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Correspondence to: "A meta-analysis of granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody treatment for COVID-19 patients."

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To the Editor,
We read with great interest the metaanalysis by Guan *et al.*[1] evaluating the role of granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies in COVID-19. The authors included 12 studies for review, and the metaanalysis suggests potential benefit of anti-GM-CSF therapy in COVID-19 including lower risk of mortality and enhancement of ventilation.

GM-CSF is involved in steady state myelopoiesis, and induces production of granulocytes, monocytes, dendritic cells, and macrophages from progenitor cells. In COVID-19, pathological overactivation of myeloid cells cause by dysregulated GM-CSF expression has been proposed to be contributory in causing cytokine storm and tissue death via release of proinflammatory cytokines including interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF).[2,3] Elevated levels of GM-CSF as well as these proinflammatory cytokines have been observed in patients with COVID-19, thus raising interest in potential role of their blockage as potential treatment of COVID-19.[4,5]

The metaanalysis by Guan *et al.* is titled "A meta-analysis of granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody treatment for COVID-19 patients" and implies this metaanalysis evaluates anti-GM-CSF therapy. However, as mentioned in the study methods and search strategy, the authors did not limit the search to anti-GM-CSF therapy. Studies evaluating role of IL-6 inhibitors including (tocilizumab, siltuximab, sarilumab) in COVID-19 were also included in search methods for this metaanalysis. Although the inclusion criteria for this metaanalysis suggests inclusion of studies evaluating anti-GM-CSF therapy, of the 12 studies included in this metaanalysis, only 2 studies evaluated anti-GM-CSF therapy (Temesgen *et al.* and De Luca *et al.*), while all the remaining studies evaluated IL-6 inhibitors compared to control groups.[6,7]

The 2 studies in this metaanalysis that evaluated anti-GM-CSF therapy are both small single center cohort studies. De Luca *et al.*[7] prospectively evaluated the role of mavrilimumab, an anti-GM-CSF receptor-α monoclonal antibody in inpatients with severe COVID-19. Use of mavrilimumab was associated with clinical improvement, days to clinical improvement, days to discharge, days to fever resolution and C-reactive protein reduction. However, the study did not reach statistical significance in improvement in mechanical ventilation or death. Temesgen *et al.*[6] retrospectively evaluated the role of lenzilumab, a recombinant monoclonal antibody targeting human GM-CSF in hospitalized patients with severe COVID-19. Use of lenzilumab was associated with days to clinical improvement and days to discharge. However, no statistically significant improvement was noted in mortality, need for mechanical ventilation, incidence of clinical improvement or days to fever resolution. Given the small sample sizes, heterogenicity of results and both studies not showing improvement in mortality or need for mechanical ventilation, no conclusion can be drawn about the efficacy of anti-GM-CSF therapy in COVID-19 based on these studies.

Although this metaanalysis aims to evaluate role of GM-CSF inhibition in COVID-19, most of the studies in this metaanalysis do not evaluate GM-CSF inhibition and rather evaluate IL-6 inhibition. GM-CSF inhibition is not equivalent

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to inhibition of specific "downstream" cytokines such as IL-6, IL-1 or TNF. While GM-CSF inhibition can lead to decrease in reduced levels of these downstream cytokines by inhibiting the myeloid precursor cell maturation, GM-CSF also plays an important role in alveolar macrophage maturation and improving antigenic clearance by promoting lung sentinel cell-mediated immunity.[2] Further, as with other immunosuppressive agents, risk of secondary infections exists with GM-CSF inhibitors. Until better further clinical trials can prove their efficacy, the use of GM-CSF inhibitors in COVID-19 shall be limited to clinical trials under strict medical supervision.

Author contributions

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