Potential Agents Therapy Strategies Rounding up Immunopathology of COVID-19

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Abstract

The novel coronavirus 2019 (COVID-19) pandemic, which has resulted in nearly 700 thousand deaths, is rapidly spreading across the globe despite drastic public and personal health measures. As showed in Figure 1, the direct attack from SARS-CoV-2 and hyperactivated immune response contribute to the progress and deterioration of COVID-19 infection. Eliminating virus and blocking cytokine are important check-points of COVID-19 therapy. Based on our successful experience in Wuhan and current progress of the therapeutic strategies, several agents targeting immunopathology have displayed marked effects on COVID-19 patients, including interferons, immunoglobulin, and glucocorticoid, etc. Here, we want to review the novel progress of therapy strategies related to immunopathology and share our Wuhan experience with the colleagues in the field by reviewing the underlying the pharmacologic mechanisms of these agents.

Potential Agents Therapy Strategies Rounding up Immunopathology of COVID-19

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Conflicts of interest

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[Abstract] : The novel coronavirus 2019 (COVID-19) pandemic, which has resulted in nearly 800 thousand deaths, is rapidly spreading across the globe despite drastic public and personal health measures. As showed in Figure 1, the direct attack from SARS-CoV-2 and hyperactivated immune response contribute to the progress and deterioration of COVID-19 infection. Eliminating virus and blocking cytokine are important check-points of COVID-19 therapy. Based on our successful experience in Wuhan and current progress of the therapeutic strategies, several agents targeting immunopathology have displayed marked effects on COVID-19 patients, including interferons, immunoglobulin, and glucocorticoid, etc. Here, we want to review the novel progress of therapy strategies related to immunopathology and share our Wuhan experience with the colleagues in the field by reviewing the underlying the pharmacologic mechanisms of these agents.

[keyword] : immunotherapy; cytokines; corticosteroids; inflammation;monoclonal antibodies;

The novel coronavirus 2019 (COVID-19) pandemic is rapidly spreading across the globe despite drastic public and personal health measures. Until this report is written, COVID-19 has resulted in nearly 800 thousand deaths. The lack of potent antiviral countermeasures is one of the main reasons of this rapid outbreak. Therefore, it is urgent to seek effective agents to rescue more patients with COVID-19. Based on our successful experience in Wuhan and current progress of the therapeutic strategies, several agents targeting immunopathology in COVID-19 have displayed marked therapeutic effects on COVID-19 patients, including interferons, immunoglobulin, and glucocorticoid, etc.

The direct attack from severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) and hyperactivated immune response contribute to the progress and deterioration of COVID-19 infection [1, 2]. As showed in Figure 1, the decrease of lymphocytes (lymphopenia) caused by direct attack of SARS-CoV-2, including T cells, B cells, and natural killer (NK) cells, is thought to be associated with the delay for virus elimination and increased mortality[3-5]. It was reported that plasmatic T lymphocyte count 0.8×10^9/L, 1.0×10^9 /L and 1.1×10^9 /L corresponded to the mortality of 4.6%, 1.9% and 0.9%, respectively [6]. Meanwhile, hyperactivated immune response was indicated by high proportions of HLA-DR (CD4+ 3.47%) and CD38 (CD8+ 39.4%) double-positive fractions [3]. In turn, these trigger the cytokine storm by producing large amount of cytokines including IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G- CSF, GM- CSF, IP10, MCP1, and MIP1α,*etc.* [7]. IL-6 is a crucial protagonist for the development of cytokine storm with increased level and lasted for longer duration in severe patients [5, 8, 9], and further promotes a waterfall-like release of inflammatory mediators [7, 10, 11].Besides, monocytes and neutrophils could also involve in cytokines releasing of IL-1β, IL-6, and TNF-α in severe disease [12, 13]. Eventually, cytokine storm leads to the multiple organs dysfunction syndrome (MODS) and death. Thus, the agents rounding up the immunopathology have become major treatment strategies against COVID-19 (Figure 1).

Type I interferons (IFNs), including interferon-α and interferon-β, help to eliminate the SARS-CoV-2 by improving the phagocytic function of macrophages and the immune activity of T lymphocytes, or by inducing the synthesis of antiviral protein (AVP) of host cells. Type I IFNs have emerged as potentially effective drugs against SARS-CoV-2 [14]. Zhou and colleagues [15] found IFN-α2b, with or without oral umifenovir hydrochloride, significantly reduced the duration of detectable virus in the upper respiratory tract in 53 moderate COVID-19 patients than those who used umifenovir hydrochloride only (21.1 days *vs.* 27.9 days), and over the time period day 12 to day 42 (from onset of symptoms), patients without treatment of IFN-α2b had higher IL-6 levels (by 33.5 pg/mL) and higher CRP levels (by 25.7 mg/L) than the patients treated with IFN-α2b. Chinese guidelines listed interferon-α as an alternative for antivirus combination therapy [16]. Interferon-β has also been recommended at the early stage of COVID-19 [17] . A multicenter study reported that the antivirus therapy combined with Interferon-β (subcutaneous injection of interferon beta-1b 8 million international units on alternate days) had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4·37 [95% CI 1·86–10·24], p=0·0010), and days of hospital stay in 86 patients with

mild to moderate COVID-19 (9.0 days [7.0–13.0] vs 14.5 days [9.3–16.0]; HR 2.72[1.2–6.13], p=0·016)[18]. A further study should be conducted to explore the effects of IFNs on severe and critical patients who also have obvious immunosuppression. A recent study demonstrated that the severe and critical patients, who were characterized by no interferon-β and low interferon-α production and activity, were often associated with a persistent blood viral load and an exacerbated inflammatory response. This appears to suggest that type-I interferons deficiency in the blood might be an important marker of severe COVID-19 and provide a rationale for combined therapeutic approaches [19]. Besides, IFN III (IFN-λ) imposes the antivirus effects via binding and inducing signaling through the heterodimeric IFN-λ receptor (IFNLR). However, IFN-λ has been showed to increase susceptibility to pneumonia caused by methicillin resistant Staphylococcus aureus in response to influenza virus infection in mice[20]. Broggi and co-workers [21] showed that IFN-λ induced barrier damage of airway epithelium in mice and the amounts of IFN-λmessenger RNA (mRNA) from bronchoalveolar lavage fluid and naso-oropharyngeal samples were correlated with disease morbidity in SARS-CoV-2–positive patients. Thus, it is needed to outweigh the benefit of a deficient epithelial IFN-l response in the lungs for SARS-CoV-2 infection.

The use of commercial intravenous γ-Immunoglobulin, convalescent plasma, and protective monoclonal antibodies is a potential antiviral immunotherapy for COVID-19[22, 23]. (1) The commercial intravenous γ-Immunoglobulin (IVIG) exerts non-specific antiviral effect, and been used as an adjunctive drug in the treatment of severe pneumonia caused by influenza[24]. In critically ill patients with COVID-19, the innate immunity is not enough to limit virus, and the adaptive immune usually establishes about 10 days after the onset. Thus, injection of IVIG may help to eliminate the virus partially. Cao and colleagues investigated 58 cases of severe or critical illness due to COVID-19 who received intravenous immunoglobulin at 20 g/day when the absolute lymphocyte count fell to $< 0.5 \times 10\ 9$ /L. The results showed that treatment with IVIG within 48 h of admission reduced duration of ventilator use, hospital and ICU length of stay, and ultimately improving 28-day mortality. Currently, the pool of recovered patients with COVID-19 increases globally, immunoglobulin from these population will contain specific antibodies to SARS-CoV-2. (2) The convalescent plasma containing neutralizing antibodies could reduce mortality in patients with severe influenza A, MERS-CoV and SARS-CoV infections[25],which meant immunotherapeutic potential of convalescent plasma for patients with COVID-19 for virological and clinical characteristics among SARS, MERS, and COVID-19 were comparable[26]. Duan and colleagues [27] reported that 200ml of convalescent plasma brought clinical improvement of oxygen saturation, lymphopenia, and CT scan in 10 patients with severe COVID-19. With the lack of prospective random controlled trials, the optimal dose and treatment time point, as well as the therapeutic indications of convalescent blood products in COVID-19 remain uncertain. (3) The specific human monoclonal antibody CR3022 of SARS-CoV can also bind to the receptor binding domain of SARS-CoV-2 effectively, suggesting that the antibody may become a potential therapeutic choice [28]. It is cautious for the use in the patients with antibody-dependent enhancement (ADE) of SARS-CoV-2 infection, which may associate with worse outcome [29, 30]. ADE has been observed in various viral infections, characterized as increased IgG response and a higher titer of total antibodies, leading to antibody-mediated enhancement of viral entry and induction of a severe inflammatory response.

Glucocorticoid (GC) can suppress the binding of NF-κB to GC response elements on DNA directly, reducing the expression of cytokines like IL-6, TNF-α, and IL-1β, etc. It can also activate the inhibitory nuclear factor IκBα, initiating the transcription of anti-inflammatory factor IL-10 [31]. It is reported that GC can inhibit pulmonary inflammation of acute respiratory distress syndrome (ARDS) with strong inflammatory response effectively [32]. Medium-to-low-dose glucocorticoids may play a protective role in the respiratory and digestive systems by activating ACE2 and suppressing cytokine storm in severe or critical patients with COVID-19[33]. A recent randomized clinical trial showed that dexamethasone reduced 28-day mortality among the patients with COVID-19 receiving invasive mechanical ventilation or oxygen at randomization [34]. In this study, 2,104 patients allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care, Dexamethasone(6 mg, once daily, oral or intravenous for up to 10 days) reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%), but did not

reduce mortality in patients not receiving respiratory support at randomization (17.0% vs.13.2%, p=0.14). However, the immunosuppressed effect of GC should be considered for it may bring an unfavorable side for delaying virus clearance and increasing risk of secondly infection. Thus, a suitable GC administration juncture timepoint might be subjected to further exploration to prevent the progression of ARDS. Based on Chinese experience, it is recommended when the onset of cytokine storm was indicated by increased resting respiratory rate ($>$ 30 breaths/minute), ongoing deterioration in oxygenation index, multi-lobular progression ($>$ 50%) on imaging within 48 h, consistent lymphopenia, etc.[35, 36].

Tocilizumab (TCZ), a humanized IgG1k monoclonal antibody, can specifically bind soluble or membrane-type IL-6 receptors (Sil-6R and Mil-6R), and has been widely used in the treatment of autoimmune diseases such as rheumatoid. It was found to reduce the 28-day mortality of patients with sepsis (IL-6$>$1000 pg/ml) [37]. For COVID-19 infection, clinical studies have shown that serum levels of inflammatory mediators in severe patients are significantly higher than those in common patients. Excessive inflammation response can trigger cytokine storms and cause damage to multiple target organs[12]. As IL-6 played major role in the development of cytokine storm, and is an indicator of poor outcome of severe patients with COVID-19, Tocilizumab was recommended to the patients with COVID-19 who have elevated IL-6 levels to suppress the cytokine storm[9]. Thus, the efficacy of tocilizumab could be expected in severe and critical patients. A case report showed [38] that in 42-year-old male suffering from respiratory failure due to SARS-CoV-2 infection, after 4 days of TCZ treatment, the CRP decreased from 225 to 33 mg/L and ultimately clinically fully recovered. A retrospective study analyzing 15 cases of COVID-19 by Luo and colleagues found that Tocilizumab deceased the plasm level of CRP and IL-6 in 10 patients[39]. A clinical study (registration number: ChiCTR2000029765) showed that quick control of fever and improvement of respiratory function in 21 patients with severe COVID-19. However, a cautionary case report by Radbel et al. demonstrated that two patients were diagnosed with COVID19 complicated by cytokines release syndrome (CRS) and treated with TCZ, and unfortunately, both patients progressed to severe hemophagocyic histiocytosis (HLH), and one developed to viral myocarditis.

Thymosin is widely used for antiviral treatment of hepatitis B and HIV. Acting as an immune potentiator, thymosin promotes the differentiation and maturation of thymocytes, increases the number and activity of T cells [40]. It can also promote the recruitment of precursor NK cells, differentiation and function enhancement of bone marrow-derived dendritic cells (DC) [41]. Although scarce of clinical evidence, thymosin might restrict the progression of COVID-19 by stimulating the production and activity of lymphocytes in theory especially for those with lymphopenia.

In conclusion, the development and evolution of covid-19 is closely related to immune function. Maintaining appropriate immune response of patients promotes to eliminate SARS-CoV-2 without causing immunopathological injury by cytokine storm. Immune dysfunction can contribute to the spread of virus, and immunopathological damage play an important role in the progression of the disease. Crucially, the agents rounding up the immunopathology for COVID-19 may bring hope under the scenario of the lacking in ineffective antiviral drugs. Based on our successful experience in Wuhan and the novel progress of therapy strategies related to immunopathology, the agents listed above are worthy of further exploration in practice.

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