Non-steroidal anti-inflammatory drugs in COVID-19 patients- What is the verdict?

To the Editor,

In patients who have a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab indicating COVID-19 infection because of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the severity of the cytokine storm decides the overall outcome of the illness. When the pandemic of COVID-19 was announced and researchers were still fathoming the complex pathophysiology because of SARS-CoV-2, it was announced that non-steroidal anti-inflammatory drugs (NSAIDs) should not be used in these patients for managing pyrexia, inflammation, and other constitutional symptoms like myalgia and headache.[1] The popular NSAID ibuprofen has been implicated to increase the levels of angiotensin-converting enzyme-2 (ACE2), its expression within the renin-angiotensin-aldosterone system which is the coreceptor for the entry of SARS-CoV-2 into lung parenchymal cells. Therefore, it is hypothesized that the use of NSAIDs could lead to an increased risk of contracting COVID-19 disease or worsening of COVID-19 infection if consumed once the disease is confirmed.[2] This hypothesis is still under evaluation.

In a retrospective cohort study of 403 COVID-19 patients from a single-centre, Rinott *et al*.[3] analyzed the need for respiratory support including assisted ventilation and mortality in patients who received either ibuprofen or paracetamol as an antipyretic during treatment. On analysis, the authors concluded that the use of ibuprofen was not associated with worse clinical outcomes when compared to paracetamol. In a prospective cohort study involving 503 COVID-19 patients which involved patients who received acute NSAID therapy, patients on chronic NSAID/aspirin, and non-NSAID users; Abu Esba *et al*.[4] concluded that acute or chronic use of any NSAIDs was associated with adverse outcomes. The limitations of this study were its observational nature, many confounding factors, presence of selection bias, and that it was a single institute experience.

The mechanism of action of NSAIDs is by inhibiting cyclooxygenase I and II (COX-I and COX-II), which mediates prostaglandins leads to its anti-inflammatory properties. It has been demonstrated that prostaglandin inhibition modifies the expression of angiotensin-converting enzyme 2 (ACE2), regulates replication of SARS-CoV-2 in host cells, and modulating the immune response to SARS-CoV-2. This was demonstrated in a study by Chen *et al*. involving human cell cultures and mouse systems.[5] The authors demonstrated that COX inhibition did not affect ACE2 expression, viral entry, or viral replication. On the contrary, there was a dampening of the inflammatory response owing to its anti-inflammatory effects and production of protective antibodies. The limitation of this study is that the data is from human cell cultures and animal studies. Animal studies have demonstrated a decrease in IL6 and TNF-α when COX2 inhibitor celecoxib is used. These properties have not been effectively explored in the current pandemic.

The cytokine storm in severe COVID-19 infection leads to the release of proinflammatory cytokines in the circulation which leads to acute respiratory failure, shock, multiorgan dysfunction, and shock. The cytokine storm is also responsible for lymphopenia which has shown to be directly related to mortality (lymphocyte count of less than 1.5×10^9/L, is associated with a 3-fold increased risk of severe COVID-19 infection). There was a significant reduction in T-cells and natural killer cells as well. Neutrophil-lymphocyte-ratio is found to have a good predictive value on the severity of COVID-19 illness and mortality.[6]

Based on this understanding, it was hypothesized that if NSAIDs are used early in COVID-19 infection for their anti-inflammatory properties, it could help in reducing the intensity of cytokine storm. Anti-inflammatory agents or cytokine antagonists like tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist), Janus kinase inhibitors are being advocated in indicated patients which interferes with cytokine storm at various levels. Several studies are currently prospectively investigating the efficacy and safety of NSAID in COVID-19 illness.

The beneficial effects of NSAIDs, although anecdotal, should be taken with a pinch of salt. NSAIDs causing prostaglandin inhibition leads to PGI2 inhibition and also potentiates thrombosis, which can be harmful in COVID-19 patients. The use of NSAIDs has been responsible for serious thrombotic phenomena like major adverse cardiovascular, cerebrovascular, and lower limb thrombotic events. NSAIDs use can precipitate bronchospasm in susceptible patients which could complicate pre-existing respiratory status.[7] Acute kidney injury in COVID-19 patients is associated with significant morbidity and mortality. The use of NSAIDs could thus be detrimental in patients with borderline renal functions especially in patients who are hypertensive, diabetic, coronary artery disease, and the elderly population.[8] This leaves with clinicians a selective

proportion of patients in whom NSAIDs could be used safely, with close monitoring.

To conclude, the safety of NSAIDs as an anti-inflammatory and antipyretic is not established yet. Well-designed, prospective studies might be able to establish the efficacy, timing, dose, and duration of NSAIDs in selected COVID-19 patients. Paracetamol when used in appropriate doses appears to be safer and reasonably effective for managing pyrexia and myalgia.

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