

PERSPECTIVE

The impact of the hypoxia-VEGF-vascular permeability on COVID-19-infected patients

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Abstract

Effective treatment of patients with severe COVID-19 to reduce mortality remains one of the most challenging medical issues in controlling unpredictable emergencies caused by the global pandemics. Unfortunately, such effective therapies are not available at this time of writing. In this article, I discuss the possibility of repurposing clinically available anti-VEGF (vascular endothelial growth factor) drugs that are routinely used in oncology and ophthalmology areas for effective treatment of patients with severe and critical COVID-19. Our preliminary findings from a clinical trial support the therapeutic concept of using anti-VEGF for treating patients with severe COVID-19 to reduce mortality. The aim of this article is to further provide mechanistic insights into the role of VEGF in causing pathological changes during COVID-19 infection.

KEYWORDS

COVID-19, therapy, VEGF

On March 11 of 2020, the World Health Organization (WHO) announced Coronavirus disease-19 (COVID-19) as a pandemic infectious disease that affected nearly all countries around the globe. At this time of writing of May 6, 2021, the total number of COVID-19-infected cases exceeds 155,000,000 and 3,240,000 deaths and new cases continue rising in most countries.^[1] According to statistics on May 4, 2021, 617,721,160 people have received the 1 dose of COVID-19 vaccine and 285,448,913 people become fully vaccinated.^[2] The uncontrollable situation of COVID-19 virus poses unprecedented challenges for political decision makers, medical specialists, feasibility of medical facilities, economic supports, education, service sectors, and basic research. Although stringent protective procedures such as physical isolation are recognized as the most effective approach for prevention, different countries have implemented various policies to battle the COVID-19 pandemic. Vaccination remains the most effective approach to control the pandemic situation around the globe, provided future mutant COVID-19 viruses remain sensitive to the vaccine-triggered neutralizing antibodies.

Similar to severe acute respiratory syndrome-coronavirus (SARS-CoV), COVID-19 virus belongs to a positive-sense single-stranded ribonucleic acid (RNA) betacoronavirus.^[3] Respiratory droplets spread within short distances are the main transmission pathway between humans. Among the four structural proteins, that is, the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins, the spike protein is responsible for attaching to and fusing with the membrane of a host cell through angiotensin converting enzyme 2 (ACE2) receptor.^[4,5] The receptor-binding domain (RBD) of S protein exhibits the most variable part of the COVID-19 genome.^[5,6] Mutations of critical amino acids in RBD may change ACE2 binding affinity and pathology in humans. ACE2 is widely expressed many cell types, including, pneumocytes, cardiovascular cells, macrophages, and T-lymphocytes.^[7] Thus, COVID-19 virus likely infects these ACE2⁺ cells. Owing to high ACE2 expression, pneumocytes are the primary targets for COVID-19.

COVID-19-infected patients manifest a wide-spectrum of symptoms, including asymptomatic infection, mild upper

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respiratory tract illness, and severe pneumonia with respiratory failure.^[8,9] Most patients belong to normal and mild, and their mortality is lower than SARS-CoV and middle east respiratory syndrome-coronavirus (MERS-CoV). Common symptoms on admission were fever and dry cough, followed by sputum production and fatigue. Lymphocytopenia was observed in 82.1% of patients.^[10] On admission, 50% of the patients presented ground-glass shadow on chest CT.^[8] Comorbidities were present in nearly half of patients, with hypertension being the most common comorbidity, followed by diabetes and coronary heart disease.^[11] CT scans of the chest provide a diagnostic value even before clinic symptom develops. Typically, CT-scan reveals bilateral multilobar ground-glass opacities with a peripheral, asymmetric, and posterior distribution.^[12] Subpleural dominance, crazy paving (lobular septal thickening with variable alveolar filling), and consolidation develop along the disease progression. Pathological features include pleurisy, pericarditis, lung consolidation, and pulmonary edema. Mild pneumonia shows pulmonary edema, pneumocyte hyperplasia, large atypical pneumocytes, interstitial inflammation with lymphocytic infiltration, and multinucleated giant cell formation.^[13,14] At the advanced and severe pneumonia, diffuse alveolar damage (DAD) with diffuse alveolar exudates becomes apparent and diffuse DAD is responsible for the acute respiratory distress syndrome (ARDS) and severe hypoxemia was observed in this disease.^[14] At the healing phase, reorganization of exudates in alveolar cavities and pulmonary interstitial fibrosis occurs. These pathological features indicate COVID-19 severe patients suffer from high-degree of pulmonary hypoxia.

Development of effective drugs for treating patients with severe COVID-19 and reducing mortality is of the utmost importance and among the most urgent tasks. Although development of effective vaccines would provide a curative approach for prevention and treatment, there are a few challenging issues for vaccine development, including: (1) Timeline. Although a significant population has received vaccine, the pace of vaccination is far behind the expected schedule. Given the fact that a majority of population has not been vaccinated in most countries, the COVID-19 pandemic-associated mortality continues to rise to new records in certain countries; (2) COVID-19 RNA viruses are genetically unstable and mutations frequently occur, creating new strains of COVID-19 virus. The mutated COVID-19 viral strains may become resistant to vaccines. At this time of writing, several mutations and genetic variants of COVID-19 have been identified, especially in the S-protein-RBD.^[15] Genetic variations pose a challenge for development of effective and stable COVID-19 vaccines; (3) Authority approval. Before immunization of human populations, anti-viral vaccines need to be fully assessed for therapeutic and preventive efficacies and toxicity tolerance; and (4) Defective immunity. A majority of COVID-19 patients show defective immunity by manifesting lymphopenia with very low counts of lymphocytes in their body.^[8] If so, it would be very challenging to evoke the immune system by immunization.

In confronting vaccine challenges, current therapeutic strategies are focusing on treating critical patients with life-threatening severe symptoms such as ARDS to reduce mortality. To this end, repurposing existing drugs with diverse principles to alleviate clinical symptoms has received great attention.^[16,17] Numerous trials have been launched to treat COVID-19 patients by targeting virus and host pathological processes.^[16,17] We provide a few examples, including (1) Anti-inflammatory drugs. Blocking COVID-19-triggered cytokine storms by antibodies neutralizing various cytokines such as IL-1 (interleukin-1), IFN (interferon)- γ , IL-6 (interleukin-6), and granulocyte-macrophage colony-stimulating factor (GM-CSF) is an undisputed approach for treating severe patients.^[16,18] Several pharmaceutical companies and medical research centers are sponsoring these trials and results are inconclusive; (2) Hydroxyquinoline shows both prophylactic and therapeutic advantage displays by displaying potent antiviral effects on COVID-19 infection.^[19,20] Mechanistically, quinolone elevates endosomal pH and interferes with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2, which negatively influences the virus-receptor binding and abrogates the infection; (3) Stem cell therapy. Although mechanistically unclear, a few stem cell-based trials are ongoing for treating COVID-19 infection;^[21] (4) ACE2 inhibitors. Soluble ACE2 and small molecules have been developed to interfere COVID-19-ACE2 interaction for cell entry;^[22] (5) Protease inhibitors. Ritonavir and ASC09 are two examples to block viral protease activity;^[23] (6) Targeting endocytic and autophagy pathways;^[20] and (7) Antiviral drug nucleotide analogs. Remdesivir is an adenosine analog that incorporates into nascent viral RNA chains and causes their pre-mature termination;^[24] (8) Corticosteroids. In the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial of a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, corticosteroids showed that the mortality from COVID-19 was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care;^[25] (9) Antithrombotic therapy. Hospitalized non-pregnant adults with COVID-19 are recommended to receive a prophylactic dose of anticoagulation.^[26]

Along COVID-19 infection, patients often develop dyspnea, shortness of breath, owing to lung inflammation, plasma extravasation, deflated alveoli, and atelectasis. Dyspnea triggers local hypoxia in the lung tissue and systemic hypoxia in all tissues. Hypoxia induces a series of pathological responses by transcriptional activation of hypoxia-inducible factor (HIF)^[27] (Figure 1). Vascular endothelial growth factor (VEGF) is one of the key HIF-targeted genes and hypoxia is a potent driver for upregulation of VEGF expression.^[28] VEGF is a vascular factor that displays multiple biological functions under physiological and pathological conditions, including embryonic development, hematopoiesis, vasculogenesis, angiogenesis, vascular permeability, inflammation, neurogenesis, metabolism, endocrine regulation, tumor growth, cerebrocardiovascular disease, and ophthalmological disease.^[29] Among these known functions, angiogenesis and vascular

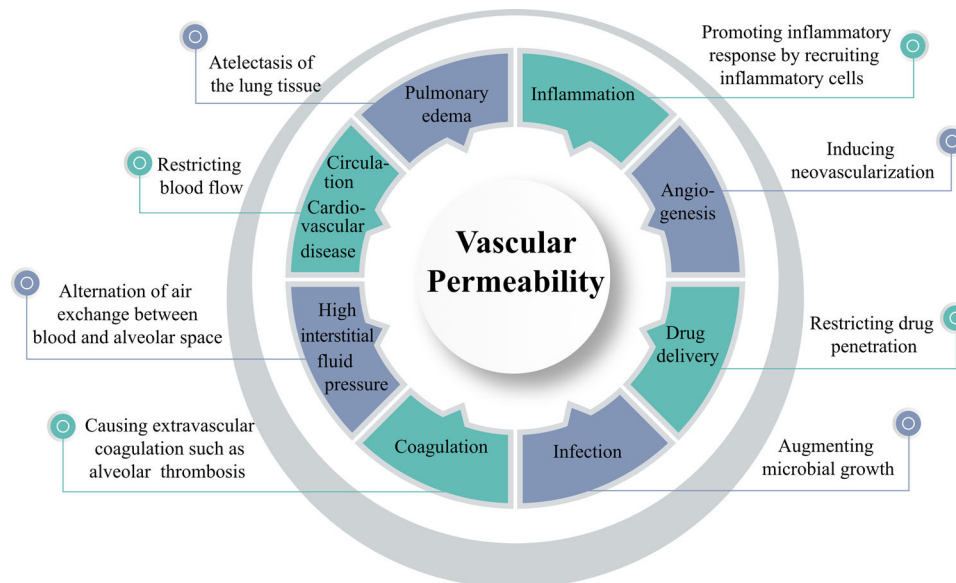


FIGURE 2 The hallmark of vascular permeability in development of clinical symptoms of COVID-19. Vascular permeability plays a central role in causing pathological changes of the COVID-19-infected lung tissues and other tissues, including exacerbation of inflammation, angiogenesis, infection, extravascular coagulation, and pulmonary edema. The increase of interstitial fluid pressure restricts blood perfusion in capillaries and microvessels, which further exacerbates tissue hypoxia and dyspnea. Therefore, targeting vascular permeability provides an imperative approach for treating patients with severe COVID-19. This therapeutic concept can be extended to other infectious and non-infectious diseases in which vascular degeneration and leakage participate in pathological alterations

COVID-19-infected patients. If these findings are further validated by randomized controlled trial in large cohort studies, this anti-VEGF-based therapeutic approach would likely become an important therapeutic component for treating COVID-19 patients.

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CONFLICT OF INTEREST

Yihai Cao is a member of the *Exploration* editorial board. The author claims no conflict of interests.

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