REVIEW

Is COVID-19 a cytokine storm driven viral sepsis?

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ABSTRACT

The new pandemic, COVID-19 has become a global health issue causing unprecedented emergency in the recent history. The etiological agent, SARS-CoV-2, belongs to β-coronavirus family, and is quite different (genetically and infectivity-wise) from the known viruses showing similar clinical manifestations. The RNA virus is positive stranded enveloped one. Hyper-activated immune system leading to aberrant cytokine storm, ensuing in sepsis like pathological conditions, is thought to be the reason behind severity of COVID-19. As of now, there are no confirmed drugs managing the severe pathological state effectively. Many clinical trials with re-purposed molecules and vaccine developmental programs are underway in anticipation of finding a better management strategy. This mini review tries to highlight different pathophysiological aspects of COVID-19 relating to severity and progression of the infection, also postulating probable therapeutic interventions with repurposed molecules.

KEYWORDS: COVID-19, Cytokine storm, Sepsis, SARS-CoV-2, coronavirus, hypercoagulation

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INTRODUCTION

In November 2019, there was an outbreak in the Wuhan province, China with clinical manifestations of acute respiratory distress and viral pneumonia like symptoms. The outbreak has now spread globally, infecting more than 6 million and about 3.7 lac fatalities, leading to a pandemic declaration by the World Health Organization (WHO) on March 11, 2020. The etiological agent behind the infectious respiratory disease (COVID-19) was identified to be SARS-CoV-2. Sequence analysis of early admitted Wuhan patients showed the virus to be 88% similar to bat derived SARS-like corona viruses- bat-SL-CoVZC45 and bat-SL-CoVZXC21 (Lu et al, 2020). Phylogenetically, it was found to be quite distant from the known SARS-CoV (79%) and MERS-CoV (50%) causing similar clinical manifestations (Lu et al, 2020). Later, another bat virus RaTG13, was identified to be the closest matched sequence (96%) to SARS-CoV-2 (Zhou et al 2020). Bats are probably the original source of the virus and also there are reports stating that they have been known to harbour asymptomatically many deadly RNA zoonotic viruses such as- Ebola Virus, Nipa Virus, Rabies Virus, Melaka Virus, SARS Coronavirus and MERS Coronavirus (Banerjee et al 2020). In bats, NLRP3 inflammasome activation is dampened in response to these viruses, attributing to defective transcriptional priming of NLRP3 (Ahn et al 2019). SARS-CoV-2 gains entry into the host cells by engaging its glycosylated spike protein to Angiotensin-converting enzyme 2 (ACE2) receptor. The spike protein of SARS-CoV-2 was found to bind 10-20 times more strongly to ACE2 than the spike protein of SARS-CoV (Wrapp et al 2020),and the presence of Furin recognition motif (PRRARSV) in the spike protein of SARS-CoV-2 further explains the high infectivity of the virus over SARS-CoV (Wrapp et al 2020, Zhang et al 2020). Pangolins can also be intermediate hosts of SARS-CoV-2 before infecting humans. The whole genome sequence of Pangolin-CoV showed 91.02% similarity with SARS-CoV-2. However, five key amino acid residues of receptor binding domain of the spike protein, which are critical in interactions with ACE2, are conserved between Pangolin-CoV and SARS-CoV-2, but not with RaTG13 (Zhang et al 2020). Interestingly, neither the Pangolin-CoV nor the SARS-CoV has furin recognition motif, which raises the possibility of recombination as an evolutionary mean for the emergence of this virus.

Cytokine storm heralds the inflammatory state in COVID-19 pathogenesis

The Chinese centre for disease control and prevention reported about 80% of COVID-19 patients are with mild symptoms (asymptomatic or no pneumonia), 14% of patients were severely ill (with more than 50% having pulmonary pathologies) and 5% were critically ill (respiratory distress and multi-organ failures) (Merad M and Martin JC 2020, Siddiqi and Mehra 2020). The trend is similar around the globe with about 20% of the patients needing hospital interventions (albeit, deviations in some populations). The most common complication of the severely and critically ill patient is Acute Respiratory Distress Syndrome (ARDS). ARDS is recognized to be the hallmark of respiratory related immune pathologies, and were similarly previously observed in SARS-COV and MERS-CoV infections. It leads to injury in alveolar membranes, leading to an increase in lung permeability and deposition of fluid in pulmonary cavities (Coperchini et al 2020). In fact sepsis like phenomena precedes ARDS in COVID-19 progression (Zhou et al 2020). Viral load may be the triggering cause for initiation of symptoms in COVID-19 patients, but ensuing hyper-activated inflammatory response (Cytokine storm) is the major cause for severity and disease progression in the patients. The pathogenesis phenomena can be divided into three phases- mild (Stage I, viremia is maximum), moderate (Stage II, cytokine storm picking up with hypoxia) and severe (Stage III,

deregulated cytokine storm) (Siddiqi and Mehra, 2020). Perhaps some of the patients who need hospitalization in stage II with mild hypoxic condition deteriorate fast with severe hypoxia with more intense cytokine storm (Stage III), culminating into sepsis, ARDS and multi-organ dysfunction (MOD). The cytokine storm is characterized by high level of pro-inflammatory cytokines and chemokines, acute lymphopenia (CD4 and CD8 T reduction), NK cell reductions, infiltration of macrophages and monocytes in lungs and different organs (Merad M and Martin JC 2020, Vabret et al 2020, Huang et al 2020, Li et al 2020). The ICU admitted patients have higher concentrations of chemo-attractants like- CXCL10, CCL2, MCP-1and MIP-1 and TNFα, in comparison to non-ICU patients, reflecting a Th1 cellular response (Coperchini et al 2020, Huang et al 2020). This further supports the infiltration of the inflammatory cells, fuelling up the pathological state. Contrastingly, patients also showed Th2 driven anti-inflammatory cytokines such as IL4 and IL10 (Coperchini et al 2020, Huang et al 2020). COVID-19 patients have been shown to produce high expression of different array of pro-inflammatory cytokines and chemokines such as- IL6, IL1β, TNFα, G-CSF, MCP-1, MIP1, CCL2, CCL3, CXCL8, CXCL9, CXCL10, CXCL2, CCL8 (Huang et al 2020, Blanco-Melo et al 2020). Of the cytokines, IL6 seems to be the prominent readout marker for COVID-19 pathogenesis. However, IL1β and TNFα are known to activate IL6 family proteins involving STAT3 transcription factor (Mori et al 2011). The individual expression profile of the cytokines/chemokines had some variation amongst patients, perhaps due to differences in age, co-morbidities, sex and demographics. The drastic drop in T cell counts in severe COVID-19 patients is perhaps not due to SARS-CoV-2 infecting T cells (ACE2 negative), but due to Activation-Induced Cell Death (AICD) phenomena showing high expression of FAS receptors) (Merad and Martin, 2020).

Sepsis, the underlying cause for critical illness and death in COVID-19 patients

Pathologically, sepses like clinical manifestations are frequently observed in severely ill COVID-19 patients contributing much to the morbidity and mortality (Li et al 2020). Sepses like phenomena are making the pandemic more intriguing and difficult to manage. The clinical study at Wuhan (Zhou et al 2020), mentioned sepsis to be the most observed complication in the patients admitted to the hospital. A comparative study on survivor (n=137) and non-survivor (n=54) patients showed the inflammatory readout markers: D-dimer, Ferritin, IL6, Cardiac Troponin, Lactic dehydrogenase to be consistently increasing with time in patients who eventually expired. The study also showed 59% of survivors and 100% of non survivors had sepsis manifestations. Presumably, It's the hyperactivated immune system leading to the over stimulation of pro-inflammatory cytokines, termed as cytokine storm, which causes vascular endothelial hyper-permeability and hyper-coagulability enroute sepsis and multi organ dysfunction (Li et al, 2020, Jose and Manuel 2020, Merad and Martin 2020). The cytokine storm kick starts the aberrant activation of coagulation cascades and complement system which leads to compromised epithelial-endothelial barrier culminating in thrombosis (clot formation), lung tissue inflammation, respiratory distress and death (Jose and Manuel 2020, Magro et 2020). The pro-inflammatory cytokines (IL1β and IL6) are known to activate the coagulation pathways by increasing the expression of tissue factor (TF) on monocytes and vascular endothelial cells (Nawroth et al 1986; Huet et al 2020; Merad and Martin 2020). TF is known to upregulate the conversion of prothrombin to thrombin, which in turn activates platelets and converts fibrinogen to fibrin threads required for blood clotting. Thrombin is known to be engaged to PAR-I receptors and activate downstream platelet aggregation cascades (Jose and Manuel 2020). In fact, fibrin degradation product (D-dimer) concentration is a good read

out marker for thrombosis and severity of the pathological state (Zhou et al 2020). The thrombin generation is regulated by anticoagulants like-antithrombin III, Protein C and tissue factor inhibitor. During sepsis, the anticoagulants production gets impaired, leading to imbalanced procoagulant-anticoagulant ratio, culminating in clots, microthrombi, disseminated intravascular coagulation and multi-organ failures, as seen in severe COVID-19 patients (Jose and Manuel 2020). The induction of TF by IL1β occur simultaneously by down-regulating the anticoagulant protein C functioning in the endothelial cells, proving it to be a potent pro-coagulant (Nawroth et al 1986). Lung autopsies of patients showed alveolar damage due to deposition of fluid (possibly hyaluronic acid) and massive infiltration of neutrophils and macrophages (Magro et al 2020, Shi et al 2020). Incidentally, IL1β and TNFα are known to be the inducers of hyaluronic acid production (Shi et al 2020). Perhaps the fluid and the micro clots restrict the movement of oxygenated blood in lungs, accounting for the respiratory distress observed in critically ill patients. COVID-19 infected lung tissues also showed significant fibrin deposition and complement components like C5b-9, C4d and mannose binding lectin associated serine protease 2. The skins of the infected patients also showed deposition of C5b-9 and C4d, characteristics of thrombogenic vasculopathy (Magro et al 2020). The high expression of ACE2 receptors in the endothelial cells, lining the different organs and blood capillaries increases the probability of SARS-CoV-2 infection in these cells. In fact, endothelial cells have been shown to be infected by the virus and inflammatory cells have been found in endothelium lining of heart, lung and small bowel (Huet et al 2020). This leads to compromised epithelial-endothelial barriers culminating in rapid systemic collapses as seen in septic critical COVID-19 patients. A respiratory virus damaging endothelium is not much known of, making it more precarious. COVID-19 is also characterized by a substantial reduction in peripheral CD4 and CD8T lymphocyte count (Lymphopenia), which greatly increases the propensity for secondary infections (Zhou et al 2020). Further investigations are required to know whether the secondary infections are indeed fueling up the pathophysiological state. More so, with the immune-compromised recuperating patients, there might be possibilities of re-infection by SARS-CoV-2, making them more vulnerable.

Therapeutic interventions

Based on NIH clinical trials ongoing/completed (https://clinicaltrials.gov/ct2/results?cond=COVID-19) and basic research findings, probable therapeutic interventions can be empirically testing anti-inflammatories, antivirals and anticoagulants in the management of COVID-19.

Anti-inflammatories

COVID-19 is primarily a cytokine driven pathophysiology in severely ill patients (Stage III), hence anti-inflammatories should be the most appropriate intervention strategy. Anakinra for IL1β/tocilizumab (Actemra) for IL6/Adalimumab for TNFα to abate the cytokine storm perhaps could be good choices. Anakinra and Actemra are both recognized for treating severe inflammatory disorders. (Siddiqi and Mehra, 2020; Gupta, 2020). Recently, a French cohort study (n=52) has shown Anakinra (IL1 receptor antagonist) to significantly reduce mortality and need for mechanical ventilation (25% v/s 73%) in severe COVID-19 patients with 10 days treatment regime. The Anakinra survivors didn't require any ventilation support (Hu et al 2020). A randomized clinical trial (n=4848) has shown IL1β blocker (canakinumab) to reduce inflammation marker IL6 (43.2%) in plasma, targeting atherothrombosis (Ridker et al 2019). Tocilizumab, monoclonal antibody against IL6 has also been tested against COVID-19. 75% of severe patients (n=20) had lowered intake of oxygen with lung opacities reduced by 90.5% within 5 days of treatment (Xu et al 2020). TNFα is also an important mediator in inflammation, specifically in lung milieu. TNFα blocking antibody, Adalimumab

warrants efficacy testing in COVID-19 scenario (Feldmann et al 2020).

Antivirals

COVID-19 initiates with SARS-CoV-2 replication with viral load increasing gradually with time. With 80% of patients being asymptomatic for the infection but RT-PCR positive, antivirals should be the first line of intervention for this category (Gupta 2020, Siddiqi and Mehra 2020). Remdesivir, a nucleoside analogue pro-drug, has been tested with clinical improvements, but with reported side effects (Wang et al 2020). Favipiravir, an RNA polymerase inhibitor was shown to clear virus faster and significant improvement in chest imaging was observed with lesser side effects (Cai Q et al 2020). These are nonspecific anti-virals used previously for different viral infections. Interferon β treatment also showed killing of SARS-CoV2 virus in Vero E6 cells, which are IFN deficient. Recent Phase 2 Hong Kong triple combination clinical trials with Interferon β1b and anti-virals showed promise in alleviating symptoms in COVID-19 patients, warranting a deeper study on Interferon β1b as an intervention arm (Gupta 2020, Hung et al 2020).

Anti-coagulants

The COVID-19 pathophysiology gets complicated with sepsis symptoms like-clot, microthrombi, thromboembolism exacerbating the severity and infection progression, which perhaps emphasizes the need for anti-coagulant interventions. Low molecular weight heparin, Antithrombin, Antifactor Xa, Tissue plasminogen activator and PAR-1 antagonist can be thought of as effective anticoagulants for managing thrombosis (Jose and Manuel 2020, Gupta 2020).

CONCLUSION

The mini review provides an overview and analyzes various pathophysiological aspects of COVID-19 patients with emphasis on severely ill and critical patients. It also tried to speculate some intervention strategies for the better management of the infection state. Perhaps a combinatorial approach of anti-inflammatories and anti-coagulants/anti-virals would be suggestive for the patients who need ICU interventions with cytokine storm and hypercoagulation/viral load on higher side. On the contrary, only anti-virals should be good for asymptomatic RT-PCR positive patients. However, more basic research and large controlled clinical studies are required to know the exact cytokine and the downstream signalling crosstalk responsible for the pathophysiologies of the infection.

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Authors' contributions

RG conceptualized the idea and wrote the manuscript. The funders, if any, had no role in preparation of the manuscript or the decision to publish it.

Declaration of originality

The author declares that he has not copied text, figure or data from a particular source without appropriately citing it.

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