EDITORIAL

Use of Tofacitinib in the Management of COVID-19 Pneumonia

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Moderate-to-severe coronavirus disease-2019 (COVID-19) (severe acute respiratory syndrome coronavirus 2—SARS-CoV-2) infection is characterized by acute respiratory distress syndrome (ARDS), caused by pulmonary endothelial dysfunction and hyperinflammation.[1] Variety of drugs have been tried to treat this dreadful disease. Main categories for this purpose are antiviral agents, virus-targeted antibodies, immunomodulators, and glucocorticoids. Later, two groups are known to change host response favorably, minimizing the local tissue injury in the lungs. Immunomodulators combined with dexamethasone have shown promising outcome benefits in moderate as well as severe COVID-19 ARDS patients on invasive ventilation.[2] Various immunomodulators studied are anticytokines, i.e., interleukin-1 (IL-1) and interleukin-6 (IL-6) antagonists (e.g., tocilizumab, sarilumab, and siltuximab); tumor necrosis factor inhibitors (e.g., adalimumab and infliximab); granulocyte–macrophage colony-stimulating factors (e.g., gimsilumab, lenzilumab, and namilumab); and many others, like bevacizumab, itolizumab, baricitinib, and tofacitinib. The most preferred agents are tocilizumab and baricitinib, but in case of their nonavailability, others were also tried. If baricitinib is not available, the National Institute of Health (NIH) COVID-19 guidelines recommend tofacitinib as an alternative to baricitinib for the treatment of COVID-19.

Baricitinib was studied previously to show some favorable impacts on the outcomes of COVID-19 pneumonia.[3] In the second stage of Adaptive COVID-19 Treatment Trial (ACTT-2), baricitinib in combination with remdesivir was found to be superior to the remdesivir alone, improving the recovery in cases of moderate-to-severe COVID-19 ARDS.[4]

Tofacitinib is a similar alternative agent studied. Tofacitinib is a Janus Kinase (JAK) inhibitor molecule, currently approved to be used in the treatment of rheumatoid arthritis, ankylosing spondylitis, and ulcerative colitis.[5] It is an orally administered agent that blocks the intracellular transduction pathway after the cytokine binds to its receptor, thus suppressing the consequent hyperimmune response and cytokine storm. Tofacitinib, given orally, in the dose of 10 mg two times a day (BID), is also known to modulate the actions of interferon and IL-6, decreasing the release of cytokines by type-1 and type-17 helper T cells, which form an integral part of ARDS pathogenesis. In a recent study by Guimaraes et al., tofacitinib showed a decrease in 28-day mortality in the patients of respiratory failure, when compared to placebo.[6]

In this issue of IJCCM, Singh et al. have reported that their retrospective analysis of 50 patients of COVID-19 pneumonia found that there were reduced intubation rates in 25 patients treated with tofacitinib as compared to 25 others treated with standard care, i.e., (8 vs 32%, $p = 0.034$), but this did not reflect in the number of deaths by day 21 where the difference was not statistically significant (12 vs 20%, $p = 0.44$). Also, there were no instances of new bacterial or invasive fungal infections or treatment-emergent adverse effects in either of their two groups.

As per the Infectious Diseases Society of America (IDSA) Guidelines on the Diagnosis of COVID-19, tofacitinib, in addition to the standard of care, is recommended for the hospitalized adults with severe COVID-19 having oxygen saturation ≤94% on room air and those patients on supplemental oxygen therapy, but not on mechanical ventilator support.[7]

Tofacitinib is known to have minor side effects in terms of headache, abdominal pain, nausea, vomiting, rashes, anemia, angioedema, diarrhea, dehydration, dyspepsia, and major ones, like hyperlipidemia, hepatitis, lymphoma, lymphopenia, neutropenia, blood clots, pulmonary embolism, acne vulgaris, and GI perforations.[5] However, in the Brazilian multicenter study of 289 patients, by Guimaraes et al., they did not find any alarming rise in secondary infections or thromboembolic events.[6] In the alerts by Health Canada and by the United States Food and Drug Administration (US-FDA), in JAK Inhibitors Safety Review (September 2021), they cautioned against the side effects of thromboembolic events caused by tofacitinib.[8]

Based on the earlier study by Paranjpe et al.,[9] most of the patients of moderate-and-severe COVID-19 pneumonia are essentially on therapeutic anticoagulation with initially enoxaparin or later apixaban. Possibly because of this, the thromboembolic complications were hardly reported by Hyek et al.[10] In this single-center retrospective analytical study, they concluded that the addition of dexamethasone did not matter as long as tofacitinib was accompanied by anticoagulant, anti-inflammatory, and antiviral agents. This could be an effect of broader anti-inflammatory effect of toficitinib.[11] Further, they observed that the incidence of anticoagulation-related bleeding was higher as compared to the normal population but did not have any direct impact on mortality

and bleeding tendency could be managed easily with cessation of anticoagulation. There was no difference in infectious complications in tofacitinib and dexamethasone groups. Hyperglycemia was significantly higher in dexamethasone group as compared to tofacitinib group, indicating the possible benefit of metabolic neutrality of the later. There was a caution expressed about the deleterious effect, in case of very early use of tofacitinib without antiviral cover, similar to the high mortality reported in RECOVERY study, with rather early use of dexamethasone.

In a meta-analysis of four randomized controlled trials (RCTs) using four different JAK inhibitors, baricitinib, tofacitinib, ruxolitinib, and nezulcitinib, in 1,338 patients, it was found that JAK inhibitors are promising agents to be used in COVID-19 pneumonia. They decreased a mortality risk by 43% and the risk of mechanical ventilation and extracorporeal membrane oxygenation (ECMO) by 36%. However, it was perceived that larger RCTs will be needed to establish their definitive role in the management of COVID-19 pneumonia.[12,13]

There are many ongoing trials (with baricitinib—NCT04390464, NCT04640168, NCT04421027, and NCT04381936; with tofacitinib—NCT04415151 and NCT04750317) which may provide further insights regarding the effects of JAK inhibitors in patients with COVID-19 pneumonia.[6]

NCT04415151, a randomized, double-blinded, placebo-controlled study of 60 moderate COVID-19 pneumonia patients, requiring supplemental oxygen but not requiring mechanical ventilation, developed by the Yale University, mainly will focus on the safety and even the efficacy potential of tofacitinib.[6]

NCT04750317, also labeled as TOFA-COV-2 and titled as Efficacy and Safety of Tofacitinib in Patients with COVID-19 Pneumonia, is a trial conducted by the three clinics of the Sechenov University (Moscow, Russia). It has four arms to study the adult patients of moderate COVID-19 pneumonia, not needing mechanical ventilation support, above 18 years of age. Two groups are with oxygen saturation <93%, receiving the standard of care and a combination of tofacitinib with the standard of care, and the other two groups with oxygen saturation >93%, receiving similar treatment. The aim of the study was to test the risk (that of needing mechanical ventilation and death) reduction with the addition of tofacitinib to the standard of care.[6]

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