



Chinese Medicine Treatment of Cytokine Storm Caused by COVID-19

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Abstract

Context: COVID-19 has turned into a pandemic, threatening the lives of millions of people worldwide. Research has found that some COVID-19 patients will suddenly aggravate, resulting in a cytokine storm, respiratory distress syndrome, and death. It is necessary to articulate the mechanism of cytokine storm and propose a Chinese medicine treatment strategy for COVID-19.

Evidence Acquisition: A literature search was conducted using five databases on April 30, 2020, including PubMed, Google Scholar, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data with the keywords of “cytokine storm AND Chinese medicine AND COVID-19”, “cytokine storm AND Chinese medicine AND SARS-CoV-2”. The outcome of interest was the concept and mechanism of cytokine storm, the characteristics, and the Chinese medicine treatment of COVID-19 cytokine storm, etc. A total of 43 articles were retrieved after removing duplicate articles.

Results: The cytokine storm is also called cytokine cascade. The body overreacts with positive feedback without negative feedback, making a variety of abnormal cytokines accumulations, triggering a cytokine storm. COVID-19 cytokine storm does not occur in the early stages, but only after a period of development, it attacks not only the lungs but also the heart, kidneys, and other organs. The key pathogenesis is “toxins and blood stasis, lung failure” in Chinese medicine. The treatment is detoxification, removing blood stasis, and nourishing the lung. Chinese medicine should comprehensively regulate multiple targets and multiple pathways to intervene in the immune regulation of the body to intercept the progress of inflammation and focus on the integration of Chinese medicine with Western medicine to combine anti-virus and anti-inflammatory therapy.

Conclusions: The immune response caused by cytokine storm is a complex signal network with multiple targets and pathways and various cytokines acting together. Immunomodulation can balance the excessive inflammatory response and effectively control the replication and spread of SARS-CoV-2. Returning the immune response to a balanced state is an ideal method for treating COVID-19 cytokine storm. Chinese medicine can achieve overall coordination and balance. Nevertheless, the pharmacology of Chinese medicine must be further studied, and the mechanism of cytokine storm treatment should be thoroughly clarified.

Keywords: COVID-19, SARS-CoV-2, Cytokine Storm, Chinese Medicine Treatment

1. Context

Coronavirus (CoV) is an important pathogen causing respiratory infection in humans and animals. It is a type of single-stranded positive-strand RNA virus with a capsule (1). Four types of coronaviruses belonging to the α -CoV family (HCoV-NL63, HCoV-229E, HCoV-HKU2, HCoV-OC43) and three types belonging to the β -CoV family (SARS-CoV, MERS-CoV, SARS-CoV-2) have been found. The SARS-CoV and MERS-CoV have caused severe harm to the society (2). SARS-CoV-2 is the seventh coronavirus that can infect humans and is a cousin of SARS-CoV (3). HCoV-NL63, HCoV-229E, HCoV-HKU2, and HCoV-OC43 only cause mild inflammation in the immune function, causing general cold symptoms, which are mild and easy to cure; SARS-CoV-2 is less pathogenic than SARS-CoV (10%) (4) and MERS-CoV (40%)

(5). Estimated R_0 for SARS-CoV-2 ranges from 3.3 to 5.5, which is higher than those of SARS-CoV ($R_0:2-5$) and MERS-CoV ($R_0 < 1$) (5, 6), demonstrating that SARS-CoV-2 has low fatality rate and high transmissibility (7). A cohort study of 1590 hospitalized subjects showed that non-survivors were mostly older people, patients with chronic illnesses, dyspnea, and laboratory abnormalities on admission (8).

COVID-19 can cause severe inflammatory damage. The immune system can be damaged in the early onset of the disease, resulting in a decrease in lymphocytes and an increase in C-reactive protein (CRP) and erythrocyte sedimentation rate; mononuclear and macrophage infiltration can be seen in the lungs, heart, kidneys, spleen, liver, and gallbladder; immune histochemistry shows a decrease in CD4+T and CD8+T cells (9). The clinical report of COVID-19 published in The Lancet shows that the severity

of the disease is related to the cytokine storm (10-12). The severity of SARS-CoV-2 infection is related to the strength of the virus and the body's inflammatory response. At the same time, the inflammatory response is also the transformation point of the disease development. Excessive stress on the immune system violently attacks the sites of infection, resulting in the aggravation of COVID-19, such as severe lung injury, acute respiratory distress syndrome (ARDS), multiple organs failure, and even death. The real killer in COVID-19 is the cytokine storm.

Chinese medicine is a multi-components, multi-targets, multi-paths field of medicine for regulating and treating diseases, which has a significant advantage in blocking the cascade of inflammatory factors. It is necessary to articulate the mechanism of cytokine storm and propose a Chinese medicine treatment strategy for COVID-19.

2. Evidence Acquisition

A literature search was conducted using five databases, including PubMed, Google Scholar, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data, with the keywords of "cytokine storm AND Chinese medicine AND COVID-19", "cytokine storm AND Chinese medicine AND SARS-CoV-2" on April 30, 2020. The outcome of interest was the concept and mechanism of cytokine storm, the characteristics and the Chinese medicine treatment of COVID-19 cytokine storm, etc. A total of 43 articles were retrieved after removing duplicate articles.

3. Results

3.1. The Concept of Cytokine Storm

The cytokine storm is also called cytokine cascade, or hypercytokinemia, the essence of which is an excessive inflammatory response, which is the body's excessive immunity to external stimuli (11, 12). After the body is stimulated by the outside world or infected with microorganisms, the innate immunity will modulate the body's immune cells and remove the pathogen from the body. If the immune regulation is unbalanced, the body's cytokines will abnormally accumulate at the site of infection through a specific positive feedback mechanism. Thus, a cytokine storm erupts, triggering the attack of the immune system to tissues and organs, such as the lungs, heart, kidneys, etc., causing severe lung injury, ARDS, multiple organs failure, and death.

In the end stage of many diseases, cytokine storms will occur due to various reasons, such as severe bacterial

and viral infections, inappropriate treatment, etc., leading to immune regulation dysfunction. Cytokines are an essential part of the body's immune system, including interleukin family (ILs), tumor necrosis factor (TNF), interferon (IFN), chemotactic cytokine ligand (CCL), colony-stimulating factor (CSF), and growth factor (GF). These cytokines interact with each other in the body and participate in the inflammatory response. They have both antagonistic and promotion effects, forming a complex immune regulatory network. A cytokine storm is an excessive inflammatory response after an immune disorder.

3.2. The occurrence of Cytokine Storm

The cytokine release in this inflammatory response is divided into two levels. When an antigen invades the body, the first level is the cytokine release and mutual stimulation of the innate immune system. Taking the SARS virus as an example, the SARS virus enters the airway and alveolar epithelial cells, and the virus-infected dendritic cells (DCs) release a small amount of IFN- α/β , an appropriate amount of proinflammatory factors TNF, IL-6, and a large amount of CCL3, CCL5, CCL2, and CXCL10; macrophages also release IFN and other proinflammatory factors; airway epithelial cells (AECs) also release large amounts of chemokines CCL3, CCL5, CCL2, and CXCL10 (13). These inflammatory cytokines released in large quantities can inhibit viral replication and eliminate pathogens. For some reason, such as viral immune escape, it can also induce innate immune disorders, accumulation of inflammatory factors, and a cytokine storm. The second level is the involvement of the adaptive immune system, which mainly involves Th1 cells. Taking the influenza virus as an example, the typical signaling process is: DCs capture viral proteins and display them in major histocompatibility complex II (MHC II) through antigen presentation; DCs enter the lymph nodes to present antigen cells to CD4+ and CD8+ T cells; CD4+ T cells differentiate into Th1 or Th2 or Treg cells; Th1 cells leave the lymph nodes and enter the inflammation site to release a large amount of IL-12 and IFN- γ to stimulate their proliferation. IFN- γ can stimulate macrophages activation, further activating the innate immune system; through a specific positive feedback mechanism between cytokines, it induces the cumulative increase of inflammatory factors and the outbreak of cytokine storm (14, 15).

3.3. COVID-19 and Cytokine Storm

COVID-19 can affect people of all ages, and the symptoms are similar to SARS. The disease will suddenly develop from mild to severe, especially in older people with low immunity or combined with underlying diseases (8). Another study showed that 17 of 99 COVID-19 patients (17%) developed ARDS, and 11 (11%) died (16).

SARS-CoV and MERS-CoV, which belong to the same group as SARS-CoV-2, also had a cytokine storm event after infection. In SARS-CoV infection, the disease shows a trend from mild fever to acute lung injury, ARDS, and even death. About 20% of patients have ARDS. In MERS-CoV infection, those with low immune function and comorbidities can develop severe respiratory diseases and usually develop ARDS (14). In 2003, a study by Peiris et al. (17) of the University of Hong Kong found that patients with severe SARS infection had significant lung tissue damage, which was associated with severe inflammatory reaction and cytokine storm. Multinucleated giant cells and macrophages in alveoli secreted large amounts of TNF, IL-1, TGF, and other inflammatory factors, inducing fibroblast activation, causing diffuse damage to pulmonary capillary endothelial cells and alveolar epithelial cells, and eventually leading to lung tissue fibers change (17).

In SARS-CoV and MERS-CoV infections, the serum levels of IFN- γ , IFN- α , IL-1, IL-6, IL-12, IL-8, TNF- α , CCL2, CXCL8, CXCL9, CXCL10, MIP1a, MIP1b, MCP1, and G-CSF increase significantly (18-20). The body's immune system initiates an immune response, which should inhibit virus replication and eliminate the virus, but the virus induces an imbalance in the immune regulation network. The body overreacts with positive feedback without negative feedback, making a variety of abnormal cytokines accumulations, triggering a cytokine storm. Therefore, some scholars believe that the culprit of ARDS is not the virus itself, but the body's immune system hijacked by virus (14).

3.4. Characteristics of COVID-19 Cytokine Storm

First, the cytokine storm caused by COVID-19 does not occur in the early stages of the disease, but only after a period of development or even after a certain treatment (11, 12). COVID-19 is different from SARS-CoV and MERS-CoV that can burst cytokine storm at the early stage of infection. Second, the COVID-19 cytokine storm attacks not only the lungs but also the heart, kidneys, and other organs (9). Besides, in COVID-19, most reports describe changes in IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-17, IL-18, TNF- α , and IFN- γ and - α , but there is little consistency between different reports (8-12). These reports all believe that COVID-19 produces a robust inflammatory response.

3.5. COVID-19 Cytokine Storm and Chinese Medicine Treatment

Based on Chinese medicine, COVID-19 cytokine storm belongs to the category of asthma and pulmonary distension, and the key pathogenesis is "toxins and blood stasis, lung failure". The treatment is "detoxification, removing blood stasis, and nourishing the lung" to achieve overall coordination and balance (21, 22). In terms of treatment

strategies in Chinese medicine, it is necessary to integrate Chinese medicine with Western Medicine to carry out antiviral therapy and balance immune response at the same time through multiple targets and pathways and a variety of cytokines (23, 24).

Chinese medicine should comprehensively regulate multiple targets and multiple pathways to intervene in the immune regulation of the body to intercept the progress of inflammation. It is recommended to use *Lianhua Qingwen Capsules* (honeysuckle, forsythia, sunburned ephedra, bitter almond, licorice, Mianma Guanzhong, Houttuynia cordata, gypsum, Radix isatidis, patchouli, rhubarb, Rhodiola rosea, and menthol), *Jinhua Qinggan granules* (honeysuckle, forsythia, scutellaria, honey ephedra, bitter almond, licorice, burdock seed, peppermint, gypsum, fritillaria, Astragalus, and Artemisia annua), *Shufeng Jiedu Capsules* (Forsythia, Astragalus, Licorice, Polygonum cuspidatum, Verbena, and Geshanxiao), *Fangfeng Tongsheng Pills* (Forsythia, Radix Scutellariae, Campanulaceae, Nepeta, Windproof, Ephedra, Licorice, Mint, Gardenia, Rhubarb, Glauber's Salt, Gypsum, Talc, Angelica, White Peony, Chuanxiong, and Fried Atractylodes), *Qingfei Detox Decoction* (Scutellaria, Aster, Ephedra, Almond, Licorice, Raw Gypsum, Guizhi, Alisma, Polyporus, Atractylodes, Poria, Bupleurum, Pinellia, Ginger, Winter Flower, Shegan, Asarum, Yam, Citrus aurantium, orange peel, and patchouli), and *Xuebijing injection* (angelica, safflower, red peony, Chuanxiong, and salvia) (9). Among them, ephedra, almond, rhubarb, Zhimu, gypsum, etc. are used in higher frequency. Literature analysis indicates that they can regulate IL-1 β , IL-6, IL-23, TNF- α , and MMP-9, and have a significant role in the cytokine storm of SARS infection (25).

The analysis of 51 cases of COVID-19 showed that *Lianhua Qingwen Capsules* could prevent COVID-19 patients from progressing to severe disease (26) and can reduce TNF- α and MCP-1 levels in alveolar lavage fluid of mice with acute lung injury, as well as serum TNF- α , MCP-1, IL-1 β , and IL-8 levels, diminish inflammation and infiltration of lung tissue, and protect the structure of alveolar epithelial cells and pulmonary vascular endothelial cells (27). *Xuebijing injection* can down-regulate the proinflammatory factor TNF- α and increase the expression of anti-inflammatory factor TGF- β 1 (24). Network pharmacology shows that it has more than 70 targets to treat COVID-19. Among them, HIF-1, PI3K-Akt, and other signaling pathways play an important role in the inflammatory response network, proving that *Xuebijing Injection* can inhibit cytokine Storm (28).

4. Conclusions

The immune response caused by cytokine storm is a complex signal network with multiple targets and path-

ways and various cytokines acting together. Immunomodulation can balance the excessive inflammatory response and effectively control the replication and spread of SARS-CoV-2. Returning the immune response to a balanced state is an ideal method for treating COVID-19 cytokine storm. Chinese medicine, with the efficacy of “detoxification, removing blood stasis, and nourishing the lung”, can achieve overall coordination and balance. Nevertheless, the pharmacology of Chinese medicine must be further studied, and the mechanism of cytokine storm treatment should be thoroughly clarified. In the critical stage, respiratory support, nutritional therapy, antiviral drugs, convalescent plasma, and even glucocorticoid therapy should be combined with Chinese medicine.

Footnotes

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