Treatment of COVID-19 by CD24FC; a mini-review to the current knowledge

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Abstract
The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is already known for its respiratory infection, but it involved more organs such as the kidney, liver, and heart. Most of the patients with COVID-19 have mild symptoms, but 5% of cases are admitted to an intensive care unit (ICU) for severe symptoms, including multi-organ failure and septic shock. Excessive immune responses play an essential role in sepsis development and are associated with worse prognosis in COVID-19 patients. Consequently, reduction of these immune responses may be helpful for managing COVID-19 patients. In this mini-review, we discuss the prospective role of CD24FC, as a recombinant protein with immunomodulatory function, in the treatment of COVID-19 patients and its mechanism of action in the regulation of the immune system.

Introduction
Coronavirus disease 2019 (COVID-19) is a mild to severe infectious respiratory disease caused by the 2019 novel coronavirus (2019-nCoV). This virus was observed in China in December 2019 for the first time and spread worldwide. In March 2020, COVID-19 caused a global crisis pronounced a pandemic by the World Health Organization (WHO) (1). Although COVID-19 is a respiratory infection, it can cause multi-organ failure (acute kidney injury, hepatic failure, and cardiac injury) and death (2). A majority of patients with COVID-19 have mild symptoms, but 14% require hospitalization and oxygen therapy, and 5% of cases need intensive care unit (ICU) admission for severe symptoms such as acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure (3). Transmission of the virus is related to various factors such as genetics, age, clinical symptoms, morbidity, and geographical location (4). Besides, death-related factors are age (older age), gender (male), comorbidities (coronary artery disease, obesity, organ failure, cancers), and admission to a hospital with inadequate ICU facilities (5).

Methods
For this mini-review, we searched the following international databases; Google Scholar, Web of Science, Scopus and PubMed for finding English language articles related to treatment of COVID-19 by CD24FC. The keywords included COVID-19, CD24FC, SARS-CoV-2, COVID-19 and Septic shock.

Key point
The interim analysis indicated that COVID-19 patients treated with CD24Fc, recovered faster (median six days) than patients receiving placebo (median ten days). Besides, CD24Fc decreased the risk of death or respiratory failure by more than 50%.

Septic shock in COVID-19
Septic shock is one of the leading causes of death in critically ill COVID-19 patients. In adults, septic shock is diagnosed when the infection is suspected/confirmed, and vasopressors are required to maintain mean arterial pressure (MAP) ≥ 65 mm Hg and serum lactate level is ≥ 2 mmol/L in the absence of hypovolemia (6). Sepsis results from an extreme immune response to infections, and its pathogenesis contains inflammation, coagulation disorder, and immune dysregulation (7). In sepsis, pattern recognizing receptors (PRRs) of the host’s immune cells are activated by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), resulting in an immune response to pathogens (8). Although this inflammation process is crucial to eradicating infections,
excessive inflammation results in some complications such as tissue injury, multi-organ failure, and death. Hence, regulation of those immune responses is required for preventing or managing sepsis.

Sialic acid-binding immunoglobulin-type lectins (Siglecs), a group of cell surface transmembrane receptors on immune cells, play an essential role in immune balance in sepsis, autoimmune diseases, and cancers (7). Human expresses large varieties of CD33-related Siglecs, including Siglecs 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, and 16, on B1 cell and other hematopoietic cells. B1 cells control inflammation by producing interleukin-10 (IL-10), IL35, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (8). These interleukins can prevent or treat sepsis, which is a significant cause of death in COVID-19 patients.

Delaveris et al revealed that various complications in severe COVID-19 cases were because of the hyperinflammatory immune response. It seemed that pro-inflammatory neutrophil extracellular traps were a critical factor inducing peripheral inflammation and pulmonary tissue damage. They also found Siglec-9 agonist as a therapeutic strategy in controlling neutrophilic hyperinflation in COVID-19 patients because of its ability to suppress NETosis (the cell death pathway associated with the net formation) (9).

Siglec-G (in mice) or Siglec-10 (in humans) is expressed on macrophages, dendritic cells, and B cells. It selectively affects the innate immune response to DAMPs instead of PAMPs and plays a unique role in helping the immune system sense infection versus tissue injuries (10). It also works as an anti-inflammatory factor in sepsis by weakening B cell signaling, increasing IL-10 expression, suppressing dendritic cell cross-presentation, and interacting with CD24 (7). Siglecs-10 binds CD24, creating the CD24-Siglec-10 checkpoint, and regulates inflammation caused by tissue injury related to DAMPs (10). Previous studies have represented that fortified CD24-Siglec-10 checkpoint could decline inflammation in joints, colon, and central nervous system (11-14). In addition, a study reported by Bai et al. They found that mutation in the CD24 gene remarkably declined the risk of developing experimental autoimmune encephalomyelitis (23).

Administration of CD24FC in COVID-19

It was observed that CD24 deficiency caused an increase in pre-B cell apoptosis in the bone marrow of mice, suggesting that CD24 is responsible for B cell development (22). As a result, CD24 can control inflammation. The relation between CD24 and autoimmune disease was reported by Bai et al. They found that mutation in the CD24 gene remarkably declined the risk of developing experimental autoimmune encephalomyelitis (23).

Another study by Li et al, using CD24FC, a recombinant protein that binds to DAMPs and works as the agonist of Siglec G, was assessed in mice (14). Administration of CD24FC protected mice against oligodendrocyte degeneration due to chronic exposure to cuprizone (14). In the above study, CD24FC stimulated the Siglec-G pathway and suppressed the inflammatory reaction (14).

Besides, more studies have shown that CD24Fc regulated the inflammatory response to tissue injuries. Tian et al investigated the protection of CD24Fc against viral pneumonia due to simian immune deficiency virus (SIV) in infected Chinese rhesus monkeys. In this study, monkeys were divided into a control group that received normal saline (NS) and a test group that received CD24FC. Its results showed that CD24Fc not only reduced the incidence of viral pneumonia but also prevented ARDS and reduced the risk of hemorrhage, giant cell formation, and perivascular inflammation (12). CD24Fc is an agonist of Siglecs and can strengthen the CD24-Siglec immune checkpoint (12). Patients with COVID-19 due to viral pneumonia are at risk of ARDS and perivascular inflammation; hence, using CD24-Fc may prevent pneumonia due to Sars-COVID-19 or ARDS.

Some clinical trials have represented the efficacy of CD24Fc in modulating the inflammatory responses to tissue injuries due to COVID-19. For instance, in phase I of a randomized, double blind, and placebo-controlled trial (NCT02650895) on healthy adults, safety and pharmacokinetics of CD24Fc were assessed. The
data from the trial demonstrated the role of CD24Fc in suppressing inflammatory cytokines. Besides, their results suggested safety administration of CD24Fc (24,25). In COVID-19 patients, cytokine storm is one of the causes of kidney damage. Therefore, suppressing cytokines may prevent kidney damage and decrease COVID-19 critically ill patients’ mortality.

Another multi-center phase IIa clinical trial (NCT02663622) used CD24Fc to prevent acute graft versus host disease (GVHD) in leukemia patients after hematopoietic stem cell transplantation (26). GVHD is an immune-mediated condition induced by the interaction of T cells and the immune system of donor and recipient tissue (27). They found that CD24Fc significantly improved the 180-day free-survival of acute GVHD in Grade III-IV (25,26).

Finally, a phase III clinical trial (NCT04317040) involved 203 hospitalized COVID-19 patients and assigned them randomly into two groups receiving placebo and SACCofil™ (CD24Fc). The interim analysis indicated that patients treated with CD24Fc, recovered faster (median six days) than patients receiving placebo (median ten days). Besides, CD24Fc decreased the risk of death or respiratory failure by more than 50%. In that trial, many patients also received other drugs, including remdesivir and corticosteroids. It was observed that adding CD24Fc to these drugs significantly reduced recovery time compared to adding placebo (28).

**Conclusion**

In conclusion, ARDS, kidney damage, and sepsis are common in critically ill patients with COVID-19. Recent evidence suggested that hyper-inflammation and cytokines were involved in severe symptoms. Hence, CD24Fc as an immune regulator and cytokine suppressor may be a therapeutic and preventive strategy in COVID-19 patients.

**Authors’ contribution**

GGD and MR the prepared primary draft. LS edited the draft. All authors read and signed the final paper.

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical considerations**

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

**Funding/Support**

None.

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