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Addressing COVID-19 Immune Storm: A Way Forward

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ABSTRACT

COVID-19 a global pandemic is a cause for panic due to the increasing numbers and the associated fatality rate of ~5%. Death due to COVID-19 is ascribed majorly to the cytokine storm a hyper immune reaction that results in acute respiratory distress syndrome. Following the WHO Solidarity initiative, a large number of clinical trials approved at breakneck speed across the globe. It is encouraging to note that almost all trials are addressing both antiviral effect and lung protection. Clinical trials with a focus on decreasing mortality indeed harbinger a positive trend, as the world waits expectantly for a solution to this dreaded COVID-19 pandemic.

Keywords: Clinical trials, COVID-19, Cytokine storm, Immunomodulation, SARS-CoV-2

1 Introduction

The Novel Coronavirus Disease 2019 (COVID-19), a global pandemic has brought the world to a grinding halt. Statistics are grim with over 10.9 million infected with SARS-CoV-2, numbers steadily rising and over 0.5 million deaths worldwide (~5% death rate) [1]. Lockdown would enable flattening the curve, but remain a will-o'-the-wisp if the fatality is not controlled [2]. The continuous research suggests the demand for clarity on COVID-19 pathophysiology, which is crucial for successful therapeutic interventions [3].

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Most COVID-19 fatalities are attributed to respiratory failure triggered by a hyper-immune response called the "Cytokine storm" [4, 5]. They usually are turned on briefly and switch off automatically. However, under a highly virulent attack as in COVID-19, the storm characterized by an upsurge of proinflammatory cytokines, interleukins (IL-1, IL-6), chemokines (CCR5), colony-stimulating factors (GM-CSF), interferons (Type I IFN) and tumour necrosis factor (TNF-α) becomes unstoppable. The result is acute respiratory distress syndrome (ARDS), and acute cardiac injury, related mortality. This condition may further be complicated by severe pneumonia, to enhance mortality [6–9]. In COVID-19 patients, this storm generally occurs during the second week as a sudden and unexpected onslaught and patients rapidly worsen. Within 24 hours, patients may need to be switched from oxygen to ventilators [3, 10]. Although SARS-CoV-2 induced pneumonia is marked by a production of the inflammatory cytokine IL-6, other cytokines like IL-1 and TNF-α, which are produced could worsen the condition and culminate in a fatal outcome as seen in patients of COVID-19 [10, 11]. Several clinical trials have approved at unimaginable speeds and are mainly based on drug repurposing approach [12, 13]. Notably, the pathogenesis of cytokine storm is complex and can be exacerbated in comorbidities, leading to death [14]. Similarly, this cytokine response is not the same in the context of all infections, and the situation gets even more complicated in patients living with coinfections [15]. Translating any drugs from past and based on addressing one immunopathology into COVID-19 associated Immune storm which involves many such pathways and many unknown mechanisms are challenging in critically ill patients, and side effects may increase mortality [4, 7, 9].

The WHO Solidarity Trial approved in March, which included Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir with Interferon β-1a, and the antimalarials Chloroquine/ Hydroxychloroquine focused primarily on antiviral activity. However, combining the anti-inflammatory cytokine interferon with the antivirals, as an inhalation, reflects that lung protection was a considered factor [16]. Hydroxychloroquine (HCQ) is reported to prevent viral multiplication and also inhibit IL-6. Nevertheless, the results of the WHO solidarity trial were not astounding or robust. Convalescent plasma therapy could only provide a stopgap during the pandemic, and vaccines need time for development [17, 18]. There is an urgent need, therefore for drugs/drug combinations that exhibit not only the high antiviral activity but also protect the lungs, to limit the mortality rate[3, 10]. In the light of such a need, this review highlights the approved clinical trials to understand the trend towards addressing the immune storm.

2 COVID-19 Immune Storm Pathogenesis

One study confirmed that SARS-CoV-2 could escape the IFN-I response [19]. Similar to SARS-CoV, it can block host innate immune responses and thus disturbs the host antiviral defence mechanism [20, 21]. It also causes T cell exhaustion and accumulation of lymphocytes in the lungs, which causes lung injury [22–25]. SARS-CoV-2 enters inside the cell through angiotensin-converting enzyme-2 (ACE2) receptors [26]. The viral entry causes downregulation of ACE2 receptor, which ultimately disturbs the renin-angiotensin pathway and causes angiotensin II generation. This angiotensin II then causes vascular damage, cell damage, inflammation and leads to acute respiratory distress syndrome (ARDS) [3, 27, 28]. The viral genome inside cell activates various proinflammatory signalling pathways, which causes continuous upsurge of several cytokines leading towards Cytokine Storm. This storm constitutes high systemic levels of Interleukins (IL-1, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-17, IL-18), Interferons (IFN), Interferon Inducible protein (IP-10), Tumour necrosis factor (TNF-α), growth factors, Colony-stimulating factors, macrophage inflammatory protein (MIP1), monocyte chemoattractant protein (MCP), and Chemokines[6–9].

3 Clinical Trials Addressing COVID-19 Immune Storm

In this section, the summary of molecules considered for COVID-19 clinical trials is discussed (Fig 1) [Clinical Trial Search: www.clinicaltrials.gov]

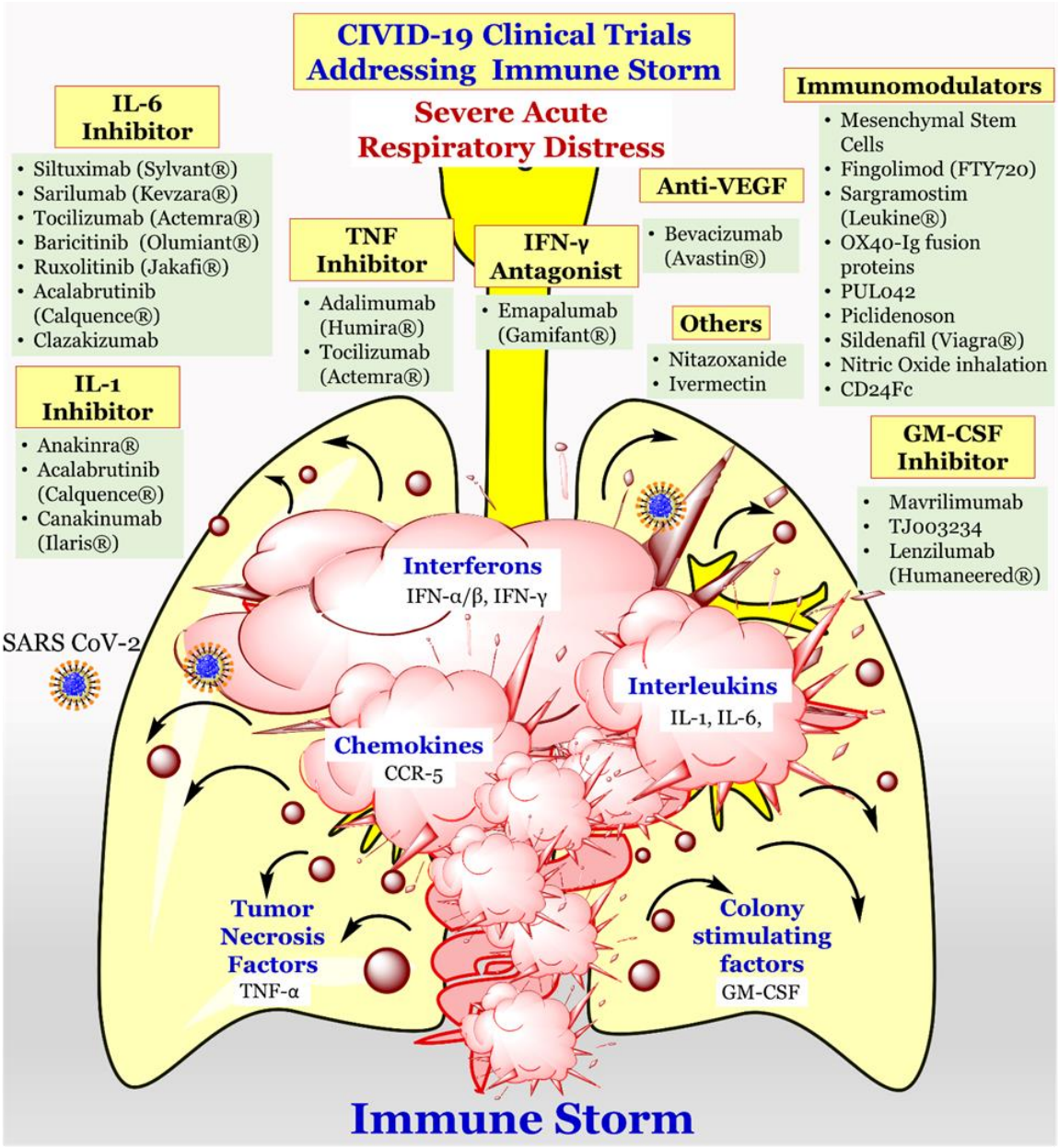

Figure 1: COVID-19 Clinical Trials Addressing Immune Storm

3.1 Anti-cytokine Therapeutics

The first randomized trial of Baricitinib (Olumiant®) identified as a potential antiviral with anti-cytokine properties, for COVID-19 in April, is an essential step in this direction. Ruxolitinib (Jakafi®) is an IL-6 inhibitor, while Acalabrutinib (Calquence®) is an IL-1 and IL-6 inhibitor [29]. Monoclonal antibodies (MAbs) which could provide such dual action are also under investigation. Tocilizumab (Actemra®) an IL-6, Janus kinase (JAK) and TNF inhibitor, which could curb inflammation and inhibit intracellular viral entry of SARS-CoV-2, has shown promise in patients with a so-called cytokine storm. The trial is approved in China for patients with elevated IL-6 and COVID-19 pneumonia [30]. Anti-CD147 humanized Meplazumab can target the virus and also prevent lung damage. It is known to block the invasion of host cells by SARS-CoV-2. A trial in China has revealed promise [31]. Other MAbs in clinical trials focus on protecting the lungs of severely ill patients by different mechanisms, on decreasing mortality. Siltuximab (Sylvant®), Clazakizumab, Sarilumab (Kevzara®) are IL-6 inhibitors [32],

Anakinra® and Canakinumab (Ilaris®) are IL-1 inhibitors [33], Adalimumab (Humira®) is a TNF inhibitor [34], while Emapalumab (Gamifant®) is a IFN gamma inhibitor [35]. GM-CSF inhibitors include Mavrilimumab, TJ003234, and Lenzilumab (Humaneered®) [36], while Leronlimab (PRO 140) is CCR5 antagonist [37]. Eculizumab (Soliris®) is reported to modulate the complement activity. Thus could help halt mortality, thereby providing the patient time to recover with supportive medical care [38]. Bevacizumab (Avastin®), an anti-VEGF drug, could facilitate suppression of pulmonary edema, and is being investigated for ALI/ARDS in COVID-19 [39].

3.2 Mesenchymal Stem Cells Therapy

Based on their anti-inflammatory and immunomodulatory properties in pulmonary diseases, Mesenchymal Stem cells, are being tested in several COVID-19 clinical trials [40]. Along with immunomodulatory activity, they can reclaim the pulmonary microenvironment, protect alveolar epithelial cells, avert pulmonary fibrosis, and cure lung dysfunction. However, significant challenges are associated with bringing stem cell therapy to the clinic [41, 42].

3.3 Immunomodulatory Agents

A number of immunomodulatory drugs are also enlisted in clinical trials against COVID-19 [39]. Thalidomide increases the secretion of anti-inflammatory interleukins, such as IL-12, activates natural killer cells, and alleviates TNFα to control lung inflammation in severe pneumonia [43]. Yet another immunomodulatory agent Fingolimod (FTY720) a sphingosine-1-phosphate receptor regulator is repositioned for COVID-19 to address the cytokine storm [44]. Sargramostim (Leukine®) the only FDA approved recombinant humanized granulocyte-macrophage colony-stimulating factor (rhuGM-CSF) can augment innate host defence and lungs health, and possibly reduce risk of secondary infections. Leukine® showed beneficial effects in patients with viral pneumonia [45]. Other drugs that can address hyper inflammation include OX40-Ig fusion proteins, PUL042 a Toll-like receptor agonist, Piclidenoson and Sildenafil (Viagra®), and Nitric oxide inhalation therapy [46, 47]. CD24Fc, a biological immunomodulatory agent, curbing the production of multiple inflammatory cytokines has entered phase III clinical trials against COVID-19 [48].

3.4 Combination of Antiviral and Anticytokine Therapeutics

The antiprotozoal Nitazoxanide [49] and anthelmintic Ivermectin [50] which demonstrated in vitro antiviral efficacy against SARS-CoV-2, are recently enrolled in the COVID-19 fight. Both drugs can inhibit the cytokine storm, and not just IL-6 but also other pro-inflammatory cytokines. Efforts to address the cytokine storm are evident in clinical trials which combine antivirals with drugs that can alleviate the inmmune storm as seen with Tocilizumab/HCQ/Azithromycin (NCT04332094; Spain), Remdesivir/HCQ (NCT04321616; Norway), Baricitinib/HCQ (NCT04373044; USA), Favipiravir/Tocilizumab (NCT04310228; China), and Favipiravir/Oseltamivir/HCQ (NCT04303299; Thailand) [51].

Clinicians are already treating patients with powerful anti-inflammatory drugs like steroids (methylprednisolone, dexamethasone), COX inhibitors (mesalamine, celecoxib), and seeing symptomatic relief [52]. However, corticosteroids might aggravate COVID-19 related lung injury and must be used with caution, immunosuppression may not always be beneficial in hyperinflammation, and may be contraindicated [53]. Since it is observed that the cytokine storm generally occurs in the second week of the infection, perhaps screening patients with severe COVID-19 for hyper inflammation using simple laboratory tests like decreasing platelet counts, increasing ferritin, or erythrocyte sedimentation rate at an appropriate time could provide an opportunity to thwart the immune storm [11, 54].

4 Conclusion

Clinical trials with a focus on decreasing mortality indeed harbinger a positive trend, as the world waits expectantly for a solution to this dreaded COVID-19 pandemic. Attempts need to be focused on Combination therapeutics to control the overall storm with rapid viral clearance and reduce severe side effects. Promising COVID-19 therapy is still awaiting.

5 Competing Interests

The author declares no competing financial interest

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