



# Coronavirus Disease 2019 Treatment—T-Cells Hold the Key in Severe Cases

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Since an unknown viral pneumonia started in December 2019 at Wuhan, China, world has witnessed too many guesses about its nature, spread, and treatment.<sup>1</sup> Initially informed about trivial flu virus, now, it has affected more than 10 million in the world and likely to affect more in coming time. It was named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by Chinese Center for Disease Control and Prevention, now known as coronavirus disease 2019 (COVID-19). It has spread to almost all countries and killed more than 0.4 million people as of now.<sup>2,3</sup> Apart from direct mortality, COVID-19 pandemic will have economic consequences and related morbidities, other health condition outbreaks, and suicides in the near future.<sup>4</sup>

COVID-19 is a betacoronavirus that is a positive sense, single-stranded RNA virus having a nucleic acid homology of 78% with SARS-CoV and 50% with Middle East respiratory syndrome (MERS)-CoV.<sup>2</sup> Its envelop has a glycoprotein spike that has an affinity to angiotensin-converting enzyme-2 (ACE-2) receptor on human cells. An abundance of these receptors on lower respiratory tract cells makes this virus a respiratory pathogen.<sup>5,6</sup> It can be spread by fomites; however, recent evidences proposed airborne spread as well, making it highly infectious.<sup>7</sup>

Scientific information about COVID-19 is still maturing and uncovering. Existing testing and management guideline are changing very frequently, in a desperate attempt to save humankind from pandemic mortality. ACE-2 receptor was considered as the gateway of entry for SARS-CoV-2 and earlier attempts were made to use ACE-inhibitors to deny entry of the virus. However, later, it was proved to be not of much use.<sup>6</sup> Any viral invasion of body has well-defined immune response. Initially, the virus is attacked by the innate

immunity of the body. On detection of viral RNA, natural killer cells and type 1 interleukin (IL) start cytolytic responses. Later on, T-cell starts killing and clearing virus-infected cells and B-cell starts antibody production against the virus. In COVID-19, the same immune response is expected; however, sick patients have shown hyperimmune response suggested by increased proinflammatory cytokines (IL-6, tumor necrosis factor, IL-2, IL-10, IL-7, and interferon gamma).<sup>8,9</sup> However, circulatory CD4+ and CD8+ cells were less. Lymphopenia is noted among sick and very sick COVID-19 cases.<sup>10</sup> Bone marrow examination of COVID-19 cases showed a picture similar to macrophage activation syndrome/hemophagocytic lymphohistiocytosis.<sup>11</sup> Autopsy findings were consistently showing both exudative and proliferative phases of inflammation. An abundance of macrophages was noted in alveolar lumina and T-cells in the interstitium. Viral particles were present in pneumatocyte.<sup>12</sup> Lymphopenia in blood was explained by T-cell exhaustion and cytokine storm having negative feedback on T-cell population.<sup>13</sup>

An alternate explanation for these findings needs attention. COVID-19 leads to T-cell stimulation and proliferation. T-cell-related signaling to B-cell leads to immunoglobulin production against COVID-19 in the late course of illness. T-cells release cytokines to contain virus particle. However, in moderately sick or severely sick cases, hyperactivity of T-cells leads to cytokine storm and tissue damage. T-cells migrate to tissues with affinity to virus particle (pneumatocyte as they have more ACE receptors) causing tissue-level cytokine storm and damage. The presence of antigen (virus particle) and reactive cells (macrophages, T-cells and cytokines) at alveolar level must be considered while managing a patient.<sup>12</sup> We postulate that tissue migration of T-cells

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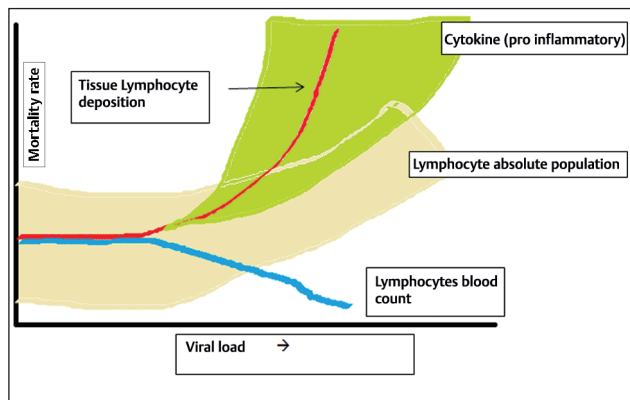
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leads to lymphopenia and T-cell exhaustion is actually shifting of war field to alveolar level. Relatively high lung damage and sparing of other tissues such as joints, brain, and heart support the hypothesis of local cytokine storm along with systemic one (► Fig. 1). Considering this model, high viral load in the intensive care unit (ICU) (due to closed air system) and higher mortality rate of frontline workers in ICU can be explained.<sup>14,15</sup>

Considering virus load, cytokine, and T-cells, as main active agents at war damaging lung tissues, treatment should be tailored. Right now, many antivirals have been tried with variable results. Immunomodulators such as hydroxychloroquine (HCQ) and dexamethasone have been found beneficial in some studies. While dexamethasone has been considered effective, HCQ showed variable reports.<sup>16,17</sup> Failure of HCQ as immunomodulator is suggesting that cytokine war is at higher pace and mild modulation is not working. Dexamethasone has high efficacy to suppress immunological reactions or ongoing war, thus showed a promising result.<sup>18</sup> It is like escalating immunosuppression rather than modulation in sick patients. Our hypothesis is congruent with the finding that immunomodulation with HCQ is effective in moderate cases, while stronger immunosuppressant like dexamethasone is effective in severe cases.<sup>16,17</sup>

We propose using other T-cell suppressive measures such as use of cyclophosphamide, cyclosporine, tacrolimus, and mycophenolate mofetil are some of candidates worth trying. Immunomodulation in haploidentical stem cell transplant has achieved enough experience to extrapolate in COVID-19 cases.<sup>19</sup> Case series showing COVID-19 among renal transplant cases has noted that immunosuppression withdrawal has neither improved outcome nor everyone succumbed.<sup>20</sup> Probably, controlled immunosuppression could have saved cases.

Even if T-cells are ablated, existing cytokines will damage tissues. Dexamethasone/methylprednisolone has been approved recently for use. From hemophagocytosis-lymphohistiocytosis management knowledge, other agents like etoposide can be used. Tocilizumab, a selective IL-6 blocker, has shown good results by countering cytokine storm, but its availability and cost are limiting factors for majority of patients.<sup>21</sup> High-dose dexamethasone will prevent cytokine-related damage and probably will save the ill.



**Fig. 1** Pictorial representation of immune-pathogenesis of coronavirus disease 2019.

**Table 1** Proposed pharmacological escalations based on severity

Proposed severity of COVID-19	Features	Laboratory markers <sup>2,3,26</sup>	Antiviral <sup>27,28</sup>	Immunomodulators <sup>16-18</sup>	T-cell suppressants <sup>29</sup>	Anticytokines <sup>21</sup>	Anticoagulants <sup>30</sup>
Mild	No Pneumonia/oxygen dependency		Yes/no	No	No	No	No
Moderate	SpO <sub>2</sub> < 94% Oxygen dependency		Yes	Yes	No	No	No
Moderate but deterioration	SpO <sub>2</sub> 90-94% Respiratory support needed	D-Dimer (0.2-0.5 µg/L) ESR (10-20 mm/1st h) Interleukin 6 (5-10 pg/mL) Absolute lymphocyte counts (>1x10 <sup>9</sup> /L)	Yes + convalescence plasma	No	Yes	Yes	Yes
Severe	Severe pneumonia ARDS Sepsis Shock	D-Dimer (>0.5 µg/L) ESR (>20 mm/1st h) Interleukin-6 (>10 pg/mL) Absolute lymphocyte counts (<1x10 <sup>9</sup> /L)	Yes + convalescence plasma	No	Yes	Yes	Yes

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ESR, erythrocyte sedimentation rate; SpO<sub>2</sub>, oxygen saturation.

While thinking about controlled immunosuppression, a practical guide to escalate or deescalate immunosuppression will be difficult. More suppression has fear and risk of opportunistic infections, while less may not work. Previous experience from MERS-acute respiratory distress syndrome has shown no benefit of steroid for 90-day mortality of ICU stay.<sup>22</sup> However, COVID-19 might be more of an immunological disease, rather than infectious. We propose escalation of immune suppression on basis of clinical parameters (►Table 1). Last comment is about considering a sound medical practice. The World Health Organization has started multinational multicentric solidarity trial for COVID-19 management. A similar approach of controlled liberalization of protocols can deliver results in lesser time. Although chances of error and protocol retractions are high without a properly phased clinical trial it might outweigh the risk of mortality with ongoing pandemic. Awareness regarding volunteer donation of convalescent plasma is as important as preventive strategies.<sup>31</sup> Meticulous search for cure in all directions is the need of the hour. As oncologists, hematologists, and transplant physicians are more involved in T-cell manipulations by chemotherapy and immunotherapy, we propose that they should be roped in for tailoring treatment plans.

#### Conflict of Interest

None declared.

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