International Archives of Allergy and Immunology

Clinical Immunology – Letter to the Editor

Int Arch Allergy Immunol
DOI: 10.1159/000509198

Received: June 2, 2020
Accepted: June 2, 2020
Published online: June 12, 2020

Combination of JAKinibs with Methotrexate or Anti-Cytokine Biologics in Patients with Severe COVID-19

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Dear Editor,

We read enthusiastically the letter of Khan and Durairaj [1] about the double-edged-sword nature of JAK inhibitors (JAKinibs) and methotrexate (MTX) combination therapy in patients with severe COVID-19 [2]. They declared that this hypothesis was a plausible option for cytokine blockade, especially IL-13 [1]. The focus of our review article was on JAK2 inhibition to suppress not only cytokine signaling via the JAK-STAT pathway but also angiotensin II receptor (AT1-R) signaling in the infected cells, which notably employs JAK2 for signal transduction. The latter is the novelty of the treatment suggestion. Therefore, JAK inhibition may play a dual role in inhibition of both cytokine storm and inflammatory consequences of AT1-R overactivation [2]. However, as Khan and Durairaj [1] emphasized, type I interferons (IFNα/β) are the cornerstone of the innate immune response against viruses and this may be the other side of the coin of JAK inhibition by pan JAKinibs. Acharya et al. [3] reported that the production of type I interferons was dysregulated in patients with COVID-19. On the other hand, IFNα/β does not employ JAK2 in the downstream of their receptors [4]; thus, specific JAK2 inhibition does not affect antiviral responses and deserves to be considered a promising approach for the treatment of the patients with severe COVID-19. Furthermore, since IL-1β and TNF-α employ distinct signaling pathways other than the JAK-STAT pathway, JAK inhibition is not applicable and biological anti-cytokine therapy may be beneficial. Although IL-6 transduces a signal via the JAK-STAT pathway, tocilizumab (anti-IL-6 receptor) is effective for these patients [5] and, as Khan and Durairaj [1] apparently mentioned, the combination of JAKinibs and anti-cytokine biologics such as anakinra (a recombinant IL-1β receptor antagonist) may be more convincing.

Edited by: H.-U. Simon, Bern.

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Recently, Richardson et al. [6] suggested baricitinib as a potential treatment for COVID-19 via disruption of AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), both of which facilitate clathrin-mediated endocytosis of the virus, in addition to the disruption of JAK1/2 signaling. In another study conducted by Stebbing et al. [7], the combination of baricitinib with direct-acting antivirals such as lopinavir/ritonavir or remdesivir was mentioned, but other JAK2 inhibitors such as fedratinib (either monotherapy or combination therapy with antiviral therapy or anti-cytokine therapy) might be considered for future clinical trials to assess their efficacy in COVID-19 treatment. However, low-dose consumption of baricitinib (2–10 mg orally once a day) in comparison to fedratinib (400 mg orally once a day) makes it difficult to adopt a clear strategy. Furthermore, combination therapy with baracitinib was highly recommended owing to its low plasma protein-binding potency and the least interaction with cytochrome P450 enzymes and drug transporters [7].

The basis of our treatment suggestion is that we always witness a mixture of cytokines in any inflammatory disease, which contribute synergistically, redundantly, or even in antagonist and pleiotropic manners. In this regard, single-cytokine targeting may not obviate the need to target other cytokines involved in COVID-19 immunopathogenesis. Interestingly, MTX can inhibit the JAK/STAT pathway and decrease the levels of IL-12, TNF-α, and IL1-β while upregulating IL-4 and IL-10 as anti-inflammatory cytokines. Moreover, MTX inhibits NF-kB activity in T cells (which regulates a lot of cytokines, chemokines, mediators, and adhesion molecules) while increasing IL1Ra as a decoy receptor [8]. These features make MTX a possible candidate for inhibition of the development of the cytokine storm. However, the concern of Khan and Durairaj [1] of whether MTX combination therapy is feasible is logical because of the long period during which MTX might build up the desired effect. In addition, the intravenous MTX dose has to be adjusted proportionally to the body surface area as intermediate or high doses at 1.5 g/m^2 or 3–8 g/m^2, respectively. If JAK inhibition is implemented for 7–14 days, a single intravenous injection of MTX is the most reasonable option [1]. Stebbing et al. [7] also suggested that the use of baricitinib for 7–14 days might be trivial. Therefore, combination of these drugs within this period may be safe. Wright [9] described the Jarisch-Herxheimer reaction as a transient manifestation of a cytokine storm that occurred after antibiotic therapy and proposed that meptazinol, an opioid, might be a possible alternative monotherapy or combination therapy with anti-TNF-α biologics [9]. Based on this attitude and given JAK-STAT pathway inhibition properties, as well as its inexpensive and easy prescription (particularly in Iran, where MTX is a licensed drug), we shared this hypothesis to pour cold water on the cytokine fire in patients with COVID-19.

Acknowledgment

We would like to express our sincere gratitude to John J. O'Shea, who taught us the JAK-STAT signaling pathway.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

The authors received neither funding/support nor grants for the publication of this work.

Author Contributions

Farhad Seif wrote the first draft of this letter. Davood Mansouri and Majid Pornour revised this letter for important intellectual content. All of the authors read and approved the final version of this letter.

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