

Tocilizumab

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Neutropenia following off-label use: case report

A 65-year-old man developed neutropenia during off-label treatment with tocilizumab for COVID-19 infection.

The man presented to the emergency department with a few days' history of fever and complaints of a presyncopal episode. His medical history included hypertensive cardiomyopathy, paroxysmic atrial fibrillation and chronic stage II renal insufficiency. Due to poor compliance, he had not been receiving any medications. Subsequent physical examination was unremarkable with oxygen saturation of 99% on room air, heart rate 83 beats/min, BP 160/80mm Hg and body temperature 38.1°C. Blood tests showed mild leukocytosis with left shift (neutrophils $9 \times 10^9/L$), increased C-reactive protein, slightly elevated creatinine and normal urea and liver function tests. The chest X-ray revealed mild bilateral interstitial pneumonia. Real-time reverse transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab returned positive for SARS-CoV-2 and he was diagnosed with COVID-19. Subsequently, he started receiving off-label treatment with ceftriaxone and clarithromycin due to concerns that he had a superimposed bacterial lung infection. On day 3, blood test showed persistently increased CRP levels. Therefore, antibiotic treatment was switched from ceftriaxone to off-label piperacillin/tazobactam. Additionally, he started receiving off-label combination therapy with hydroxychloroquine and lopinavir/ritonavir for 5 days. During hospitalisation, his clinical conditions worsened with type 1 hypoxaemic respiratory failure. Blood gas analysis on room air showed mild respiratory alkalosis with hypoxaemia. His oxygen saturation dropped at 92% on room air and fine diffuse crackles were heard on lung auscultation. At that time, blood test showed leukocytosis with neutrophilia and subsequent lymphopenia, significantly increased CRP level and microcytic anaemia with prolonged prothrombin time. Subsequent chest-CT scan showed bilateral diffuse lung consolidations and groundglass opacities. He also exhibited mild pleural effusion and mediastinal lymphadenopathy. Following infectious disease screening tests and evaluation of IL-6 levels, he received two off-label IV tocilizumab injection 8 mg/kg administered 12 hours apart on day 8 of hospitalisation. Subsequently, his clinical condition improved. Blood test showed rapid decrease in CRP and WBC count, particularly his absolute neutrophil count ($0.89 \times 10^9/L$) [*duration of treatment to reaction onset not stated*]. His haemoglobin and creatinine levels improved. A repeat chest CT after a week showed improvement in lung opacities. After two days of tocilizumab administration, blood test showed persistence of leukopenia with mild lymphopenia and progression of neutropenia ($0.52 \times 10^9/L$). His serial blood test showed worsening of neutropenia. A nadir ($0.25 \times 10^9/L$) was reached 12 days after the tocilizumab injections. Severe neutropenia was persisting for at least 4 weeks. On day 30 after the tocilizumab injections, his ANC started to improve ($0.62 \times 10^9/L$), which was far from normal values.

Bernardo L, et al. Severe prolonged neutropenia following administration of tocilizumab in a patient affected by COVID-19: a case report and brief review of the literature. *Drugs and Therapy Perspectives* 36: 568-572, No. 12, Dec 2020. Available from: URL: <http://doi.org/10.1007/s40267-020-00777-z>

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