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Letter to the editor

New therapeutic opportunities for COVID-19 patients with Tocilizumab: Possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws

To the Editor

A novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; previously known as 2019-nCoV) emerged in Wuhan (Hubei, China) in December 2019 and spread rapidly across the planet. Several coronaviruses can cause light respiratory disease in humans but SARS-CoV-2 can cause a pneumonia, called corona virus disease-2019 (COVID-19) that might result in death due to massive alveolar damage and progressive respiratory failure [1]. Similarly to the “SARS-CoV” (emerged in 2003) and “MERS-CoV” (emerged in 2012), SARS-CoV-2 was probably hosted by bat and transmitted from other animals to humans [2]. The World Health Organization declared COVID-19 pandemic on March 12, 2020 [3].

COVID-19 is clinically manifested by fever, cough, dyspnea up to respiratory failure. Clinical management is principally symptomatic treatment, but severe cases requires respiratory assistance with organ support in intensive care for seriously ill patients. Most of these patients are over the age of 60 and have comorbidities. No specific anti-viral treatment exists, but antiviral and antimalarial drugs are administered empirically [4].

Excessive and aberrant immune responses in intensive care patients lead to fibrosis and lung damage, causing functional disability and reduced quality of life. Considering the absence of specific drugs, a range of existing host-directed therapies could potentially be repurposed to treat COVID-19 [5].

Tocilizumab is a humanized antiinterleukin-6-receptor (IL-6R) monoclonal antibody that inhibits interleukin-6 (IL-6) signaling used as treatment in rheumatoid arthritis (RA) [6].

Tocilizumab is administered intravenous experimentally in the treatment of COVID-19 in China and Italy with encouraging results [7]. Whether tocilizumab can restore T cell counts in COVID-19 patients by suppressing IL-6 signaling remains uninvestigated [8].

After a literature research, we highlighted a possible correlation between tocilizumab and medication-related osteonecrosis of the jaws (MRONJ), an infectious complication of antiresorptive and anti-angiogenic drugs. In a recent review on MRONJ unrelated to bisphosphonates and denosumab, a wide range of medications classified as tyrosine kinase inhibitors, monoclonal antibodies, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants have been implicated in MRONJ, but tocilizumab is not reported [9].

Bindakhil and Mupparapu reported in 2018 a case of osteomyelitis of the mandible exhibiting features of MRONJ in a patient with osteoporosis, without history of bisphosphonate use, treated with tocilizumab for RA, without getting the attention of the scientific community [10].

In 2013 Ebker et al. reported a fulminant course of MRONJ in a patient under treatment with oral bisphosphonates for osteoporosis (20-

month course of risedronate, 35 mg/week) and tocilizumab for RA, assuming a possible correlation between the risk of developing MRONJ and anti-cytokine treatment [11].

Recently, Wakabayashi et al. suggested that inhibition of IL-6 signaling may become a preventive therapeutic option for breast cancer and bone metastases [12].

The evolution of the COVID-19 pandemic could put a strain on healthcare systems around the world. At the time of writing, the COVID-19 pandemic seems to have been overcome in China and is affecting Italy and other western countries in a potentially serious way. The tocilizumab pharmaceutical company has made the drug available free of charge to continue the experimentation on COVID-19 patients in Italy after the encouraging results in China [13].

Further studies are required to elucidate the possible correlation between tocilizumab and MRONJ, but the scientific community should be aware of this potential risk.

Declaration of Competing Interest

The authors declare that they have no competing interests related to this study. No financial support was received for this study.

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