Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia?

Dear Editor,

We have read with interest the excellent review by McGonagle et al. discussing the possible role of hyperinflammation secondary to macrophage activation syndrome (MAS) or cytokine storm also known as secondary haemophagocitic lymphohistocytosis (sHLH) in the immunopathology of severe COVID-19 pneumonia [1]. High levels of interleukin-6 (IL-6) associated with poor outcome in the setting of COVID-19 pneumonia evoked the use of tocilizumab (an IL-6 receptor monoclonal blocking agent) approved for the treatment of rheumatoid arthritis in Japan (2008), Europe (2009) and USA (2010) [2–5]. The drug has been approved in China for COVID-19 pneumonia and elevated IL-6 (ChiCTR2000029765) and in Italy, following the outbreak that involved our country from February 21, it was extensively used *off-label* before the Italian Regulatory Agency of Drug (AIFA, Agenzia Italiana del Farmaco) approved a randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (Tocilizumab 2020-001154-22).

Although an increased risk of infections, especially among patients treated with the 8 mg/kg of tocilizumab has been shown in a systematic literature review and meta-analysis as well as in a recently published registry of RA patients, a clear association with fungal infections has been not formally demonstrated [6–8].

During an eleven-days period (March 10 to March 18,2020) 43 patients with severe COVID-19 pneumonia were treated with tocilizumab at our Department (either in ICU and Infectious Diseases wards) and 3 patients (6.9%) developed candidaemia, one with endophthalmitis and endocarditis. Interestingly, only one of the three patients (Table 1) had been previously hospitalised in the ICU (pt#1) and, at the time of diagnosis of candidaemia, only one had a central venous line on site (pt#3) and his blood infection can be considered catheter-related. All the patients had received parenteral nutrition during hospitalization and two had been treated with antibiotics. All three patients received a dose of 8 mg/kg tocilizumab (maximum dose 800 mg/d) repeated within 12 h from the first administration. The median time from the last dose of tocilizumab and the diagnosis of candidemia was 13 days. The diagnosis was obtained by blood cultures taken because of an increase of white blood cells (median value 16,850/μL) in the absence of fever and with normal value of C-reactive protein in two patients. Although the high prevalence of candidemia observed by us in a very short period of time among patients treated with tocilizumab can be the consequence of multiple well known risk factors it can be speculated that the suppression of IL-6 response might contribute to this blood infection [9]. IL-6 is a pro-inflammatory cytokine involved in the regulation of multiple aspects of innate immune response. Interestingly, previous studies conducted in interleukin-6 deficient mice showed that they were more susceptible to systemic *Candida albicans* infection, had a decreased survival and an increased fungal load in their organs when compared with IL-6 positive controls [10,11].

In conclusion, we recommend to use selective cytokine blockade as well as JAK inhibitors for possible cytokine storm syndrome during COVID-19 pneumonia only in the context of well-designed clinical trials. Moreover, since most of the inflammatory response (i.e., fever, high C-reactive protein) can be blunted following such treatment an high index of suspicion for candidemia together with proactive surveillance should be deserved for these patients.

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Table 1
Characteristics of the three patients developing candidemia following treatment with tocilizumab for severe COVID-19 pneumonia.

Patient #	Age/ gender	Comorbidities/co-medications	Date of hospital admission/Days in ICU	IL-6 level before starting tocilizumab	Date of first tocilizumab dose/ total dose	Risk factors for candidemia	Date of first blood culture positive for *Candida*/*Candida* species/Organ localisation	Fever/WBC per μL/ CRP mg per dL at time of candidemia diagnosis	Treatment/outcome
1	67/M	Cerebral ischemia/ aspirin	March 14, 2020/ eight	325 ng/L	15 March/560 mg repeated after 12 h	Parenteral nutrition (8 days); antibiotics (2 days); central venous catheter (11 days)	27 March/*C.albicans*/Eye (endophthalmitis); aortic valve (endocarditis)	Absent/16,850/10	Caspofungin + fluconazole/still hospitalised
2	58/M	Hypertension/ ramipril	March 9, 2020/ none	116 ng/L	13 March/600 mg repeated after 12 h	Parenteral nutrition (13 days)	26 March/*C. tropicalis*/none	Absent/16,590/ 43	Caspofungin/still hospitalised
3	78/M	Diabetes; Obesity/ metformin	March 18, 2020/ none	105 ng/L	18 March/800 mg repeated after 12 h	Parenteral nutrition (13 days); antibiotics; steroid; CVC	1 April/*C. parapsilosi*/none	Absent;/25,850/0,8	Caspofungin + fluconazole/still hospitalised

M, male; ICU, intensive care unit; WBC, white blood cell; CRP, C reactive protein; CVC, central venous catheter.

References

[1] McGonagle D, Sharif K, O'Regan A, Bridgewood C. Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome. Autoimmun Rev 2020. https://doi.org/10.1016/j.autrev.2020.102537.

[2] Wu C, Chen X, Cai, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020. https://doi.org/10.1001/jamainternmed.2020.0994. [March 13].

[3] Mehta P, DF McAuley, Brown M, et al. COVID-19. consider cytokine storm syndromes and immunosuppression. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30628-0. [March 13].

[4] Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020. https://doi.org/10.1016/j.ijantimicag.2020.105954.

[5] Ogata A, Kato Y, Higa S, Yoshizaki K. IL-6 inhibitor for the treatment of rheumatoid arthritis: a comprehensive review. Mod Rheumatol 2019;29:258–67.

[6] Campbell L, Chen C, Bhagat SS, Parker RA, Ostor AJK. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology 2011;50:552–62.

[7] Morel J, Constatin A, Baron G, et al. Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry Regate. Rheumatology 2017;56:1746–54.

[8] Schiff MH, Kremer JM, Jahreis A, et al. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13:R141.

[9] Antinori S, Milazzo L, Sollima S, Galli M, Corbellino M. Candidemia and invasive candidiasis in adults: a narrative review. Eur J Intern Med 2016;34:21–8.

[10] Romani L, Mencacci A, Cenci E, et al. Impaired neutrophil response and CD+ T helper cell 1 development in interleukin-6-deficient mice infected with *Candida albicans*. J Exp Med 1996;183:1345–55.

[11] Vand Enckevort FHJ, Netea MG, Hermus ARM, et al. Increased susceptibility to systemic candidiasis in interleukin-6 deficient mice. Med Mycol 1999;37:419–26.

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