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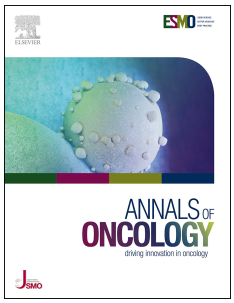

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Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report

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Running title: Tocilizumab to treat respiratory failure related to Covid-19

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Letter to the editor.

The pathogenesis of coronavirus disease 2019 (Covid-19) remains unclear and there is presently no evidence for efficient therapeutics. The pathogenesis of severe acute respiratory syndrome (SARS) related to coronavirus involves a cytokine storm with high serum levels of pro-inflammatory cytokines and chemokines interleukin 6 (IL-6), tumor necrosis factor (TNF-alpha), interferon-gamma, IL-1 and IL-12, and IL-8 [1–4]. Similarly, in Covid-19, higher plasma levels of cytokines IL-6, IL-2, IL-7, IL-10, interferon gamma inducible protein (IP10), monocyte chemo attractant protein (MCP1), macrophage inflammatory protein (MIP1A) and TNF-alpha have been found in patients admitted to intensive care units, and the cytokine storm syndrome was proportional to the severity of disease [5]. The proinflammatory IL-6 appears as one of the key cytokines leading to the inflammatory storm, which may result in increased alveolar-capillary blood-gas exchange dysfunction [4, 6]. The pro-inflammatory cytokine IL-6 seems to have a prominent role in this inflammatory cascade [4].

These data suggest that IL-6 may be a potential actionable target cytokine to treat Covid-19-related acute respiratory distress syndrome (ARDS). We report here the case of a patient with a respiratory failure linked to Covid-19 who had a rapid favorable outcome after two infusions of the anti-interleukin 6 receptor inhibitor tocilizumab. This suggests that anti-IL6 receptor inhibitor treatment could decrease the risk of progression toward SARS by mitigating the cytokine storm in the lungs with Covid-19.

Case description

A 42-year-old male recently diagnosed with metastatic sarcomatoid clear cell renal cell carcinoma, had been hospitalized for fever, symptomatic bone metastases pain management and first-line systemic treatment decisions. The patient had no other significant medical history. He presented initially with isolated fever of 39.0°C on March 12th, 2020 for which he received ceftriaxone outside our center. On Day 6, he developed mild cough and fever (38.3°C) prompting SARS-Cov-2 real time polymerase chain reaction test, which was positive. The patient was

admitted to the Covid-19 ward of our hospital and closely monitored. Chest computerized tomography (CT) scan revealed bilateral patchy ground glass opacities related to Covid-19 (***Figure 1***). Antiviral therapy lopinavir-ritonavir use (400mg-100mg orally) was begun at D7 and maintained for 5 days, according to local guidelines. On day 8, sudden dyspnea and saturation drop required oxygen supplementation increase to 6 l/min, without the need for artificial ventilation. He received two doses of tocilizumab, at 8 mg/kg intravenously for each dose, 8 hours apart, with a good tolerability. Thereafter, he experienced clinical improvement, rapidly afebrile and with gradually decreased oxygen consumption. This was fully discontinued on day 12 (***Figure 1***). Chest CT on day 12 confirmed improvement by showing partial regression of the pulmonary infiltrates and ground glass appearance (***Figure 1***). C-reactive protein in blood, a surrogate marker of cytokine storm, decreased from 225 mg/L to 33 mg/L in 4 days (***Figure 1***). No major change was observed in circulating lymphocytic subpopulations after tocilizumab, and the percentage of CD4 + CD25 + lymphocytes was found high, before and after tocilizumab. (***Figure 2***). The Patient ultimately clinically fully recovered from Covid-19 symptoms.

Discussion and conclusion.

As a recombinant humanized anti-human IL-6 receptor monoclonal antibody, tocilizumab can specifically bind soluble IL-6 receptor and inhibit signal transduction [7]. Tocilizumab is currently mainly used to treat patients with rheumatoid arthritis. It is given every 4 weeks, for up to 24 weeks, with a favorable safety profile [8]. Other indications for tocilizumab are juvenile arthritis, giant cell arthritis, and -- more recently-- cytokine release syndromes associated with chimeric antigen receptor T cell therapies [7, 9]. In these mainly rheumatologic indications, the tolerance of tocilizumab is generally good, the main adverse events are a transient decrease in leukocytes and increase in liver enzymes and a slight increase of bacterial infection [7,8]. In patients with Covid-19, the safety profile, and especially the potential drug interactions with antivirals, remain to be investigated in clinical trials. Clinical trials are also required to explore whether tocilizumab can be used effectively in patients with respiratory failure due to COVID-19 and to investigate at what stage of the disease this treatment could be the most appropriate.

Here we report the first successful treatment of a patient with respiratory failure related to Covid-19 and treated with tocilizumab. The present report has several limitations. First, the patient was immunosuppressed because of

his cancer, and this case is therefore not generalizable to the non-cancer population. Interestingly, his lymphocytic subpopulation presented high level of senescence, as frequently observed in cancer patients (data not shown). To what extent this could explain sensitivity to tocilizumab should be further explored. Second, the patient received concomitant therapies, especially lopinavir-ritonavir, but it seems unlikely this changed the disease trajectory, since lopinavir-ritonavir has recently been shown not to be effective in patients with severe Covid-19 in a randomized controlled trial [10]. It thus seems likely that the rapid control of the pulmonary hyperinflammation resulted from tocilizumab treatment.

In summary, Covid-19 with hyperinflammatory pulmonary symptoms is associated with a cytokine storm involving interleukins and chemokine dysregulation. Among these, the actionable proinflammatory interleukin 6 axis seems to play a major role. We report the first observation of a patient with severe Covid-19-related lung disease successfully treated with anti-interleukin 6 receptor treatment. Blocking the cytokine axis IL6 appears to us a promising therapy to be studied urgently in patients developing severe acute respiratory syndrome related to coronavirus.

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Dr Jean-Marie Michot

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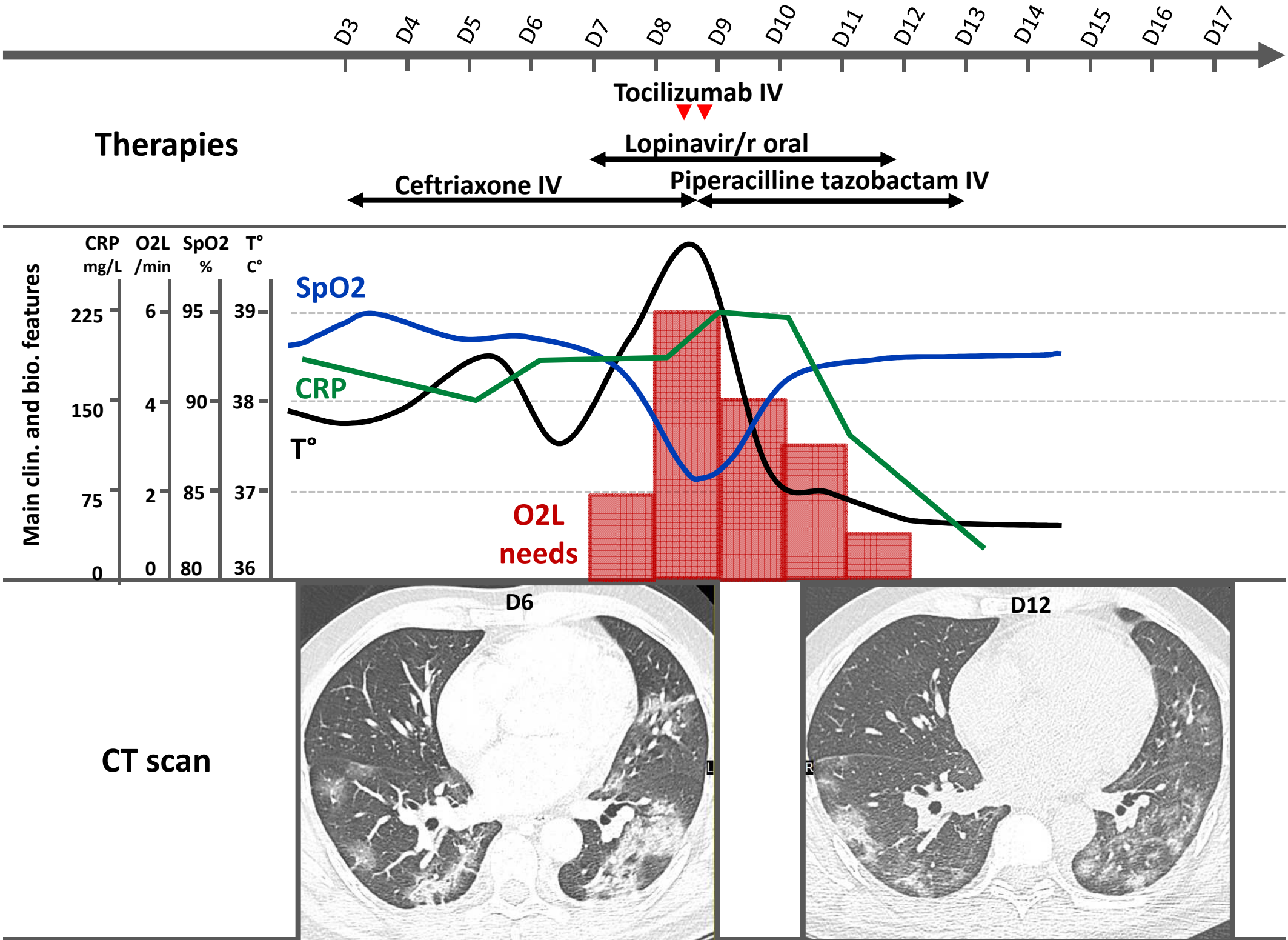
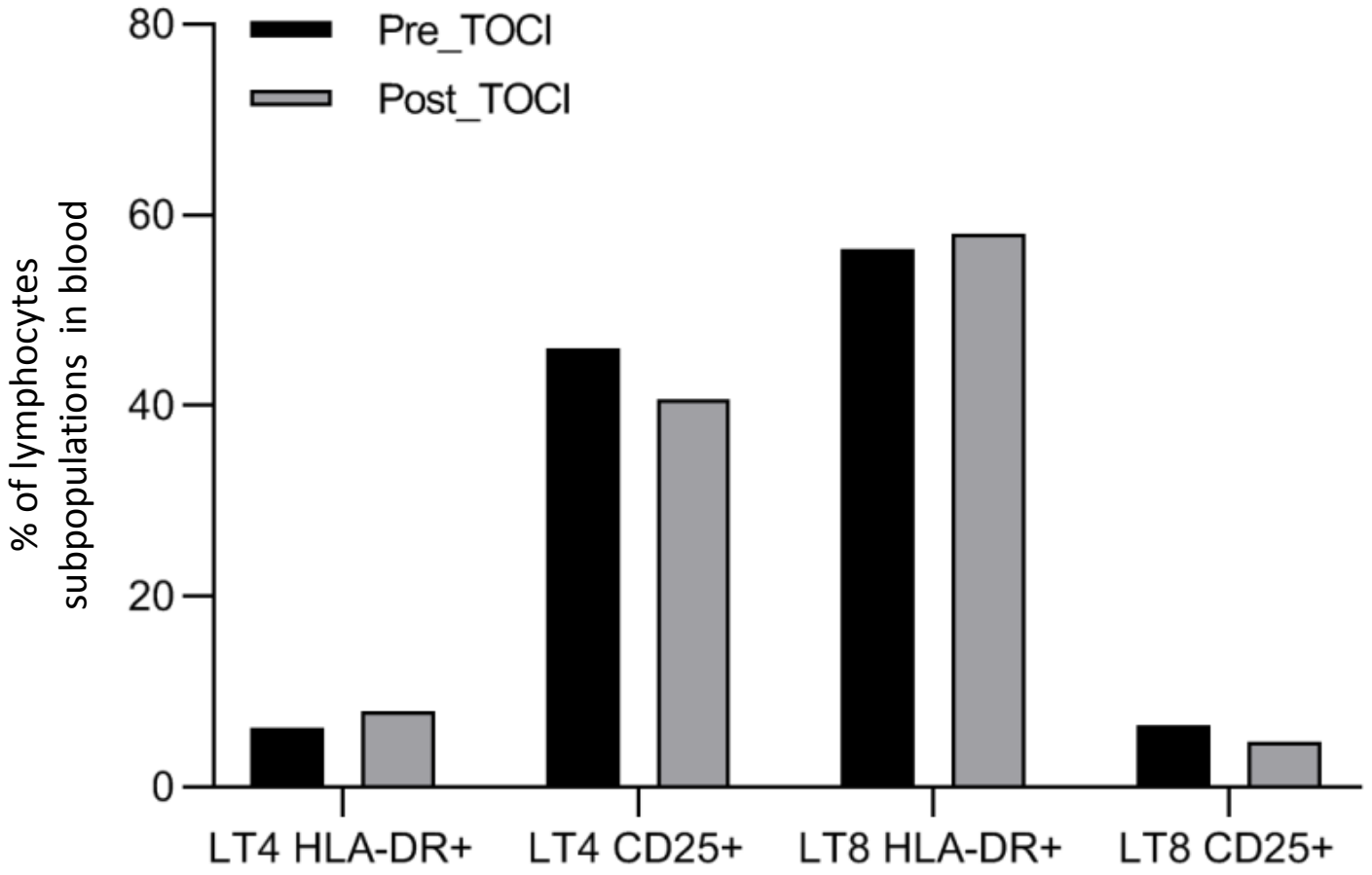
Figure 1. Outcome of patient with Covid-19 before and after tocilizumab. In the top of the figure, evolution of clinical vital signs, requirement for supplemental O2 in L/min, C-reactive protein in blood. In the bottom of the figure, pulmonary CT scanner of patient before (D6) and after (D12) tocilizumab. Patient received two doses of tocilizumab intravenously at 8 mg/kg for each dose (red arrow). All therapies given for covid-19 were summarized at the top of the figure.
Sp02: Saturation pulsed in oxygen
O2L: Oxygen supplementation in L/min
T°: Temperature in degrees Celsius
CT: Computerized tomography
Lopinavir/r : Lopinavir plus ritonavir
IV : Intravenously
CRP: C reactive protein in blood

Figure 2. CD25 and HLA-DR expression among $CD4^+$ and $CD8^+$ T cells in blood of patient with Covid-19 before and after tocilizumab. Percentage of HLA-DR (LT4 HLA-DR^+) and CD25 (LT4 $CD25^+$) among $CD3^+CD4^+$ (LT4) and of HLA-DR (LT8 HLA-DR^+) and CD25 (LT8 $CD25^+$) among $CD3^+CD8^+$ (LT8) before introduction of tocilizumab (Pre_TOCI) and 4 days after initiation of treatment (Post_TOCI).


D3
D4
D5
D6
D7
D8
D9
D10
D11
D12
D13
D14
D15
D16
D17
Therapies
Tocilizumab IV
Lopinavir/r oral
Ceftriaxone IV
Piperacilline tazobactam IV
Main clin. and bio. features
CRP mg/L
O2L /min
SpO2 %
T° C°
225
150
75
0
6
4
2
0
95
90
85
80
39
38
37
36
SpO2
CRP
T°
O2L needs
CT scan
D6
D12


80
60
40
20
0
Pre_TOCI
Post_TOCI
% of lymphocytes subpopulations in blood
LT4 HLA-DR+
LT4 CD25+
LT8 HLA-DR+
LT8 CD25+