Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

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Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and pro-inflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, which is secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, regulates macrophage number and function. It acts as a pro-inflammatory signal, prompting macrophages to launch an immune cascade that ultimately results in tissue damage.\(^1,2\) GM-CSF is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines.\(^1-6\) Anti-GM-CSF monoclonal antibodies (mAbs) may mitigate inflammation by inhibiting this signaling axis upstream and thus minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of COVID-19.\(^7\) Gimsilumab, lenzilumab, naminumab, and otilimab target GM-CSF directly, neutralizing the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.\(^1,8,9\) Mavrilimumab targets the alpha subunit of the GM-CSF receptor, blocking intracellular signaling of GM-CSF.\(^8,10\) None of these agents are currently FDA approved for any indication.

**Recommendation**

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.

**Rationale**

Clinical data are lacking to definitively establish the potential benefits and risks associated with the use of GM-CSF inhibitors in patients with COVID-19. Data from a double-blind randomized controlled trial of lenzilumab did show a significant improvement in the primary endpoint of ventilator-free survival through Day 28 among those who received the GM-CSF inhibitor.\(^11\) However, preliminary data from a large, double-blind randomized trial of otilimab (primary endpoint: alive and free of respiratory failure at Day 28) and published results of a small, double-blind, randomized trial of mavrilimumab (primary endpoint: proportion alive and off supplemental oxygen at Day 14) did not show a survival benefit for the GM-CSF inhibitors compared to placebo.\(^12-14\) The study populations differed; the lenzilumab and mavrilimumab studies primarily included patients on room air or low-flow oxygen and excluded patients receiving mechanical ventilation, whereas the otilimab study included only patients receiving high-flow oxygen, noninvasive ventilation, or mechanical ventilation. Lenzilumab and mavrilimumab continue to be investigated, whereas clinical development of otilimab for the treatment of COVID-19 has ceased.

**Clinical Data for COVID-19**

Lenzilumab, mavrilimumab, naminumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-Co-2 pneumonia.\(^12-15\) Clinical data are not yet published for gimsilumab. The Panel’s recommendations are based on the results of the available clinical studies. Selected clinical data on the use of anti-GM-CSF mAbs for the treatment of COVID-19 are summarized in Table 6f.

**Clinical Trials**

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of ongoing clinical trials that are evaluating the use of GM-CSF.
Adverse Effects

The primary risks associated with GM-CSF inhibitors being reported and evaluated are related to bacterial infection. Other adverse events that have been reported with these agents include acute kidney injury and elevated liver transaminases. Autoimmune pulmonary alveolar proteinosis has been associated with a high-titer of anti-GM-CSF auto-antibodies.

Considerations in Pregnancy

Pregnant patients have been excluded from clinical trials evaluating GM-CSF inhibitors for the treatment of COVID-19. There is insufficient evidence to recommend for or against their use in pregnant individuals with COVID-19.

Considerations in Children

There are no data on the use of GM-CSF inhibitors in children.

References


