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Letters to *Blood*

TO THE EDITOR:

Tocilizumab not associated with increased infection risk after CAR T-cell therapy: implications for COVID-19?

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As of 28 April 2020, COVID-19 has been confirmed in >2.9 million people worldwide, with an estimated overall global mortality of up to 6.9%; it is even higher (up to 50%) in older populations with comorbidities.[1,2] Healthcare systems around the world are stretched to the point of collapse, with no treatment proven to be effective. There is an urgent need for therapeutic interventions that can reduce the rate of respiratory failure, the leading cause of mortality. The current focus is on the development of novel antiviral therapeutics, as well as vaccines. Accumulating evidence suggests that a subgroup of patients with COVID-19 develops a severe inflammatory response akin to macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), or chimeric antigen receptor (CAR) T-cell–mediated cytokine release syndrome (CRS), which may contribute to the acute respiratory distress syndrome (ARDS) seen in up to 20% of patient.[3-5] Antibody therapies to block cytokines are used in the management of CRS in other settings and are highly effective. This approach may be useful to decrease pulmonary inflammation in patients suffering from COVID-19, but there is concern about the potential for increasing direct infection-related morbidity and mortality.

CRS encompasses the syndrome of fevers, hypotension, capillary leak, hypoxemia, and end-organ dysfunction that is seen, to some degree, in most patients shortly after CAR T-cell infusion, most commonly for lymphoma, leukemia, or multiple myeloma. In early studies, CRS resulted in rates of vasopressor use and mechanical ventilation of up to 25% and 15%, respectively.[6-8] CRS/MAS/HLH are hyperinflammatory syndromes that are characterized by multiorgan failure that is typically triggered by viral infections or lymphomas, leading to excessive and uncontrolled immune activation.[9] Characteristics of MAS/HLH include fever, and hyperferritinemia with pulmonary involvement (including ARDS) is seen in ~50% of patients.[10] Cytokine profiling of patients with MAS/HLH overlaps with that seen in patients with severe COVID-19 and includes elevated levels of interleukin-1 (IL-1), IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. Furthermore, severe cases of COVID-19 infection are associated with higher levels of lactate dehydrogenase, ferritin, and D-dimer compared with moderate cases, further emphasizing the potential overlap between these syndromes.[2,11,12] Given the efficacy of tocilizumab (an anti–IL-6 receptor antibody) for CAR T-cell–associated CRS (for which it is approved by the US Food and Drug Administration), anecdotal use in MAS/HLH,[13-15] and evidence suggesting overlap between these syndromes and COVID-19,[16] multiple randomized trials of IL-6 modulation are underway in patients with COVID-19–associated pneumonia syndrome (NCT04317092 [tocilizumab], NCT04315298 [sarilumab], ChiCTR2000029765 [tocilizumab]). Case reports, press releases, and single-center experiences using tocilizumab in cases of severe COVID-19, with or without ARDS, are entering the literature.[17,18]

The core phase 3 studies of tocilizumab for autoimmune diseases raise concerns that such immunomodulation may impair host immune responses and lead to additional infectious complications. Among 4200 recipients in an integrated safety analysis, the serious infection rate was 4.7 per 100 patient-years (most notably pneumonia, gastroenteritis, and urinary tract infections) with an opportunistic infection rate of 0.23 per 100 patient-years (primarily tuberculosis, candidiasis and other fungal infections, mycobacterial infection, *Pneumocystis jiroveci* pneumonia and cryptococcal pneumonia), including herpes zoster. Notably, unlike the current use of tocilizumab for CRS/MAS and the proposed use of tocilizumab in COVID-19, the mean duration of treatment in these trials was monthly dosing for >2.4 years.[19]

Unlike these pivotal studies for chronic inflammatory conditions, tocilizumab utilization in the context of CAR T-cell–related CRS and MAS/HLH involves a much shorter course of treatment that is implemented early, as is proposed for therapy of COVID-19–associated pneumonia syndrome. It is unclear whether infectious complications observed during long-term use of tocilizumab are relevant to this unique limited circumstance and patient population. Therefore, we investigated infectious complications after tocilizumab use for CAR T-cell–related CRS reported to the Center for International Blood and Marrow Transplant Research for inclusion in the Cellular Immunotherapy Data Resource.[20] Among 1397 adult patients with hematologic

Table 1. Patient demographics, infections, and causes of death among recipients of CAR T cells for treatment of hematologic malignancies who subsequently developed grade 1 CRS, with or without tocilizumab therapy

Characteristic	No tocilizumab for CRS	Tocilizumab for CRS	P*
Patients, n	225	166	
Age at infusion ≥65 y	67 (29.8)	58 (34.9)	
Males	153 (68)	112 (67.5)	
Karnofsky performance score prior to treatment 90-100%	109 (48.4)	66 (39.8)	
Neurotoxicity/ICANS of any stage	92 (40.9)	100 (60.2)	<.001
Corticosteroids for ICANS or CRS	39 (17.3)	88 (53)	<.001
Infections†			
Clinically significant infections within 100 d	67 (29.8)	52 (31.3)	.85
Bacterial	38 (16.9)	37 (22.3)	
Fungal	6 (2.7)	7 (4.2)	
Yeast	4 (1.8)	5 (3)	
Mold	3 (1.3)	2 (1.2)	
Viral‡	32 (14.2)	19 (11.4)	
Respiratory virus	22 (9.8)	8 (4.8)	
Herpes family virus	6 (2.7)	12 (7.2)	
GI/liver	4 (1.8)	0	
GU	4 (1.8)	4 (2.4)	
Other viral infections	2 (0.9)	0	
Other	1 (0.4)	0	

Unless otherwise noted, data are n (%).

GI, gastrointestinal; GU, genitourinary.

*Pearson $\chi 2$ test.

†Number of patient-reported infections. Types of infections are not mutually exclusive; several infections may occur in each patient.

‡Respiratory virus: coronavirus excluding SARS-CoV-2, influenza A and B, metapneumovirus, parainfluenza, respiratory syncytial virus, and rhinovirus. Herpes family virus: cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and human herpesvirus-6. GI/liver: hepatitis A and B and enterovirus. GU: BK polyomavirus. Other viral infections: parvovirus B-19.

malignancies with ≥3 months of follow-up after CAR T-cell infusion between 2016 and 2019, 882 developed CRS and might have been eligible for tocilizumab therapy. To limit confounding factors, only patients with grade 1 CRS were included, because very few patients with grade ≥2 CRS did not receive tocilizumab, and most also received other immune-suppressive agents, such as corticosteroids, which could confound the analysis. Among the 391 patients from >50 reporting academic centers with grade 1 CRS, 166 (42%) received tocilizumab. Although the exact number of doses received by each patient is not known, standard recommendations are 1 to 3 doses.

Patient characteristics are shown in Table 1, with approximately one-third of patients aged 65 years and older, most with a Karnofsky performance status ≤ 80%. Patients receiving tocilizumab were more likely to experience neurotoxicity/immune effector cell–associated neurotoxicity syndrome (ICANS) of some grade (60% tocilizumab vs 41% no tocilizumab, $P < .001$) and more frequently received corticosteroids in addition to tocilizumab (53% tocilizumab vs 17% no tocilizumab, $P < .001$). Importantly, there was no difference in the overall incidence of clinically significant infections or infection density within 100 days of treatment in the 2 groups (31% tocilizumab vs 30% no tocilizumab, $P = .85$), nor were there differences in the individual incidences of bacterial, fungal, or viral infections (Table 1). Of note, patients receiving CAR T cells typically undergo lymphodepletion with chemotherapy (eg, fludarabine and cyclophosphamide) prior to infusion and remain quantitatively cytopenic and qualitatively immunocompromised for several weeks to months, including the time period of CRS onset and tocilizumab use. With a median follow-up of 9.4 months (range, 3.3-36.2), there was not a significant difference between the groups with regard to overall survival or infectious deaths within the first 100 days of follow-up (n = 2, 15.3% of total deaths with tocilizumab vs n = 3, 13% of total deaths without tocilizumab).

Although limited, these data suggest that early and limited intervention with tocilizumab and blockade of IL-6 signaling does not increase the infectious risk in a significantly immunocompromised group of patients with relapsed/refractory hematologic malignancy.[21] Admittedly, CAR T-cell recipients typically do not have concurrent viral pneumonias, and the patients with grade 1 CRS analyzed here are not those who develop an inflammatory ARDS following CAR T-cell infusion. However, although the evaluation of tocilizumab and other cytokine-directed biologics within the context of ongoing clinical trials must be prioritized to better understand their safety and efficacy in patients with COVID-19, our data should provide some support that short-term use of tocilizumab to treat CRS/MAS/HLH does not significantly increase susceptibility to infectious complications.

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Authorship

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Footnotes

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Requests for original data can be made via e-mail to the corresponding author.

REFERENCES

1. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med*. 2020;382(21):2012-2022.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
3. Frigault MJ, Maus MV. State of the art in CAR T cell therapy for CD19+ B cell malignancies. *J Clin Invest*. 2020;130(4):1586-1594.
4. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629.
5. Zhu J, Ji P, Pang J, et al. Clinical characteristics of 3,062 COVID-19 patients: a meta-analysis [published online ahead of print 15 April 2020]. *J Med Virol*. doi:10.1002/jmv.25884.
6. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
7. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42.
8. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56.
9. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516.
10. Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest*. 2016;149(5):1294-1301.
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
12. Teachey DT, Lacey SF, Shaw PA, et al. Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. *Cancer Discov*. 2016;6(6):664-679.
13. Faguer S, Vergez F, Peres M, et al. Tocilizumab added to conventional therapy reverses both the cytokine profile and CD8+Granzyme+ T-cells/NK cells expansion in refractory hemophagocytic lymphohistiocytosis. *Hematol Oncol*. 2016;34(1):55-57.
14. Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol*. 2015;42(4):712-722.
15. 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.
16. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science*. 2020;368(6490):473-474.
17. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? *J Transl Med*. 2020;18(1):164.
18. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience [published online ahead of print 6 April 2020]. *J Med Virol*. doi:10.1002/jmv.25801.
19. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther*. 2011;13(5):R141.
20. Center for International Blood and Marrow Transplant Research. Cellular Immunotherapy Data Resource (CIDR) shares knowledge. Available at: https://www.cibmtr.org/About/WhatWeDo/CIDR/Pages/default.aspx. Accessed 28 March 2020.
21. Michot JM, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report [published online ahead of print 2 April 2020]. *Ann Oncol*. doi:10.1016.j.annonc.2020.03.300.

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