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.

Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019

To the Editor: Temesgen et al[1] carefully depicted the clinical benefit provided by lenzilumab in cases of coronavirus disease 2019, sustained by the novel severe acute respiratory coronavirus 2 (SARS-CoV-2), where cytokine storm may lead to fatal multiorgan failure. Lymphopenia is a typical finding occurring at early onset of the disease and lenzilumab administration showed a significant improvement in terms of lymphocyte count, which has not been fully understood by the investigators, suggesting that granulocyte-monocyte colony-stimulating factor might have a direct impact on T cells.

SARS-CoV-2–related hyperinflammatory pattern resembles the cytokine release syndrome occurring in chimeric antigen receptor T cell therapy, where the host monocyte-macrophage system is the major source of cytokine production (eg, interleukins 1 and 6).[2] In this setting, lenzilumab was shown to be effective in reducing chimeric antigen receptor T-cell–mediated cytokine release syndrome and neuroinflammation at the same time, enhancing adoptive T cell therapy as well.[3]

Previous preclinical data in SARS-CoV–infected mice showed that inflammatory monocyte-macrophage response, secondary to dysregulated type-I interferon activity during SARS-CoV infection, results in lethal pneumonia and cytokine-induced apoptosis of T cells (specifically mediated by tumor necrosis factor alpha).[4]

As already known, granulocyte-monocyte colony-stimulating factor inhibition turned out to broadly modulate monocyte-macrophage activity by simultaneously reducing a spectrum of inflammatory cytokines, including tumor necrosis factor alpha.[3] We therefore suggest that the direct regulation of monocyte-macrophage activity by lenzilumab, with subsequent broad cytokines shutdown, could provide a more favorable micro-environment where effector T cells could also be protected from cytokine-induced apoptosis. This would preserve a non-exhausted T-cell phenotype, being more effective against infections and performing more potently T-cell specific antiviral immunity to achieve viral clearance.

Aware of the good safety profile of lenzilumab in this current study and previous analysis,[1,5] the treatment is feasible and safe and the ongoing randomized phase III trial (NCT04351152) will extensively confirm the lymphocyte recovery in SARS-CoV-2 infection and the impact of the drug on coronavirus disease 2019 clinical improvement.

Andrea Aroldi, MD
San Gerardo Hospital
University of Milano-Bicocca
Monza, Italy

Roberto Chiarle, MD
Children's Hospital Boston and Harvard Medical School
MA
University of Torino
Italy

Carlo Gambacorti-Passerini, MD
San Gerardo Hospital
University of Milano-Bicocca
Monza, Italy

Potential Competing Interests: The authors report no potential competing interests.

ORCID
Andrea Aroldi: https://orcid.org/0000-0002-3428-5353

1. Temesgen Z, Assi M, Shweta FNU, et al. GM-CSF neutralization with lenzilumab in severe COVID-19 pneumonia: a case-cohort study. *Mayo Clin Proc*. 2020;95(11):2382-2394.
2. Agarwal S, June CH. Harnessing CAR T-cell insights to develop treatments for hyperinflammatory responses in patients with COVID-19. *Cancer Discov*. 2020;10(6):775-778.
3. Sterner RM, Sakemura R, Cox JC, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood*. 2019;133(7):697-709.
4. Channappanavar R, Fehr AR, Rahul Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV–infected Mice. *Cell Host Microbe*. 2016;19(2):181-193.
5. Patnaik MM, Sallman DA, Mangaonkar AA, et al. Phase I study of lenzilumab, a recombinant anti-human GM-CSF antibody, for chronic myelomonocytic leukemia. *Blood*. 2020;136(7):909-913.

https://doi.org/10.1016/j.mayocp.2020.12.030

In Reply — Clinical Benefit of Lenzilumab in Cases of Coronavirus Disease 2019

To The Editor: We thank Dr Aroldi and colleagues for their letter in response to our manuscript "GM-CSF Neutralization with Lenzilumab in Severe COVID-19 Pneumonia: A Case-Cohort Study."[1]

We agree that lenzilumab may benefit patients with severe acute respiratory syndrome coronavirus 2 through modulation of monocyte-macrophage activity by reducing a spectrum of hyperinflammatory cytokines. We are also intrigued by the observation that lenzilumab may improve lymphocyte counts. Although the mechanism remains to be elucidated in full, we have observed improved lymphocyte proliferation and lymphocyte effector function in preclinical models with lenzilumab.[2,3] We agree that modulation of the monocyte-macrophage activity may provide a more favorable micro-environment for T cells resulting in reduced apoptosis.

We look forward to replicating the positive signal in clinical and laboratory markers as well as the excellent