Letter to the Editor

# Role of IL-4 in Cytokine Storm Syndrome due to COVID-19 Infection

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## Dear Editor

The 2019 novel coronavirus (the cause of COVID-19) was announced as a global pandemic by the World Health Organization on 11th March 2020 (1). COVID-19 viral pneumonia is caused by a Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), following the rapid outbreak from Wuhan, China, to all other parts of the world (2). This virus is the third member of the human coronavirus family which leads to acute respiratory distress syndrome (ARDS) after the SARS-CoV in 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (3). It seems that these highly contagious coronaviruses use the same immune-pathology mechanism linked to ARDS, originated from an excessive immune response, also called a "cytokine storm syndrome" (4). This toxic immune overreaction is a type of systemic inflammatory response due to the marked release of various pro-inflammatory cytokines and chemokines by immune effector cells (5).

Although the cytokine storm secretion profile in COVID-19 disease is generally similar to SARS-CoV and MERS-CoV infections, some critical differences existed, especially on the levels of T-helper-2 (Th2) cytokines concentrations (6). It has been observed that the levels of Pro-inflammatory cytokines such as interleukin 1β (IL-1β), interferon γ (IFN-γ), interferon-inducible protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1) are increased in patients with 2019-nCoV, SARS-CoV and MERS-CoV infections (6, 7). However, SARS-CoV-2 infection is different from other coronaviruses in terms of various concentrations of Th2 cytokines. IL-4 and IL-10 are key cytokines of Th-2 lymphocytes and has immune regulatory functions through the inhibition of Th-1 cytokine secretion (7). IL-4 could trigger a secondary hemophagocytic lymphohistiocytosis (HLH). HLH is a kind of cytokine storm syndrome in-dependent on T cells or IFN-γ (8).

Also, elevated serum concentrations levels of some Th2 cytokines such as IL-4 were detected in individuals with SARS-CoV-2 whereas, the levels of IL-4 in subjects of MERS or SARS patients showed a decrease (2). Thus, it can be one of the noteworthy differences between cytokines profiles in the pathogenesis of COVID-19 infections compared to SARS and MERS coronavirus.

It is well-known that the over-production of Th-2 cytokines could result in chronic inflammatory diseases including atopic dermatitis (AD), asthma, and allergic

rhinitis (9). Dupilumab is a fully human monoclonal antibody that inhibits the signaling pathway of the common receptors of IL-4 and IL-13. Dupilumab can control the AD inflammatory disease with a favorable safety profile (10). It is considered that it does not augment the risk of viral infections (11). According to the increased level of IL-4 in the COVID-19 pandemic, the suppression of elevated IL-4 probably could be an ideal immuno-modulating option.

Recently, Ferrucci et al reported the dupilumab therapy course in two patients who had concurrently AD and Covid-19 infection. Both patients had been undergone dupilumab treatment a few months before being infected with COVID-19. Furthermore, the patients' first-degree relatives (father of one patient and the husband of another one) were also affected with COVID-19, too. Interestingly, both of the patients developed a mild form of COVID-19 disease and showed a progressive improvement in the clinical symptoms, while their infected first-degree relations died for interstitial pneumonia (12). More interestingly, the same authors enrolled 245 patients with COVID-19 infection in Milan, Italy, a geographic area with a high incidence of Covid-19, in a trial using dupilumab therapy. They found that only 2 patients (0.82%) progressed COVID-19 infection and eventually none had serious sequels of the disease. Suggestively, they approved that dupilumab was an effective and safe treatment option for individuals with systemic inflammatory response associated infections (12).

In conclusion, according to the above-mentioned evidence, IL-4 functions differ in various coronavirus infections. Due to the high morbidity and mortality rate associated with the COVID-19 infections, the increased serum levels of IL-4 may exacerbate pathological conditions, however, the consequence of elevated IL-4 levels in the infected people needs much more attenuation and more clinical trials are required to confirm the positive outcomes of IL-4 inhibition in SARS-CoV-2 infected individuals with elevated IL-4.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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