DOI: 10.1002/jmv.25897

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

Off-label use of tocilizumab in patients with SARS-CoV-2 infection

Dear Editor,

We read with interest the work by Pan et al,[1] who described the use of tociluzumab in 15 patients with moderate-to-critical novel coronavirus infection (COVID-19) caused by SARS-CoV-2.

The emergence of COVID-19 in the Hubei province of China in early 2020 and its rapid global spread, poses a great challenge for healthcare systems worldwide.[2] No specific treatment for COVID-19 is currently available,[3] with lopinavir/ritonavir failing to demonstrate superior efficacy compared with standard care[4] and clinical trials evaluating the efficacy of remdesivir[5] and chloroquine[6] currently underway. Recently, much interest has been aroused by the possibility of using tocilizumab, a humanized anti-human inteleukine-6 receptor antibody of the IgG1 subclass, with the rationale of preventing or treating the cytokine storm that has been observed in patients progressing to cardiovascular collapse, multiple organ dysfunction, and death.[7]

Data on the use of this molecule in the treatment of SARS-CoV-2 infection are still preliminary but the promising results have prompted the Chinese Health Commission to update its national guidelines to include tocilizumab for the treatment of severe COVID-19.[8] Italian guidelines[9] also support the use of tocilizumab (at the dosage of 8 mg/kg, with a second dose 12 hours after the first and a possible third dose after further 24-36 hours, according to clinical response), in case of rapid clinical and/or radiological worsening, after excluding contraindications to its use (transaminases levels >5 times the upper limit of normal, neutrophils count <500 cells/μL, platelets count <50 000 cells/μL, presence of documented sepsis, complicated diverticulitis/intestinal perforation, cutaneous infection, immunosuppressive anti-rejection therapy).

We hereby describe the outcomes of 3 patients hospitalized in a III level Italian Hospital following the diagnosis of COVID-19 by real-time PCR on oropharyngeal and nasopharyngeal swabs and developing rapid respiratory insufficiency. They were prescribed tocilizumab after verbal consent to drug administration, and they also agreed to clinical data collection for study purposes.

Patient 1 was a 71 years old hypertensive male. On the 5th of March he was hospitalized after 12 days of worsening flu-like symptoms. He was dyspneic, with mild bilateral interstitial involvement at chest X-ray. After diagnosis, he started antiviral therapy (lopinavir/ritonavir plus hydroxycholoroquine) on the 6th of March. The fever continued and respiratory exchanges worsened (PaO_2-to-Fio_2 ratio: 129 the 14th of March). Repeat chest X-ray showed multiple enlarging areas of consolidation. C-reactive protein (CRP) at that time was 117 mg/L (normal value: <5 mL/min). Two doses of tocilizumab 12 hours apart were administered, starting March 14th. The fever resolved after 3 days, together with improvement in the PaO_2-to-Fio_2 ratio (210 the 21st of March). CRP was within normal range on the 20th of March. Also, the 19th and 21st of March, repeat nasopharyngeal swabs tested negative for SARS-CoV-2.

Patient 2 was a 45 years old, previously healthy male, hospitalized on the 10th of March because of fever, worsening dyspnea and chest pain. A chest X-ray showed reduced diaphany in the lower right lobe. After COVID-19-diagnosis, antiviral therapy was started. Despite initial improvement, he developed dyspnea for mild efforts, accompanied by increase in CRP (151 mg/L) and appearance of bilateral interstitial pneumonia at chest X-ray. Two doses of tocilizumab were prescribed, starting the 14th of March. The clinical condition improved, with resolution of fever after 48 hours and rapid reduction in CRP (13 mg/L the 18th of March).

Patient 3 was a 53 years old, hypertensive male, who came to first aid on the 13th of March for non-resolving flu-like symptoms. His chest X-ray showed interstitial bilateral pneumonia. CRP at first aid was 250 mg/L. After diagnosis, antiviral therapy was immediately started. After 48 hours, the respiratory symptoms worsened and before the new chest-X-ray (which confirmed the bilateral interstitial involvement), tocilizumab was administered in three doses, starting March 15th, with progressive resolution of dyspnea (oxygen saturation was 98% with FiO_2 0.31 on the 21st of March). After 48 hours, CRP was 92 mg/L and subsequent control (on the 25th March) was within the normal range.

Our observations highlight the efficacy of tocilizumab in the treatment of COVID-19 even after a short time and seem in line with the work of Pan et al.[1] Rapid relief of respiratory symptoms, resolution of fever, and reduction in CRP were the first effects following tocilizumab administration. Of note, no adverse events were registered during the follow-up of our three patients.

Despite the lack of IL-6 levels' determination for selecting the best candidates for tocilizumab therapy at the time of our case series, our work gives further evidence that tocilizumab may represent an effective and safe option in the treatment of SARS-CoV-2-infected patients with severe pneumonia. Randomized trials are urgently needed to confirm our findings.

ACKNOWLEDGMENTS

This study was performed as part of our routine work.

Members of the GEMELLI AGAINST COVID-19 group: ENDOCRINOLOGY: A. Bianchi, E. Capristo, A. Giampietro, A. Iaconelli, P. Locantore, D. Milardi, and A. Pontecorvi; GENERAL MEDICINE: R. Cianci, G. De Matteis, F. De Vito, A. Porfidia, and G. Gambassi; GERIATRICS: F. Landi, A. Bellieni, V. Brandi, A. Carfì, E. D'Angelo, D. Fusco, G. Landi, R. Lo Monaco, A. M. Martone, E. Marzetti, F. Pagano, A. Russo, S. Salini, M. Tosato, A. Tummolo, and R. Bernabei; INFECTIOUS DISEASES: S. Di Giambenedetto, A. Borghetti, A. Ciccullo, A. Cingolani, K. de Gaetano Donati, A. Dusina, D. Faliero, M. Fantoni, D. Moschese, R. Murri, G. Scoppettuolo, E. Taddei, E. Tamburrini, G. Ventura, E. Visconti, and R. Cauda; INTERNAL MEDICINE AND GASTROENTEROLOGY: L. Zileri Dal Verme, V. Abbate, S. Bibbò, F. D'Aversa, D. Feliciani, B. Funaro, M. Garcovich, M. Impagnatiello, L. Lopetuso, L. Miele, A. Nicoletti, A. Papa, M. Pizzoferrato, F. Pizzolante, M. Pompili, G. Rapaccini, F. Santopaolo, C. Settanni, A. Tosoni, and A. Gasbarrini.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

Simona Di Giambenedetto[1,2]
Arturo Ciccullo[1]
Alberto Borghetti[1]
Giovanni Gambassi[3,4]
Francesco Landi[3,5]
Elena Visconti[1]
Lorenzo Zileri Dal Verme[6]
Roberto Bernabei[3,5]
Enrica Tamburrini[1,2]
Roberto Cauda[1,2]
Antonio Gasbarrini[6]

[1]*UOC Malattie Infettive, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy*
[2]*Dipartimento di Sicurezza e Bioetica Sezione Malattie Infettive, Università Cattolica del Sacro Cuore, Roma, Italy*
[3]*Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*
[4]*Institute of Internal Medicine, Agostino Gemelli Hospital, Catholic University of the Sacred Heart, Rome, Italy*
[5]*Institute of Internal Medicine and Geriatrics, Università Cattolica del Sacro Cuore, Rome, Italy*
[6]*Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*

Correspondence
Alberto Borghetti, UOC Malattie Infettive, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italia.
Email: alberto.borghetti@policlinicogemelli.it

ORCID

Alberto Borghetti http://orcid.org/0000-0002-7910-021X

REFERENCES

1. Pan L, Yi L, Lin Q, et al. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020;92(7):814-818.
2. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55(3):105924.
3. Sun P, Lu X, Xu C, Sun W, Pan B Understanding of COVID-19 based on current evidence [published online ahead of print, 25 Feb 2020]. *J Med Virol*. 2020;92(6):548-551.
4. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19 [published online ahead of print, 18 Mar 2020]. *N Engl J Med*. 2020;382:1787-1799.
5. Gilead. Gilead Sciences Statement on the Company's Ongoing Response to the 2019 Novel Coronavirus (2019-nCoV). https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-the-company-ongoing-response-to-the-2019-new-coronavirus
6. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care*. 2020;57:279-283.
7. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
8. National Health Commission & State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. Trial Version 7. Released on 3 March 2020. Available at https://www.who.int/docs/default-source/wpro—documents/countries/china/covid-19-briefing-nhc/1-clinical-protocols-for-the-diagnosis-and-treatment-of-covid-19-v7.pdf?sfvrsn=c6cbfba4_2
9. SIMIT Società Italiana di Malattie Infettive e Tropicali. Linee guida sulla gestione terapeutica e di supporto per pazienti con infezione da coronavirus COVID-19. Edizione 2.0, 12 marzo 2020.