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Immune Response and Effectiveness of COVID-19 Therapies

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Abstract

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is highly pathogenic with relatively high mortality and morbidity. In addition to pneumonia, acute respiratory distress syndrome and microembolic disorder, a high proportion of patients with SARS-CoV-2 develop lymphopenia and cytokine storm disorder. This review explores the underlying mechanisms behind the pathogenesis of SARS-CoV-2, especially the immune mechanisms, which could be potentially used as therapeutic targets for the management of COVID-19.

Keywords: COVID-19, Immune response, Lymphopenia, cytokine storm syndrome

Introduction

Infection of SARS-CoV-2 in lungs results in stimulation of macrophages and monocytes, the release of cytokines, and adaptive immune responses [1,2]. In certain instances, this immune response can overcome viral infection and the patient recovers. However, in some instances, dysfunctional immune response will result in pneumonia and multiorgan failure [3]. Dysfunctional immune response in some patients activates a cytokine storm which results in widespread inflammation of the lungs. There is some evidence to show that lymphopenia and cytokine storm results in worse prognosis. Managing the inflammatory response due to dysfunctional immune response is found to be as crucial as controlling the infection. Medications that prevent viral infection as well as regulate defective immune defenses can potentially prevent development of multi-organ failure [4].

Virus entry

SARS-CoV-2 is a solitary strand RNA virus with four main basic proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins which infect human respiratory tract cells. . They enter cells by connecting the S protein to the human angiotensin-converting enzyme 2 (hACE2) following S protein priming by host serine protease TMPRSS2. Another receptor, CD147, is also associated with SARS-CoV-2 entry into the host cells[5]. The virus enters the cells by endocytosis after binding to its receptor and viral RNA is discharged into the cytosol. The virus utilizes the cell hardware for multiplication and is then removed from the cell through exocytosis. Patients with relatively high viral burdens tend to develop more severe COVID-19 disease. Furthermore, downregulation and shedding of hACE2 by viral S protein may disrupt the renin-angiotensin framework and increase vascular penetrability resulting in more severe lung injury [6].

Immune responses in COVID-19 disease

The immune responses induced by SARS-CoV-2 have two principal stages: the initial stage of protective response and the second stage of inflammatory response. COVID-19 causes an imbalance of the immune system and hyperactivation of the immune response. Adaptive immune

response is needed during the asymptomatic phase to get rid of infection [7]. Thus strategies related to improving the immune system are essential at this point. Patients must be in good health and favourable genetic makeup (e.g., HLA) that could contribute to the first line of defence against the virus [8,9]. However, if this response is not adequate, the virus will spread mainly to tissues with high angiotensin-converting enzyme 2 (ACE2) expression, such as intestines and kidneys. The infected cells can cause latent pulmonary inflammation which is principally mediated by pro-inflammatory macrophages and granulocytes. At this stage, strategies to reduce inflammation could be potentially helpful. Effective intervention at this stage will bring down the virus load and prevent hyperinflammation. In this regard, type-I Interferon (IFN) is crucial for early viral clearance to minimize viral replication, T-cell exhaustion, and cytokine storms (Figure.1)[10].

Innate Immune Responses in COVID-19

Role of cytokines and chemokines

SARS-CoV-2 stimulates the expression of numerous IFN-stimulated genes (ISGs) [11,12]. Such ISGs has the immunopathogenic capacity, through overexpression of the inflammatory genes. Type-I IFN is essential for the protection against viral diseases as it facilitates intracellular destruction of RNA and recovery from viral infections, induces tissue repair, and activates a continuous adaptive immune response [13]. Type-I IFN is delivered by plasmacytoid dendritic cells (pDCs) because they are less susceptible to active viral infection and virus-mediated cytotoxicity. They also release inflammatory cytokines, including tumor necrosis factor (TNF) α and IL-6 to control T cell reaction. PDCs disperse immune cells that serve as guardians and are activated after physical contact with virally infected cells as part of a process called interferogenic synapse. This results in the transition of pathogen-associated molecular pattern molecules (PAMPs) to Toll-like Receptor (TLR7) receptors in pDCs [14]. This synapse facilitates the development of type-I IFN at the infected area, therefore restricting viral replication and thereby potentially harmful systemic response. The reduced IFN type-I response is associated with higher COVID-19 severity. Hypercytokinemia in COVID-19 patients is related to the severity

of COVID-19 disease [15]. The most crucial cytokines in this regard are chemokines, such as neutrophil-recruiting chemokines and monocyte attractants [16].

Monocytes and macrophages in COVID-19

Bronchoalveolar fluid (BALFs) from individuals with severe COVID-19 showed an increased expression of CCL2 and CCL7, two most essential chemokines for the recruitment of CCR2 + monocytes. BALF analysis of single-cell RNA sequencing of moderate COVID-19 patients reported increased concentrations of mononuclear phagocytes [11]. In COVID-19 patients, there is an increased concentration of the group of macrophages that are enriched in tissue-repaired genes and promotes the generation of fibrosis, as found in liver cirrhosis. This suggests that the pathogenicity of invading macrophages may go farther than acute inflammation to fibrosis in ventilated patients [11,17]. Park et al. have referenced macrophages as a trojan horse in COVID-19. ACE2-expressive CD68+CD169 + macrophages were found in the splenic marginal zone and marginal sinuses of the lymph node which expresses nucleoprotein antigen SARS-CoV-2 and produces a significant rise in IL-6 concentrations. This suggests CD169 + macrophages can facilitate viral spread during SARS-CoV-2 disease, heighten inflammation and activation-induced lymphocytic cell death [18].

Role of complement in COVID-19

Complement is one of the essential factors helpful in shielding from pathogens. However, the excessive and deregulated response of complement can trigger injury to the tissue. Complement is both an integral part of the innate immune system of the pathogens, and a pro-inflammatory reaction orchestrator. In C3-lacking mice infected with SARS-CoV, there was a reduced pulmonary injury, lower neutrophil and monocyte infiltration, and diminished cytokine and chemokine levels in both the lungs and the sera. This suggests that the inactivation of C3 in the inflammatory lung may likewise reduce the severity of SARS-CoV-2 injury in tissues. The reduction in lung-invading neutrophils and the reduced intrapulmonary and plasma IL-6 levels observed in C3-deficient mice infected with SARS-CoV suggest the opportunities for utilizing C3

blockers with anti-IL-6 agents [19]. C3 inhibition can simultaneously block the development of C3a and C5a, as well as intrapulmonary activation of C3 and releasing of IL-6 from alveolar macrophages or other cells expressing C3a (C3aR) and C5a (C5aR) receptors, thereby limiting lung injury. Ex vivo experiments of whole blood infection with the receptor AMY-101, C3 inhibitor, have demonstrated that it will reduce IL-6 levels. The lung biopsy specimens from individuals with extreme COVID-19 revealed extensive activation of the complement, characterized by the production of C3a and deposition of C3-fragment. There was also a rise in the serum C5a levels[20]. Patients with an anti-C5a antibody showed better lung oxygenation and diminished inflammatory responses [21,22].

B cell immunity

In patients with COVID-19, B cell reactions emerge around the same time as T follicular helper cell responses, beginning about 1 week after the inception of symptoms. B cell response mainly occurs in patients with SARS-CoV disease for the most part against the nucleocapsid (N) antigen. Antibody responses to S protein were seen within 4–8 days of the beginning of symptoms. Neutralizing responses of antibodies that are immune to S antigen begin to increase by week 2, and by week 3 most patients develop neutralizing antibodies, however, doesn't appear to create durable SARS-CoV-2 antibodies [23]. The neutralization of the virus is viewed as a fundamental mode of action for antibodies, although the specific titer of antibodies remains unresolved[10,23].

T cell immunity

CD8+T cells are expected to attack and destroy virus-infected cells specifically, while CD4+T cells are essential to activate both CD8+T cells and B cells. CD4 + T cells likewise produce cytokines to activate immune cells [10]. It seems that SARS-CoV-2 can cause a protective immune response mediated by the T-lymphocyte, in comparison to other CoVs. Patients with COVID-19 has increased monocytes and T cells in the lungs and a significant reduction in the amount of CD4 + and CD8+T cells in the peripheral blood due to insufficient activation as seen

by elevated HLA-DR and CD38 double-positive fractions [9]. Such outcomes demonstrate that T cells are attracted to monitor virus infection away from the blood and towards the affected region. Likewise, the intense stage response in patients with SARS-CoV is associated with a significant reduction in CD4 + T and CD8 + T cells. Albeit additional precautionary measures ought to be taken in patients determined to have SARS-CoV-2 who are hospitalized with lymphopenia, cellular immune reactions also appear to be reduced. A cellular immune response efficiently destroys SARS-CoV-2-in the safest-case scenario without any (or mild) clinical signs of infection though, this is not always the way, as the virus also induces immunosuppression that reduces and sometimes overcomes the host 's defense [8].

Proinflammatory Th17 lymphocytes and disease progression

Xu et al. observed that in patients with severe COVID-19 infection had high concentrations of CCR4+CCR6 + TH17 cells in the peripheral blood, thereby indicating a TH17 type cytokine storm. This research has demonstrated a crucial role of Th17 inflammatory response in the pathogenesis of COVID19 pneumonia. This involves releasing essential cytokines such as IL-17 and other factors to intensify viral immunopathogenesis by down-regulating Treg cells, facilitating neutrophil relocation, while likewise inciting Th2 reactions simultaneously. IL-17 can induce severe eosinophilic reactions and allergic disease, to some degree, extravasation into the lungs [24]. Most recent outcomes show that the SARS N protein is a potential inducer of IL-6 reactions that could intervene in coronavirus lung pathology [24,25].

Lymphopenia and COVID-19

Lymphopenia is one of the most noteworthy markers of COVID-19. All lymphocyte subsets, which incorporate CD4 + and CD8 + cytotoxic T cells, natural killer (NK) cells, memory and regulatory T cells along with B cells, have been diminished in COVID-19 disease. Lower levels of lymphocytes are strongly related to the seriousness of disease [26]. T cell numbers in inversely related with serum levels of IL-6, IL-10, and TNF-α and elevated levels of

programmed cell death protein 1(PD-1) or T-cell immunoglobulin (Ig) and mucin domain-containing molecule-3 (TIM-3) [27].

Evidence suggests that SARS-CoV-2 targets T cells by receptor-dependent, S-protein-mediated membrane fusion. T cells have a low level of ACE2 expression, suggesting both an alternate receptor and a strong S-sensitivity to the protein. Invasion of T cells is abortive, showing that replication of SARS-CoV-2 inside T cells is not possible, yet causes cell death instead. Second, impaired lung macrophages or epithelial cells (in the first stage of hypercytokinemia) build up a variety of inhibitory cytokines, particularly TNF-α causing T cell apoptosis, IL-10 restraining T cell expansion, and Type-I IFN in the guideline of lymphocyte distribution. Thirdly, lymphopenia was accepted to be the result of immune cell redistribution, with lymphocytes proliferating in the lungs or lymphoid glands [28]. Immunohistochemical staining of spleen and lymph nodes has shown decreased levels of CD4 + and CD8 + T cells. Finally, metabolic molecules generated by metabolic disorders such as lactic acidosis are blocking lymphocytes. The severe type of COVID-19 patients had high blood lactic acid levels which can limit lymphocyte expansion [29].

Exhausted T lymphocytes, associated with COVID-19 disease severity

The immune system homeostasis represents a vital role in preventing COVID-19 pneumonia [28]. Yong-Tang Zheng provides substantial differences in the levels of exhaustion modules between the three target groups (healthy, mild, severe), in particular PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and T-cell immunoglobulin and ITIM domain (TIGIT), and functional modules, such as interferon-gamma (IFN-γ), TNF-α, and IL-2. In the severe group, the amount of multi-functional CD4 + T cells declined significantly relative to the healthy control and mild group, whereas the number of non-functional subgroups (IFN −TNF-α−IL-2−) increased. The disturbance of CD4 + T cells could also have predisposed COVID-19 patients to severe diseases [28]. Prior research from Guang Chen et al. demonstrated that the Treg (CD4 + CD25 + CD127low+) and CD45RA+ Treg rates lowered in practically every severe and moderate case, with CD45RA+ Treg falling more significantly in severe cases than in moderate. It should be remembered that in certain patients with extreme and moderate COVID-19, CD4+T, CD8+T, and NK cells, levels of IFN-γ secretion are reduced [30]. Early IFN response is fundamental for an effective T-cell reaction; a delayed IFN response may reduce

T-cell expansion or T-cell departure from lymphoid organs; it might bring about T-cell depletion and cell death. In patients with extreme COVID-19, the lung damage correlated with cytokine release syndrome suggesting an expected failure to trigger opportune immunosuppressive systems. Even so, regulatory T (Treg) cell counts have been suggested to be associated inversely with the seriousness of the disease in patients with COVID-19[15]. IFNs are viewed as significant controllers for Treg cell development. Meijuan Zheng et al. showed that the total amount of NK and CD8 + T cells diminished significantly in patients with SARS-CoV-2 disease. With the increased production of NKG2A in patients with COVID-19, the activity of the NK and CD8 + T cells has been reduced. Interestingly, the amount of NK and CD8 + T cells with decreased NKG2A expression has been increased in patients convalescing following treatment [31]. Consequently, infection with SARS-CoV-2 can destroy antiviral immunity rapidly. Hence, expression of SARS-CoV-2-induced NKG2A in COVID-19 patients with serious pulmonary inflammation that associate with an initial phase of functional exhaustion of cytotoxic lymphocytes, which may end in the progression of the disease. Persistent infection and cancer have been found to have immune-inhibitory "checkpoint" receptors that lead to dysfunction of NK and T cells. It is important to take note of that checkpoint inhibitors, for example, anti-PD-1 and anti-TIGIT help in the case of chronic infection and cancer and revitalize depleted T or NK cell responses. NKG2A is believed to be another inhibitory molecule on the immune-checkpoint blockade. Such results show the importance of improving the immune response of NK cells and CTLs at the underlying phase of SARS-CoV-2, and maintaining strategies for avoiding cytotoxic lymphocyte exhaustion[32,33].

Cytokine storm, a lethal phase

Cytokine release syndrome (CRS) tends to involve severely affected individuals. Considering that lymphocytopenia is frequently seen in severe COVID-19 patients, leukocytes other than T cells will mediate the CRS induced by the SARS-CoV-2 virus. Cytokines are highly significant for COVID-19 pathophysiology; although some are protective (type-I interferon, IL-7), others seem hazardous (IL-1β, IL-6, and TNF-α), mainly in cytokine storms. This cytokine storm appears to be more likely to occur by a combination of the defective or delayed first line of protection, accompanied by chronic hypercytokinemia and an abnormal T cell response [4]. This tends to result in incomplete removal of apoptotic cells or affected macrophages, an increase in viral

proliferation and expansion, accompanied by an IL-18 / IFN-γ activating macrophages, leading to massive secretion of cytokines, hemophagocytosis, coagulopathy, and ARDS. By examining more closely the immunopathology of SARS-CoV2-related ARDS, two mechanisms of immune failure have been identified, as COVID-19 worsens: (i) an IL-1β-driven macrophage activation syndrome (ii) immune dysregulation process guided by IL-6 [34]. The latter has been depicted by a combination of hypercytokinemia, immunoparalysis (CD14 monocytes with reduced HLA-DR molecules), and generalized lymphopenia (such as CD4 + and NK cells). Nonetheless, the blockade of IL-6 tocilizumab preserved HLA-DR expression on CD14 monocytes and increased the number of circulating lymphocytes. Cytokine storms could cause ARDS, severe cardiac attack, and secondary infection, culminating in systemic sepsis, and multisystem failure that may result in death (Figure 2)[17,35].

Coronavirus treatments: Which therapies could be effective for COVID-19?

Apoptosis inhibitors

Currently, there is no definite treatment protocol developed for COVID-19. Traditional therapies are mostly symptomatic. Evidence shows that lymphopenia is generally identical in SARS, respiratory syncytial virus infection, measles, and sepsis. The main triggers of sepsis and measles are apoptosis, which is expected to promote lymphopenia . For example, apoptosis inhibitors ameliorate inflammation and avoid mortality in sepsis models. These results have given us valuable insights concerning SARS patients [36]. The proliferation of lymphocytes or targeting drugs for apoptosis (PD1 / PD-L1 inhibitors) may forestall lymphopenia or recuperate lymphocyte in severe COVID-19 patients. Restoration of the leukomonocyte populations of COVID-19 hospitalized patients appears to be associated with viral clearance. By comparing the numbers of leukomonocytes in COVID-19 patients at different periods of the sicknesses, research showed that CD3 +, CD4 +, CD8+T cells, and B cells appear to play significant roles in viral clearance. This has been proposed that stabilization of the leukomonocyte levels may be

used as a guide for releasing and discharging patients in the COVID-19 diagnostic guidelines[37,38].

Convalescent plasma and COVID-19

Immune or convalescent plasma is plasma obtained from patients, after recovering from infection and antibody production. As can be shown, there are also many issues concerning convalescent plasma or immunoglobulins, regardless of their wide approval. They had been used to increase the recovery rate of patients with SARS, human immunodeficiency virus (HIV), severe H1N1 influenza who condition worsened despite the treatment with pulsed methylprednisolone [39]. One possible rationale behind the viability of convalescent plasma therapy might be the antibodies could forestall viremia and provide passive immunity[40]. An in vivo examination likewise found that these neutralizer activities were not only restricted for virus clearance and preventing new invasion but also increased infected cell clearance. Convalescent plasma, acquired from recovered COVID-19 patients with humoral immunity to the virus, has a large amount of neutralizing antibodies which could neutralize SARS-CoV-2 and eliminating the pathogen from the blood circulation and pulmonary tissues. The outcome might be particularly advantageous for individuals with severe or life-threatening COVID-19, and by using this medication reduce the length or extent of the illness. The neutralization antibody titers correlate with the numbers of virus-specific T cells. Given the unavailability of data of SARS-CoV-2 fundamental biology, particularly virus heterogeneity and mutation, locally acquired plasma that better represents the circulating virus in the community may be a viable treatment choice. But we need appropriate donor selection with significantly higher serum titers of antibody that are neutralizing [41].

Intravenous Immunoglobulin (IVIG)

Individuals with debilitated immune systems, in general, have a greater danger of the related complications of COVID-19. Coupled with antiviral medications, IVIG-utilizing immunotherapy, can be utilized to control or eliminate COVID-19 and improve immune response to this virus. IVIG antibodies have two fundamental parts: the F (ab') 2 piece, which is essential for the

recognition of antigens, and the crystallizable fragment (Fc), which is essential for activating the immune response by communicating with B-cells as well as other innate human immune cells with Fcγ receptors. The Fc section additionally plays a pivotal capacity in enacting the complement and evacuating the microorganisms. Elective treatment may, for the most part, be given through the enemy of COVID-19 immunotherapy with safe IVIG as an adjunctive prescription combined with antivirals. This tolerant IVIG antibodies acquired from healing patients would be successful against COVID-19 by reinforcing the immune response reaction in the recently tainted patients. Albeit no COVID-19 immunization is authoritatively accessible, the mix of insusceptible IVIG antibodies with antiviral medications gives short-and medium-term strategies against COVID-19[42,43].

Mesenchymal stem cells (MSCs) therapy

MSCs can effectively affect halting or balancing the cytokine storm because of their potential immunomodulatory capacity [44]. MSCs have been normally utilized in cell therapy. For several clinical trials, protection and efficacy have been set up, particularly for immune-mediated inflammatory disorders. MSCs play out to have an advantage in two areas, including in terms of immunomodulatory activity and differentiation [45].

MSCs has essential immune regulatory functions principally by dendritic cells to reverse the lymphocyte subsets. The gene expression analysis exhibits that MSCs were ACE2-and TMPRSS2-recommending that MSCs are released from COVID-19 contamination. In patients with COVID-19 pneumonia, particularly in patients with severe disease, the intravenous transplantation of MSCs could, therefore, be a safe and effective therapy. MSC therapy can prevent immune system overactivation and facilitate endogenous repair. Upon reaching the human body, parts of the MSCs accumulate in the lung through intravenous infusion, which will improve the pulmonary microenvironment, protect alveolar epithelial cells, prevent pulmonary fibrosis, and reinforce lung function. [46]. The serum levels of pro-inflammatory cytokines and chemokines were significantly reduced because of their remarkable immunosuppression capacity, which enrolled less mononuclear / macrophages to susceptible lungs while at the same time stimulating more controlling dendritic cells into the inflammatory tissue. The upgraded IL-10 and vascular endothelial growth factor (VEGF) permitted recovery of the lung [47].

Elia Bari et al. demonstrated that mesenchymal stem cell secretome might be a potential therapeutic solution to COVID-19 pneumonia treatment owing to a wide assortment of pharmacological activities, including anti-inflammatory, immunomodulatory, regenerative, pro-angiogenic, and anti-fibrotic activities. The evidence shows that MSCs are acting by a paracrine fashion. These cells can be used as reliable drug stores releasing secretome, biologically active compounds. MSC-secretome comprises of all soluble proteins, including a wide variety of micro- and nano-sized extracellular vesicles (EVs), cytokines, chemokines, and growth factors also stimulating endogenous stem cells [48]. Upon intravenous injection, the secretome persisted throughout the circulation, which distributed across the lungs. There, the secretomes spread across the tissues, allowing immune modulation, inflammatory reduction, and increased infectious elimination. Importantly, the usage of the secretome in therapy has several benefits compared with MSCs. Secretomes are typically more secure than cells; they lose the possibility to deliver endogenous tumors since they can't self-repeat, have low immunogenicity, and lead to a decreased development of antibodies when treated intravenously [49].

Cytokine-based interventions

Type-I interferon

Patient immune status will establish the efficacy of the COVID-19 treatments. Emerging data indicate that SARS-CoV-2 can activate a range of immune processes, allowing immunosuppressive agents in clinical trials to be beneficial in certain patients but dangerous to others. Although the primary function of type-I IFN in antiviral behavior, IFN-α and IFN-β have recognized as potentially beneficial anti-SARS-CoV-2 medications. Type-I IFN ought to be given as ahead of schedule as following diagnosis (ideally before the initiation of manifestations), however not in the late stage because of likely disturbance to tissues. Until peak viral replication, early IFN therapy saved mice from the fatal SARS-CoV or MERS-CoV challenge, while late IFN therapy disrupted viral clearance and exacerbated immunopathology [14,50].

GM-CSF

The immune state will once again determine the effectiveness of COVID-19 therapies. GM-CSF will perform the primary controlling function in cytokine production and myeloid cell-induced hyperinflammation. Besides, as referenced before, the late phases of COVID-19 will most likely be controlled not by forceful viral replication and cell lysis, but by immunopathology, especially myeloid cell immunopathology. In this manner, GM-CSF's putative pathogenic function in immune hyperactivation through several studies offers a reason for starting the continuous clinical investigations using GM-CSF-focusing on mAbs for treating COVID-19 patients. The reasoning and the risks for both therapeutic administration and inhibition of GM-CSF in COVID-19 have been established. The use of GM-CSF in COVID-19 patients may improve lung capacity by supporting the alveolar wall and enhancing viral removal; therefore, be of positive advantage in early COVID-19 phases. Conversely, GM-CSF, or GM-CSFR inhibition can be a protective treatment for cytokine storm and myeloid cell tissue invasion. As it may influence the release of several pro-inflammatory cytokines and chemokines by myeloid cells, the GM-CSF approach may have noteworthy immunomodulatory implications [51].

Anti-cytokine interventions

Interleukin-6 inhibition

Inflammation caused by SARS-COV2 results in a dose-dependent release of IL-6 from bronchial epithelial cells. In patients with SARS-CoV-2 infection, alterations in IL-6 levels could potentially be a crucial mediator when severe systemic inflammatory reactions occur. IL-6 is involved in two particular pathways in SARS-CoV-2 pathology; the classic (anti-inflammatory) and the trans-signal (pro-inflammatory). The classic signaling pathway (induced by the IL-6 receptor's membrane-bound variant, mIL6R) which is thought to be the anti-inflammatory and trans-signaling pathway (induced by the IL-6 receptor's soluble form, sIL6-R) which is presumed to have a pro-inflammatory role. Tocilizumab inhibits both, SGP130Fc hinders just the trans-signaling pathway while Ruxolitinib and Baricitinib inhibit the JAK/STAT pathway activated by IL-6. This shows focusing on just the SGP130Fc pro-inflammatory pathway might be a more promising option than focusing on IL-6 pathway inhibitors, for example, tocilizumab [25,52].

TNF inhibitors

As referenced before, SARS-CoV infection is related to a downregulation of ACE2 expression combined with activation of the renin-angiotensin system liable for the lung injury. Besides, the viral spike protein will cause a TNF-α-converting enzyme (TACE)-dependent shedding of the ectodomain ACE2, which is fundamental for the viral entry into the cell. It has been speculated that the use of TNF inhibitors may be efficient in lowering both SARS-CoV2 infection and the resulting organ damage. Subsequently, the Chinese Clinical Trial Registry (ChiCTR2000030089) has, as of late announced an investigation of adalimumab in patients with COVID-19 infection [53].

Targeting chemokine receptors

In patients with COVID-19, a significant rise of CCL2 and CCL3 expression in macrophages was seen alongside the diminished expression of CCR1, the receptor for both chemokines. Since binding CCL2 or CCL3 to CCR1, CCR2 or CCR5 causes monocyte recruitment into the lung parenchyma with eventual differentiation into inflammatory macrophages and resulting recruitment and activation of multiple immune cells, and epithelial injury, CCR1, CCR2, and CCR5 could be potent anti-inflammatory targets in COVID-19. HIV and other viral diseases target the CCR2 / CCL2 axis. The evidence did not, however, verify the production of CCR2 in the respiratory tract of COVID-19 patients (possibly due to its accelerated inhibition in monocytes as they leave the circulation and reach tissues), keeping CCR1 and CCR5 as potential targets [11,16].

Non-targeted therapies

Corticosteroids

Corticosteroids are effective cytokine inhibitors that act by various pathways but essentially through inhibiting the transcription factor of NF-κB. These are the foundation of the therapies for autoimmune and autoinflammatory disorders with cytokine storms.

Dexamethasone is a medication that has been utilized in a variety of treatments since the 1960s to minimize inflammation involving autoimmune diseases and certain cancers. According to early findings discussed with WHO, dexamethasone was found to reduce mortality by about one-third for patients on ventilators, and mortality was decreased by around one-fifth for patients needing only oxygen [54].

Remdesivir

Remdesivir, a nucleotide-analog prodrug that prevents polymerases of viral RNA, has demonstrated efficacy against SARS-CoV-2 in vitro. Remdesivir is intracellularly metabolized to an analog of adenosine triphosphate that suppresses viral RNA polymerases. Remdesivir has broad actions on a variety of viral agents, including filoviruses (Ebola) and coronaviruses (SARS-CoV and MERS-CoV). Also, in vitro assays confirms remdesivir have an action against SARS-CoV-2 [55]. The U.S. Food and Drug Administration provided an urgent usage permit for the investigational antiviral medication remdesivir for the care of suspected or laboratory-affirmed COVID-19 in hospitalized adults and children with serious illness. One study showed remdesvir reduce the period for the rehabilitation in some instances of COVID-19 [56].

Conclusion

The occurrence and development of SARS-CoV-2 depend on the interaction between virus infection and the immune system. Dysregulation of the immune system in COVID-19 patients can contribute to serious illness. Dysregulation of the immune system such as lymphopenia and cytokine storm could be a crucial factor related to the severity of COVID-19. Decreased T lymphocytes and elevated cytokines could potentially serve as COVID-19 prognostic markers. Antiviral or immunomodulatory therapies have not shown to be useful for the treatment of

COVID-19 yet. In clinical trials, interventions (if acceptable) could be timed based on immune response; for example, antivirals and immune boosters should be started soon after the start of symptoms, whereas immunosuppressants should be delivered at the very beginning of the cytokine storm.

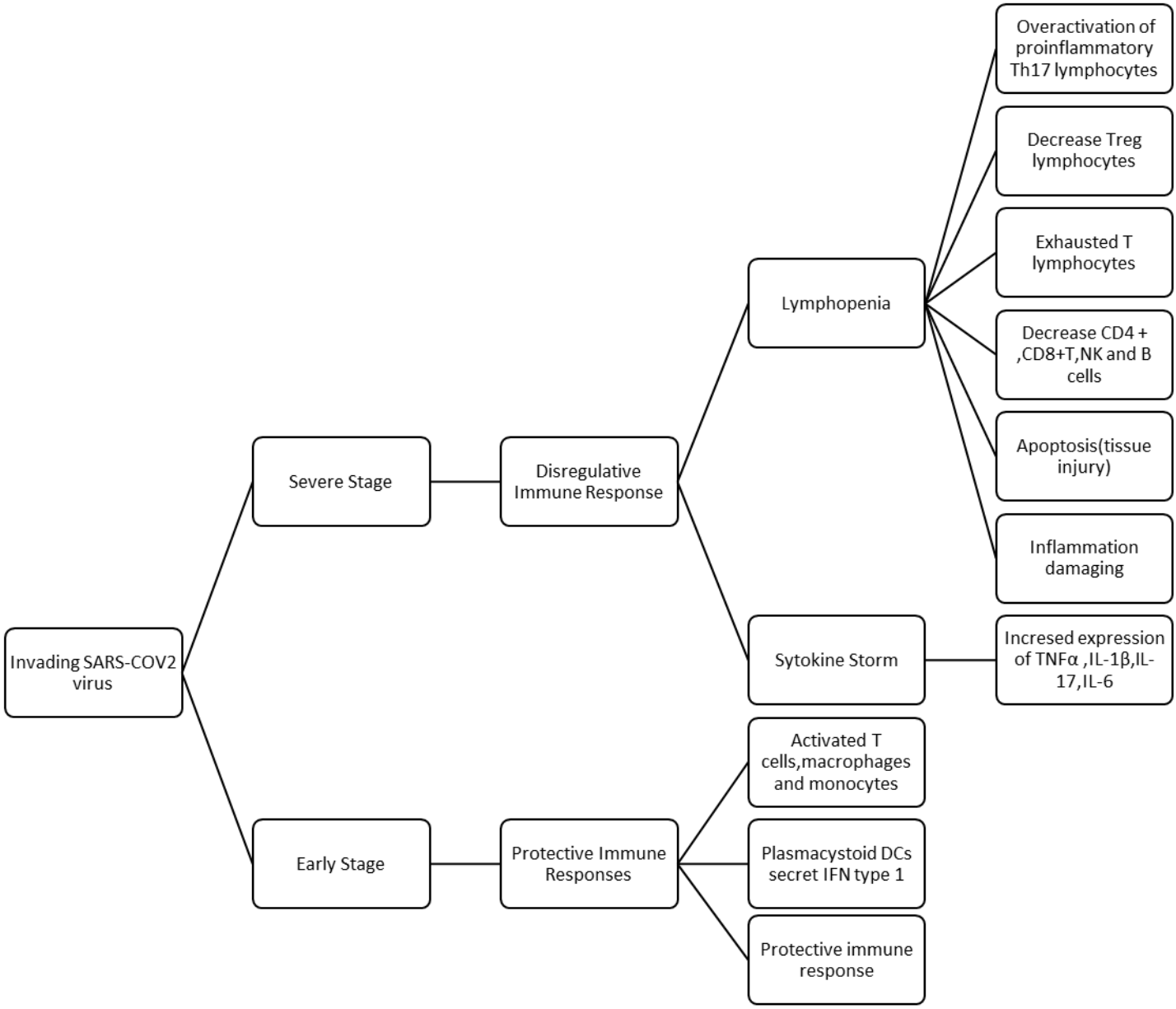
Invading SARS-COV2 virus
Severe Stage
Disregulative Immune Response
Lymphopenia
Overactivation of proinflammatory Th17 lymphocytes
Decrease Treg lymphocytes
Exhausted T lymphocytes
Decrease CD4 + ,CD8+T,NK and B cells
Apoptosis(tissue injury)
Inflammation damaging
Sytokine Storm
Incresed expression of TNFα ,IL-1β,IL-17,IL-6
Early Stage
Protective Immune Responses
Activated T cells,macrophages and monocytes
Plasmacystoid DCs secret IFN type 1
Protective immune response

Figure 1: The invading COVID-19 virus induces non-serious symptoms during the incubation period, which elicits defensive immune responses. Successful clearance of viruses relies on the state of safety. If the affected individual's general health condition does not remove the infection, then the patient reaches the severe stage of an intense and harmful inflammatory reaction, particularly in the lungs.

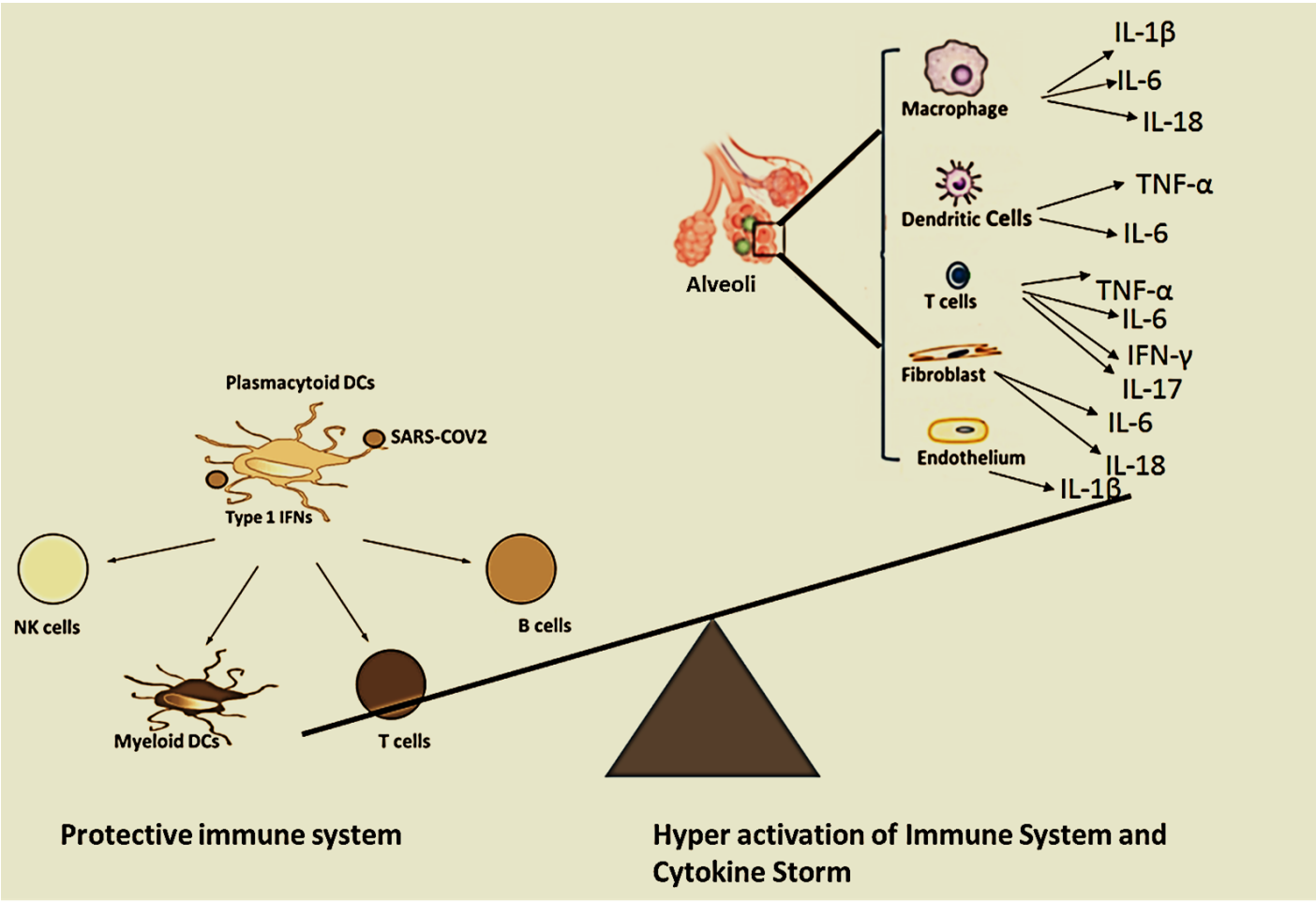

Figure2: The immune responses mediated by SARS-CoV-2 are two main phases: the Protective immune step, and the Second damage processing step done by inflammation and cytokine storm.

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