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JAK Inhibition with Methotrexate as Treatment for COVID-19 Is a Double-Edged Sword

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Dear Editor,

The review article by Farhad Seif et al. [1] on JAK inhibition as a treatment strategy for COVID-19 is a plausible option given that it would certainly block effects of severe inflammatory cytokines including IL-13 (responsible for airway reactivity and mucus secretion) [2]. Our concern is whether methotrexate (MTX) addition is feasible given that (1) oral MTX takes several weeks to build up effect; and (2) intravenous MTX dose adjusted to the body surface area may be an intermediate dose or high dose at 1.5 g/m^2 or 3–8 g/m^2, respectively [3]. On an ethical consideration, the parenteral route could only be justified if there were central nervous system complications of COVID-19. If JAK inhibition was considered for 7–14 days, a single intravenous dose of MTX is the most likely option. Even then, managing patients with severe mucositis (who are ventilated), hydration (when euvolemia is the target in severe COVID-19 and aggressive hydration is recommended after high-dose MTX) and leukovorin (folinic acid) rescue may prove to be exceedingly clinically challenging in a patient who is already struggling to control a hyper-inflammatory immune response to a novel virus.

Natural killer function is also dependent on cytokines via the JAK-STAT pathway and functional exhaustion of these cells is a feature in severe COVID-19 infection [4]. Seif and colleagues mention that JAK inhibitors can target both type I (IFN-α/IFN-β) and type II interferons (IFN-γ) but it is also important to remember that interferons are major cytokines involved in viral clearance [5]. The current recommendations from the British Society of Hematology therefore state that patients who are on ruxolitinib (non-selective JAK inihibitor) for myeloproliferative neoplasms have a weakened immune system and are therefore likely to be at increased risk of COVID-19 infection [6].

It is worthwhile to note that patients on anti-cytokine biological immunomodulatory drugs do not seem to be more vulnerable than originally presumed as evidenced by reports from Gisondi et al. [7] from Northern Italy and Haberman et al. [8] from New York. An observational study of IL-1 blockade in COVID-19 showed that patient survival at 21 days was 90% in the high-dose anakinra group as compared to 56% in the standard treatment group (p = 0.009). Mechanical ventilation-free survival was 72% (21/29) in the anakinra group versus 50% (8/16) in the standard treatment group (p = 0.15) [9]. Another

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report on 8 patients with severe COVID-19 and hemophagocytic lymphohistiocytosis suggested IL-1 blockade with anakinra as a beneficial treatment option [10]. The side effects of IL-1 blockade are much more manageable than parenteral MTX in the acute setting, and we therefore think that selective JAK inhibition with IL-1 and/or IL-6 blockade in patients with severe COVID-19 infection have more merit to be considered in future clinical trials from the perspectives of patient safety and tolerability.

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S.K., S.D. – Drafting the work or revising it critically for important intellectual content.

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