

Immunomodulation and COVID-19: Is There a Winning Combination?

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ABSTRACT

Coronavirus disease-2019 (COVID-19) has been testing the boundaries of science on several fronts. Pharmacotherapy has seen the highs of several drugs being tried as the best option as well as the lows of no drug proven to be effective. In this edition of the Indian Journal of Critical Care Medicine, Mahale et al. retrospectively evaluated a combination of drugs targeted at immunomodulation.

Keywords: COVID-19, Immunomodulation, SARS-CoV-2, Tocilizumab.

Indian Journal of Critical Care Medicine (2020); 10.5005/jp-journals-10071-23691

Ever since the coronavirus disease-2019 (COVID-19) pandemic broke out in December last year, several strategies to improve the patient outcome have been tried with varied results. The exact mechanism of pathogenesis and the consequences thereof associated with severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2) infection are yet to be completely and correctly understood. A four-stage classification system starting with early infection (stage I) through to multi-organ failure (stage IV) has been proposed as a reasonable method to understand the disease.^{1,2} Stage II seems to characterize the hyperresponsiveness of the immune system. This is the stage in which hypoxia and systemic inflammation appear to be dominant. Intervention at this stage could help in limiting progression to more advanced stages. Elevated levels of proinflammatory cytokines seem to be the feature of this stage. The so-called cytokine storm or cytokine release syndrome (CRS) is a consequence of the release of these proinflammatory cytokines.³⁻⁵ Neutralizing the effect of cytokines by blocking the receptors or the signal transduction appears to be an option.

Nonspecific immunomodulation with corticosteroids, interferons, macrolides, or hydroxychloroquine (HCQ) has been attempted. The combination that is likely to confer the greatest benefit is yet to be identified (except for a benefit with the use of steroids⁶⁻⁸). In this edition of the Indian Journal of Critical Care Medicine, Mahale et al. have attempted to correlate retrospectively, the effect of a combination of immunomodulatory agents on COVID-19 severity and outcome.

Interleukin-1 receptor antagonists like anakinra were proven to be effective in macrophage activation syndrome.⁹ This raises the possibility of a role for anakinra in the severe COVID-19 infection. Several observational studies¹⁰⁻¹² have established a benefit in terms of improved clinical and biological markers with the use of anakinra. No major controlled trial has been published yet to substantiate these observations.

Interleukin-6 receptor antagonists like tocilizumab (TCZ) have also been hypothesized to be of benefit in the management of severe COVID-19. Although initial data emerging from China seemed to indicate a benefit with the use of TCZ,^{13,14} subsequent large randomized trials have failed to establish benefit.¹⁵

Coincidental immunomodulators like HCQ, corticosteroids, macrolides, and colchicine have also been evaluated. Hydroxychloroquine is thought to act by altering the cell

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How to cite this article: Samavedam S. Immunomodulation and COVID-19: Is There a Winning Combination? *Indian J Crit Care Med* 2020;24(11):1015-1017.

Source of support: Nil

Conflict of interest: None

membrane pH needed for viral fusion. Despite a large number of trials evaluating this intervention, no conclusive support for the use of HCQ as a therapeutic agent for SARS-CoV-2 has emerged.¹⁶

Glucocorticoids have been used for managing many acute inflammatory and autoimmune disorders.¹⁷ This effect of glucocorticoids seems to be mediated by direct and indirect effects on gene expression as well as receptor-mediated effects. Moderate doses of corticosteroids in hypoxemic patients seem to be of some benefit.

The potent anti-inflammatory medication, colchicine, inhibits the polymerization of microtubules and acts through cellular adhesion molecules and inflammatory chemokines.¹⁸ It is therefore a potential agent to counter the CRS. The evidence for colchicine has been negative so far.¹⁹

Mahale et al. evaluated several combinations of therapies targeted at COVID-19. The combinations studied included HCQ, steroids, colchicine, and TCZ in various permutations. Methylprednisolone was the common steroid used in this cohort. Among the various steroids used and evaluated for COVID-19, dexamethasone seemed to have the highest benefit, especially among hypoxic patients.⁶⁻⁸ The inclusion criteria for this retrospective study included oxygen requirements. This would suggest that the patients included would be in stage II as discussed earlier. In this predominantly male cohort, nearly half the patients were either diabetic or hypertensive. This group had lower PaO₂/FiO₂ values and consequently needed more oxygen than those without the twin comorbidities. A notable observation from the data is that a small proportion of patients were actually tested for the markers of inflammation—IL-6, ferritin, and D-dimer. Since the

decision to order these tests was based on physician assessment, it is probably prudent to conclude that nearly half the cohort was not sick enough to benefit from immunomodulation. This conclusion is given further credence by the fact that more than half the cohort could be managed with nasal prongs and face mask alone.

The combination of HCQ and methylprednisolone was the most common factor in at least two subgroups, accounting for nearly two-thirds of the cohort. Hydroxychloroquine was used in nearly three-fourths of the cohort. The number of patients who were treated with TCZ and etoricoxib is too small to draw any inference. Rabbani et al.²⁰ supported the use of colchicine with favorable results in a cohort with similar numbers. Close to half the patients in this study were treated with HCQ. The addition of colchicine did not seem to have conferred any survival benefit, although this was a retrospective study. The combination also did not reduce the need for mechanical ventilation. Steroids were used consistently except for a small proportion (<5%), who were treated with HCQ alone. This aspect combined with the fact that MPS was the steroid of choice, makes the conclusion regarding the benefit a little difficult. The retrospective nature of the study and the small sample size further compound the conclusions. Etoricoxib and TCZ were used for a very small subset of patients. These two drugs were used only in combination with both HCQ and steroids. Although no patient who received etoricoxib was mechanically ventilated or succumbed to the disease, no generalization can be drawn from this small cohort. The conclusion drawn by the authors regarding higher mortality and the need for ventilation among patients receiving TCZ is at best hypothesis-generating. An interesting point to note in this study population is that 41.7% of patients succumbed to multi-organ failure and sepsis. This rather high mortality percentage needs to be evaluated against a backdrop of immunomodulation especially with a regimen dominated by methylprednisolone. Does immunomodulation targeted at COVID-19 predispose the patients to other severe infections? This is another question that arises from this retrospective analysis where the incidence of secondary bacterial infection was 13.4%. This should alert us to the need for meticulous infection control in COVID-19 patients subjected to immunomodulation. Another important determinant of ICU outcome is hyperglycemia. This was seen in nearly half this cohort. While this could be attributed to the choice of methylprednisolone as the default steroid, in a population where 44% were diabetic at baseline, its role in prolonging ICU length of stay and the need for invasive ventilation as well as predisposition to secondary infection needs to be evaluated. Prediction of mortality has always been a difficult task during the pandemic. In this small cohort of hypoxemic patients of moderate severity leukocytosis and renal dysfunction were determinants of mortality.

In conclusion, the clinical course of COVID-19 seems to be largely driven by immune-mediated mechanisms. Several pathways are likely to be involved. No single drug or a combination of drugs that attempt to alter these pathways have shown a definite benefit. The hope with which HCQ and TCZ were used in the early part of the pandemic has faded away. Steroids continue to hold some promise although the right drug and the best dose are still being researched. The data obtained during the past 6 months have raised several hypotheses which need further study even as a second wave begins in some parts of the world.

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