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A potential role for cyclophosphamide in the mitigation of acute respiratory distress syndrome among patients with SARS-CoV-2

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ABSTRACT

While humanity struggles to develop a vaccine against SARS-CoV-2, it is imperative that effective and affordable therapeutic strategies be evolved. Since a majority of the SARS-CoV-2 deaths are due to acute respiratory distress syndrome (ARDS), a strategy to mitigate the same could save countless lives. Since SARS-CoV-2 related ARDS has a strong immunological component, many investigators are utilizing monoclonal antibodies against IL-6, TNF-alpha and CCR5. However, targeting a single cytokine with an expensive monoclonal antibody could be a less pragmatic approach. We propose the use of cyclophosphamide as an immunomodulator, given its proven role in various settings including autoimmune diseases, and in the post-haploidentical stem cell transplant. Cyclophosphamide could deplete cytotoxic and effector T cell populations while relatively sparing the regulatory T cells (Tregs). Cyclophosphamide could tip the balance away from the overtly pro-inflammatory and could be a less expensive and effective alternative to the currently investigated monoclonal antibodies.

The SARS-CoV-2 virus has as of today (15 May 2020) caused in excess of 300,000 deaths world-wide. The virus has the certain ability to cause further deaths globally and could later remain endemic to cause future waves of deaths in different parts of the world. Given the expected delay in the development of a reliable vaccine, there is need for an emphasis upon developing strategies to mitigate the severity of the illness among those affected.

Acute respiratory distress syndrome (ARDS) is the commonest cause of death among patients infected with either of the three highly pathogenic human coronaviruses (COVs) namely the SARS-COV-1, the Middle East Respiratory Syndrome (MERS)- CoV, and the current SARS-CoV-2. These coronaviruses have been documented to have trophism to the lower respiratory tract which has an abundant expression of the Angiotensin Converting Enzyme-2 (ACE2) receptor [1].

Early data regarding the current SARS-CoV-2 pandemic suggests that 60% of patients admitted to the ICU required mechanical ventilation, and ARDS was diagnosed in about 40% of patients treated in the ICU [2]. If ARDS could be prevented or mitigated, we can expect a significant reduction in SARS-CoV-2 associated mortality.

Immunological basis of ARDS

A well-coordinated immune response could be important for effective viral clearance in the early phases of the SARS-CoV-2 infection. However, a dysregulated, exuberant immune response in the later phases of the SARS-CoV-2 infection could lead to hyper-inflammatory acute lung injury and ARDS. During the previous SARS-CoV-1 epidemic, immunopathological changes were documented to be involved in the genesis and progression of ARDS [1].

Generally, after pulmonary infection, alveolar macrophages secrete IL-6, IL-12, TNF-alpha, and interferons. Then, as a response, the tissue resident cytotoxic T cells, Th1 cells and Th17 cells secrete further cytokines in increased quantity and diversity. These increased levels of cytokines not only increase the cytotoxic effects of T cells, but also act as a chemoattractant towards circulating monocytes and neutrophils [3].

The development of ARDS in response to infectious agents is rather non-specific, though the severity could vary with the specific circumstance. Experiments with mice using Influenza-A viruses demonstrated that very high viral doses induced extensive neutrophil extracellular traps (NETs). These traps are a mechanism to trap and immobilize pathogens. It is plausible that high viral burden could hence lead to

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more extensive 'NETosis', thus leading to collateral damage and ultimately impairing gas exchange at the alveoli [4]. Given the high replicative potential of SARS-CoV-2, it is plausible that very high viral burden in the lung leads to a large inflammatory response, which could be fatal.

There ideally exists a balance between the 'pro-inflammatory' and the 'anti-inflammatory'. Cells such as the Th1, Th17 and M1-polarized macrophages are pro-inflammatory. At the opposite end of the spectrum, cells such as the regulatory T cells (Treg) and the M2-polarized macrophages are anti-inflammatory and regenerative. In conditions such as ARDS, it can be said that 'the balance has shifted overtly in favour of the pro-inflammatory' [3,5]. Studies with patients infected with the SARS-CoV-1 had indeed demonstrated increased pro-inflammatory cytokine levels among those who developed ARDS [6,7].

Of the various T-helper (Th) subsets, the Tregs are special in that they are vital for maintaining self-tolerance. Tregs express CD4 + CD25 + FoxP3 and produce the anti-inflammatory cytokine namely IL-10. Evidence suggests that Tregs have an ability to down-regulate TNF-alpha, IL-2 and IL-8. Thus, manipulation of T cell populations to enhance proportion of Tregs may possibly be a worthwhile exercise in the mitigation of acute lung injury [8].

Available evidence suggests that an increased Th17:Treg ratio is known to be pro-inflammatory and conducive to the development of ARDS [8]. In fact, the Th17/Treg ratio has been seen as a prognostic marker for ARDS in terms of mortality prediction [9].

Worthy of mention, the occasional manifestation of hemophagocytosis in patients infected with SARS-CoV-2 serves as a testament to excessive macrophage activation, which can in turn be attributed to excessive proliferation and activation of T-Cells [10].

Immune modulation as an option against ARDS

It is encouraging that IL-6 antagonists such as tocilizumab are being rightly investigated in SARS-CoV-2 related ARDS [11]. It is furthermore encouraging that groups are contemplating TNF-alpha antagonists such as infliximab and etanercept in the setting [12].

Drugs such as tocilizumab, and other targeted monoclonal antibodies could do well in targeting the particular cytokine which they are designed to. However, ARDS is a hyperinflammatory condition involving multiple pro-inflammatory cytokines, and thus we postulate that targeting one single cytokine could be a weak approach. The use of cyclophosphamide would strike at the root of the hyper-inflammatory condition by rapidly depleting effector T cells.

Cyclophosphamide has been more renowned for its role as an alkylating agent in various cancer specific chemotherapeutic regimens. It has also been well documented to have other roles as an immunomodulator in various auto-immune disorders with a reasonable toxicity profile [13].

Cyclophoshamide had revolutionized the scene of haplo-identical allogenic stem cell transplants (HaploSCT). HaploSCT essentially involves transplants from a donor who is 'not fully matched' to the recipient. The use of post-transplant cyclophosphamide (PTCY) has led to a dramatic reduction in likelihood of graft versus host disease (GVHD) and graft rejections. This is because PTCY works to eliminate rapidly proliferating alloreactive T-cells (in both directions) while preserving the slowly dividing regulatory-T cells (T-regs) and memory T cells. This not only leads to lesser likelihood of GVHD and graft rejection, but also leads to better immune tolerance and immune reconstitution [14–16].

Cyclophosphamide has a rich history of being used as an effective rescue therapy when other drugs failed in severe rheumatological disorders, which too have an immunological pathogenesis. This use has somewhat declined in the previous decade owing to the development of targeted monoclonal antibodies against specific cytokines [13].

If being considered as a preventive/mitigative strategy against ARDS in SARS-CoV-2, we need to ponder upon the ideal dose and the ideal timing of cyclophosphamide delivery.

The dose of cyclophosphamide used in various conditions is vastly different. Certain protocols for PTCY use doses as high as 50 mg/kg. However, we could possibly utilize lower doses given that we are aiming at a reduction of cytotoxic T cells rather than a total elimination. As an example, when cyclophosphamide is utilized as an immunomodulator in multiple sclerosis, the applied dose is many magnitudes less [17]. So, a 10–20 mg/kg dose of cyclophosphamide could be able to demonstrate proof of concept.

Regarding the ideal timing of cyclophosphamide, it would be advisable to wait to start till when ARDS is deemed inevitable. That would be at the onset of acute lung injury, with the patient yet to proceed to fully established ARDS.

Regarding the questionable safety of using an alkylating agent in the setting, we justify the same that ARDS is otherwise potentially lethal [13]. Furthermore, a one-off dose would be employed rather than multiple doses as would be in the case with malignancies. The use of broad spectrum antibiotics akin to the stem-cell transplant setting would be advisable so as to prevent bacterial and fungal opportunistic infections.

An interesting case report describes a young patient who was treated with a regimen including cyclophosphamide for glomerulonephritis. The patient later was found to have ground glass opacities on computed tomography imaging and subsequently tested positive for SARS-CoV-2. It could be possible that the use of cyclophosphamide could have prevented the particular patient from manifesting severe pulmonary symptoms [18].

If at all a strategy using cyclophosphamide is found effective in mitigating/preventing SARS-CoV-2 associated ARDS, it is plausible that it could be put into immediate global use. Unlike monoclonal antibodies the cost of cyclophosphamide is very much affordable. In addition, cyclophosphamide production can quickly be ramped up using existing pharmaceutical infrastructure, while manufacturing monoclonal antibodies on a large scale in a short time span could be problematic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No funding was sought or received for this manuscript.

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