSS) with significant morbidity and mortality [1]. The clinical entity of CSS is characterized by an intense activation of the immune system with the release of various inflammatory mediators including cytokines such as interleukin 6 (IL-6), IL-10, and tumor necrosis factor α (TNF-α) leading to systemic manifestations , end organs damage and eventually failure and unfavorable outcomes [10].

Because of circumstantial correlation with disease progression towards mechanical ventilation, prolonged hospital stays, significant morbidity and mortality, early detection of CSS is certainly beneficial. The evaluation is based upon multiple studied clinical and laboratory parameters which primarily heralded by new clinical deterioration in the cardiopulmonary status coupled with significant deterioration in laboratory parameters predominantly inflammatory markers such as WBCs, CRP , ferritin , LDH and IL-6 [11] . As a consequence, multiple guidance including the Infectious Diseases Society of America (IDSA) recommends the use of immune suppressive therapy such as Tocilizumab for hospitalized adults with progressive severe or critical COVID-19 disease who develops features of hyperinflammatory syndrome along with standards of usual care such as steroids [12].

Tocilizumab is a specific biological monoclonal antibody directed against anti-IL-6-receptors blocking its signaling pathways to activate the immune system at cellular level. It was approved by FDA for various rheumatologic conditions as well as cytokine release syndrome associated with CAR-T cell therapy [9]. The therapeutic benefit of the drug was recognized early during the pandemic in hindering immune activation thus decreasing end-organs dysfunctions as well as the need for intubation. Nevertheless, there were paucity of data about short term safety and tolerability of tocilizumab as in COVID-19 disease. The majority of previous published data was mainly reported in the context of prolonged treatment of rheumatological conditions including rheumatoid arthritis. In a network metanalysis investigated potential adverse reactions in patients with any disease conditions except HIV, tocilizumab was associated with gastrointestinal disorders, dyslipidemia, elevated liver enzymes and neutropenia. Moreover, The USA FDA’s black box warned against increased serious infections with most biological treatment such as active tuberculosis, bacterial infections as well as invasive fungal infections [13]. Therefore, the FDA emergency use authorization for Tocilizumab in COVID-19 disease; recommended screening and monitoring for existing active or latent infections as well as observing for associated neutropenia. Notably, the recommendations warned of cautious usage while monitoring in cases of remarkable neutropenia (ANC < 1000 mm3)to the point of recommending against it to discontinue or withholding treatment if ANC is less than 300 mm3 [7]. Of note, leukopenia mainly driven by lymphopenia as well as thrombocytopenia is known manifestations of COVId-19 disease since it was observed to corelates with disease severity as well as mortality [20]. Furthermore, pan-cytopenia including neutropenia has been reported as a feature of severe COVID-19 particularly in the context CSS where bone marrow suppression or immune related cytopenia has been attributed as the underlying pathophysiological mechanisms [14]. Conversely, although one of the adverse events of Azathioprine therapy is bone marrow suppression including neutropenia, our patient’s blood parameters were maintained to normal levels while on treatment for six years. Usually this established adverse events has a genetic predisposition since the recognized association stems from inadequate level of the degrading enzymes Thiopurine Methyltrasferase (TPMT) and Nudix hydrolase (NUDT15) that metabolize Azathioprine [15]

Nevertheless, our patient has stable blood counts for a long time before his current presentation, which indicates that his pan-cytopenia is probably induced by infection. Taking that into consideration, our patient presented with grade 4 severe neutropenia (ANC 0.3 x103 uL) which most likely related to the severe acute COVID-19 disease rather than prior immunosuppressants therapy with rituximab and azathioprine. The clinical dilemma encountered during management was of a patient with progressively severe COVID-19 disease with established CSS who has concomitant profound neutropenia hindering admiration of Tocilizumab, an effective therapeutic agent that has been shown to alter disease progression and deterioration. In clinical practice, the golden ethical advice is to observe patient’s autonomy while implementing the principles beneficence and doing no harm [16].

Following discussion with the patients, balancing benefits against risks, the clinical team decided to administer Tocilizumab therapy under monitoring then salvage the critical neutropenia with G-CSF (filgrastim) to stimulate neutrophil production to safe outcome and recovery. Although our approach was successful, the usage of G-CSF in COVID 19 disease is still controversial with some reports relates its administration to increase oxygen requirements, possible precipitation of cytokine storm as well as progression of alveolar damage [17,18]

This case tries to address two main issues: the use of Tocilizumab in patients with severe COVID-19 disease and profound neutropenia as well as G-CSF therapy in the context of CSS and COVID-19 disease. Since there are paucity of data and clinical experience to answer these questions during the evolving pandemic only accumulate evidence will participate towards building the needed experience. To our knowledge this will be the first case report to successful tocilizumab therapy in COVID 19 patients with profundo neutropenia. Further studies regarding tocilizumab benefits in such cohort of patients and whether the additive action of G-CSF is recommended.

**Conclusion:**

The COVID-19 pandemic is evolving with significant morbidity and mortality specially from Cytokine Storm Syndrome. Tocilizumab therapy is recommended to impede the deleterious consequences of CSS yet limited by precautionary measures in patients with severe neutropenia. In patients with severe COVID-19 disease and critical neutropenia, we recommend the cautious administration of Tocilizumab supported by G-CSF on benefits against risks assessment.

**Authors Statement CRedit:**

Ahmad Al Bishawi: Final Manuscript writing and editing.

Shiema Abdalla: Initial draft writing

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Wael Kanjo: Literature review

Amal Sameer: Literature review

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Muna Al Maslamani and Alaaeldin Abdelmajid: Supervision and final manuscript revision.

**Figure Legends**

**Table 1**

White Blood Cell counts during patient Hospital stay.

Day 3: Tocilizumab administered

Day 5: Filgrastim Administered

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline (In January 2021) | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
| WBCs (x103/uL) | 7.8 | 1.1 | 0.9 | 0.9 | 1.1 | 1 | 1.4 | 1.5 | 4.1 |
| ANC (x103/uL) | 5 | 0.3 | 0.2 | 0.1 | 0 | 0 | 0.1 | 0.1 | 1.4 |
| Lymphocytes  (x103/uL) | 2.1 | 0.6 | 0.6 | 0.7 | 0.8 | 0.7 | 1 | 1 | 1 |

**Table 2**

Serial laboratory inflammatory markers during patient Hospital stay.

**Day 3: Tocilizumab administered**

**Day 5: Filgrastim Administered**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** |
| **D-Dimer** **(mg/L)** | 4.18 | >35.2 | >35.2 |  | 0.7 | 0.84 | 0.62 | 0.22 |
| **CRP (mg/L)** | 124.6 | 148 | 153.8 | 159.3 | 86.1 | 57.2 | 35.1 | 19.1 |
| **LDH** **(U/L)** |  | 459 |  |  |  |  |  |  |
| **Ferritin** **(ug/L)** | 1185 | 6881 |  |  |  | 4776 |  |  |
| **Procalcitonin (ng/mL)** |  | 3.86 |  | 2.28 |  | 0.81 |  | 0.16 |

**Figure 1:**

Initial Chest X ray upon presentation showed bilateral peripheral faint opacities

**Figure 2:**

Patients serial WBC and CRP measurements during his hospital stay.

ANC: Absolute neutrophil count

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**Conflict of Interest:**

The authors declare no conflict of interest

**Consent form:**

A written consent form was obtained and will be available upon editorial office request

**References:**

[1]Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev*. 2020;53:25-32. doi:10.1016/j.cytogfr.2020.05.003.

[2]Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Med J Aust*. 2020;213(2):54-56.e1. doi:10.5694/mja2.50674.

[3]Bhaskar S, Sinha A, Banach M, et al. Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. *Front Immunol*. 2020;11:1648. Published 2020 Jul 10. doi:10.3389/fimmu.2020.01648.

[4]Farooqi, F., Dhawan, N., Morgan, R., Dinh, J., Nedd, K., & Yatzkan, G. (2020). Treatment of Severe COVID-19 with Tocilizumab Mitigates Cytokine Storm and Averts Mechanical Ventilation during Acute Respiratory Distress: A Case Report and Literature Review. *Tropical Medicine And Infectious Disease*, *5*(3), 112. doi: 10.3390/tropicalmed5030112.

[5]Bernardo, L., Del Sesto, S., Giordano, L., Benincaso, A., Biondi, P., & Goj, V. et al. (2020). Severe prolonged neutropenia following administration of tocilizumab in a patient affected by COVID-19: a case report and brief review of the literature. *Drugs & Therapy Perspectives*, *36*(12), 568-572. doi: 10.1007/s40267-020-00777-z.

[6]Morris AM, Stall NM, Bobos P, et al. Tocilizumab for hospitalized patients with COVID-19. Science Briefs of the Ontario COVID-19 Science Advisory Table. 2021;2(11). <https://doi.org/10.47326/ocsat.2021.02.11.1.0>.

[7] FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR ACTEMRA® (tocilizumab).Available at <https://www.fda.gov/media/150321/download>: Last Accessed : 9.2.2022.

[8] Moots RJ, Sebba A, Rigby W, et al. Effect of tocilizumab on neutrophils in adult patients with rheumatoid arthritis: pooled analysis of data from phase 3 and 4 clinical trials. Rheumatology (Oxford). 2017;56(4):541–9.

[9]Rubbert-Roth, A., Furst, D. E., Nebesky, J. M., Jin, A., & Berber, E. (2018). A Review of Recent Advances Using Tocilizumab in the Treatment of Rheumatic Diseases. *Rheumatology and therapy*, *5*(1), 21–42. <https://doi.org/10.1007/s40744-018-0102-x>.

[10]Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., & HLH Across Speciality Collaboration, UK (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*, *395*(10229), 1033–1034. <https://doi.org/10.1016/S0140-6736(20)30628-0> .

[11] Webb, B. J., Peltan, I. D., Jensen, P., Hoda, D., Hunter, B., Silver, A., Starr, N., Buckel, W., Grisel, N., Hummel, E., Snow, G., Morris, D., Stenehjem, E., Srivastava, R., & Brown, S. M. (2020). Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. *The Lancet. Rheumatology*, *2*(12), e754–e763. <https://doi.org/10.1016/S2665-9913(20)30343-X>.

[12]IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 2/8/2022 [https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Last Accessed 9.2.2022.](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.%20Last%20Accessed%209.2.2022.%20)

[13] Singh, J. A., Wells, G. A., Christensen, R., Tanjong Ghogomu, E., Maxwell, L., Macdonald, J. K., Filippini, G., Skoetz, N., Francis, D., Lopes, L. C., Guyatt, G. H., Schmitt, J., La Mantia, L., Weberschock, T., Roos, J. F., Siebert, H., Hershan, S., Lunn, M. P., Tugwell, P., & Buchbinder, R. (2011). Adverse effects of biologics: a network meta-analysis and Cochrane overview. *The Cochrane database of systematic reviews*, *2011*(2), CD008794. <https://doi.org/10.1002/14651858.CD008794.pub2>.

[14] López-Pereira P, Iturrate I, de La Cámara R, Cardeñoso L, Alegre A, Aguado B. Can COVID-19 cause severe neutropenia?. *Clin Case Rep*. 2020;8:3348–3350. <https://doi.org/10.1002/ccr3.3369> .

[15] Jena A, Jha DK, Kumar-M P, et al. Prevalence of polymorphisms in thiopurine metabolism and association with adverse outcomes: a South Asian region-specific systematic review and meta-analysis. *Expert Rev Clin Pharmacol*. 2021;14(4):491-501. doi:10.1080/17512433.2021.1900729

[16] Gillon R. Medical ethics: four principles plus attention to scope. *BMJ*. 1994;309(6948):184-188. doi:10.1136/bmj.309.6948.184.

[17] Morjaria S, Zhang A, Kaltsas Md A, et al. The Effect of Neutropenia and Filgrastim (G-CSF) in Cancer Patients With COVID-19 Infection. Preprint. *medRxiv*. 2020;2020.08.13.20174565. Published 2020 Aug 15. doi:10.1101/2020.08.13.20174565.

[18] Lazarus HM, Gale RP. G-CSF and GM-CSF Are Different. Which One Is Better for COVID-19. *Acta Haematol*. 2021;144(4):355-359. doi:10.1159/000510352