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REVIEW ARTICLE

A Perspective on Erythropoietin as a Potential Adjuvant Therapy for Acute Lung Injury/Acute Respiratory Distress Syndrome in Patients with COVID-19

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The novel coronavirus 2019-nCoV (SARS-CoV-2) infection that emerged in China in December 2019 has rapidly spread to become a global pandemic. This article summarizes the potential benefits of erythropoietin (EPO) in alleviating SARS-CoV-2 pathogenesis which is now called COVID-19. As with other coronavirus infection, the lethality of COVID-19 is associated with respiratory dysfunction due to overexpression of proinflammatory cytokines induced by the host immune responses. The resulting cytokine storm leads to the development of acute lung injury/acute respiratory distress syndrome (ALI/ARDS). Erythropoietin, well known for its role in the regulation of erythropoiesis, may have protective effects against ALI/ARDS induced by viral and other pathogens. EPO exerts antiapoptotic and cytoprotective properties under various pathological conditions. With a high safety profile, EPO promotes the production of endothelial progenitor cells and reduce inflammatory processes through inhibition of the nuclear factor-κB (NF-κB) and JAK-STAT3 signaling pathways. Thus, it may be considered as a safe drug candidate for COVID-19 patients if given at the early stage of the disease. The potential effects of erythropoietin on different aspects of ALI/ARDS associated with SARS-CoV-2 infection are reviewed. © 2020 IMSS. Published by Elsevier Inc.

Key Words: Erythropoietin, Acute lung injury, Acute respiratory distress syndrome, COVID-19, SARS-CoV-2.

Introduction

The world has been facing a major health crisis since the emergence of the novel 2019-nCoV infection in December 2019 in Wuhan (China) from which it rapidly spread across other countries (1). On February 11, 2020, the World Health Organization named the disease caused by 2019-nCoV as COVID-19. Since the respiratory presentations of this disease are predominant, the virus is named as the acute respiratory syndrome coronavirus-2 (SARS-CoV-2), in reference to the previously known similar coronavirus, SARS-COV (2). The COVID-19 outbreak has been described as the sixth Public Health Emergency of International Concern

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1) **What is current knowledge**

- COVID-19 is a global pandemic.
- There is no widely accepted management for COVID-19.
- The supposed pathogenesis of respiratory involvement caused by 2019-nCoV is due to overexpression of proinflammatory cytokines induced by host immune responses.
- Cytokine storm leads to acute lung injury/acute respiratory distress syndrome.

2) **What is new here**

- EPO has antiapoptotic and cytoprotective properties.
- EPO reduced inflammatory processes by inhibition of NF-κB and JAK-STAT3 signaling pathway.
- EPO may potentiate mobilization of iron stores and its transport to bone marrow and lessen accessible free iron for sufficient hemoglobin cycling
- EPO might be a safe and beneficial choice for better outcome of COVID-19 patients in the early stages.

(PHEIC) (3). At the time of preparing this manuscript, the World Health Organization (WHO) on July 25, 2020 reported 15,581,009 confirmed positive cases and the number of global death now exceeds 635,173 (Coronavirus disease 2019 (COVID-19) Situation report-187: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). The clinical presentations of COVID-19 seem to appear in most cases approximately five days after exposure (4). Based on patient's age, presence of underlying diseases, or immunity status, on average, it takes about 14 d from presenting with first symptoms to death (ranging from 6–41 d) (5).

The Respiratory Features of COVID-19 Pathogenesis

When COVID-19 progresses to the sever form, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) or respiratory failure may take place within few days (6,7). The imaging features on chest CT scan may indicate the severity of COVID-19 including the cases of pneumonia, RNAaemia, ALI, or ARDS (8). The chest CT scan of these patients has ground-glass opacities which are indicative of interstitial thickening, alveolar collapse or filling with transudate or exudate (9). The lung autopsy specimens of COVID-19 patients with severe ARDS further showed bilateral alveolar and interstitial edema, desquamated pneumocytes and hyaline membrane formation (10). These pathological findings are comparable to the pulmonary features of SARS and the Middle East respiratory syndrome (MERS) (11). Some patients also develop progressive infiltrate in lung upper lope with increasing shortness of breath and hypoxemia (12). The disease may develop to tremendous alveolar injury, ongoing lung failure and death (6).

The lung epithelial cells serve as the primary target host cells for viral fusion. First, cleavage of S (spike) protein of the viral capsid into S1 and S2 subunit occurs during infection. Afterwards, the S2 subunit interacts with cell surface targets such as the angiotensin-converting enzyme II (ACE2) receptor to bind to host cells (13). Alveolar epithelial cells and alveolar macrophages which are present in the lower respiratory tract, are also susceptible to infections (14). Pulmonary manifestations of SARS include activated alveolar and interstitial macrophages when viremia is dissolved. Therefore, it is assumed that alveolar damage results from the local host excessive inflammatory response (15). Plamacytoid dendritic cells sense nucleic acids of the virus through toll-like receptor-7 and excessively express type I interferon. Some pathological mechanisms involved in ALI include pulmonary endothelial dysfunction, chemotaxis of inflammatory cells to interstitium, and defective gas exchange and wall leakage as a result of pulmonary tissue injury (14). Mast cells, which are located in close proximity to respiratory blood capillaries and lymphatic vessels, also contribute to the initiation of airway inflammatory and allergic immune responses of the respiratory system (16). ALI is also a cytokine excess state in which mast cells release inflammatory mediators including histamine, leukotrienes, and neutral proteases (17). Furthermore, neutrophils mediate lung injury through robust pulmonary neutrophil infiltration into air spaces, chemotactic neutrophil migration to the site of inflammation, and downstream release of inflammatory cytokines, which substantially contribute to the pathogenesis including endothelial wall dysfunction and ALI (18). Exuberant production of pro-inflammatory cytokines, considerable cellular and humoral responses, and extensive tissue injury triggers the ''cytokine storm'' (19). This would cause apoptosis of endothelial and epithelial cells, increased vascular permeability, and exaggerated T cell and macrophages responses to promote viral clearance, which ultimately results in considerable lung inflammation, ALI/ARDS, or even death (20).

Physiological Effects of Erythropoietin

As a glycoprotein cytokine, EPO is primarily responsible for the regulation of erythropoiesis. In human, the EPO gene is located on chromosome 7 and encodes a polypeptide consisted of four α helical bundles. This protein is secreted by the kidneys to maintain tissue oxygen homeostasis in response to anemia or hypoxic stress (21). Specific cell surface EPO receptors (EpoR) are also present in the lung, liver, heart and brain tissues (22). Activation of EpoRs in bone marrow leads to stimulation of growth and induction of differentiation of blood cell precursors (23). EPO exerts its antiapoptotic properties through hematopoietic EpoR. Furthermore, Epo has been shown to have

cytoprotective effects on various pathological diseases, such as ischemia−reperfusion injury of the heart, kidney and the spinal cord (24).

Moreover, endothelial cells express EpoR. In response to exogenous EPO, they are able to promote the production of endothelial progenitor cells which reside in bone marrow, spleen and peripheral circulation (25). Through the action of EPO, proliferation and migration of epithelial cells are enhanced and their apoptosis is inhibited (26).

Immunomodulatory Properties of Erythropoietin

In Sprague-Dawley rats' experimental model of ALI/ARDS, the effect of a single dose of 3000 U/kg of exogenous EPO on acute lung injury was investigated. The results of this study showed positive histopathological features, including substantial reduction in pleural effusion volume, hemorrhage, scarred and thickened alveolar wall, and infiltration of chemotactic cells in lung tissues. Furthermore, animals in Epo arm had significantly decreased level of alveolar edema and accumulated neutrophils in alveoli. It is assumed that the mechanisms by which EPO decreases the severity of lung injury include preservation of vascular integrity, attenuation of inflammation, and inhibition of free radical production (27,28). In another experiment using Wistar rats, a single lower dose of 1000 U/kg of Epo was able to significantly decrease polymorphonuclear leukocytes (PMNL), circulatory pro-inflammatory cytokines, and pleural effusion volume in pancreatitis-induced ALI. Furthermore, Epo helped preserve microvascular endothelial cell integrity and lessen oxidative stress (26). In a further animal study of pulmonary injury, the effects of EPO, at a dose of 1000 U/kg/d for three days, was investigated on secondary pulmonary injury induced by pancreatitis. The results showed that Epo could protect endothelial cell integrity and significantly decreased mast cell counts in the lungs, alveolar hemorrhage, alveolar wall thickness, and neutrophil infiltration into lung tissues (29).

Interleukin (IL)-10 has anti-inflammatory and antiviral properties. Furthermore, IL-10 regulates both innate and acquired immunity. Although, this cytokine is only synthesized by T helper 2 cells (30,31), emerging evidences indicate that it has far diverse sources and function. For example, human recombinant erythropoietin (rhEPO) treatment of hemodialysis patients for six months has been shown to lead to reduction of inflammatory processes by elevating the production of IL-10 while suppressing the level of tumor necrosis factor-α (TNF-α). This group of patients are believed to have higher levels of T cells and macrophages activation which leads to overproduction of pro-inflammatory mediators and/or reduced level/activity of anti-inflammatory cytokines (32).

In a SARS-induced ALI model, activation of the innate immune response has been shown to lead to increased production of IL-6 by alveolar macrophages. This process takes place via the toll-like receptor 4/NF-κB signaling pathway, which ultimately leads to ALI (33). In a study using severe acute pancreatitis animal model, Epo, at a dose of 3000 U/kg, has been shown to effectively inhibit NF-κB activation leading to the regulation of inflammatory cytokines (27).

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway has a key role in modulating the immune system by maintaining the delicate balance between the production of pro-inflammatory and anti-inflammatory mediators (34). Thus, activation of the STAT transcription factor in the lung may have a critical role in stimulation of inflammatory responses and mediating ALI (35,36). In this regard, the beneficial effects of EPO were investigated in *in vivo* models of acute lung tissue damage induced by renal ischemia and reperfusion injury. In this case too, Epo markedly abrogated lung injury by inhibition of the JAK/STAT3 pathway. It also attenuated pulmonary interstitial and alveolar epithelial edema and preserve endothelial integrity in ALI. Recent reports further identified Epo as an inhibitor of the JAK-STAT3 signaling pathway (37,38).

Upon tissue injury, damage-associated molecular patterns (DAMPs) are released from damaged or dead cells, leading to activation of the host innate immunity and the inflammatory response (39). They also induce the release of inflammatory mediators through the action of pattern recognition receptors (PRRs) and cytosolic inflammasome NOD-like receptor pyrin domain containing-3 (NLRP3) (40,41). However, uncontrolled inflammation results in necrosis, apoptosis, or autophagy and ultimately leads to cell death. There are also a growing evidence that show the presence of DAMPs in broncho-alveolar lavage fluid of patients with ALI and upregulation of PRRs in lung tissues (42). Hence, DAMPs may be considered as potent therapeutic targets in the prevention and/or treatment of ALI and ARDS (40).

Erythropoietin as an Iron Mobilizer

Iron is essential for normal function of many proteins/enzymes and survival of all organisms. Simultaneously, it could be toxic via initiating the generation of reactive oxygen species (ROS) through the Fenton reaction (43). Hence, its availability starting from its absorption from the intestine, as well as its transport, storage and utilization is tightly regulated. The majority of iron in the body is employed to produce hemoglobin and stored intracellularly by chelation with proteins such as ferritin. Most of the iron required for erythropoiesis is provided by red blood cell turnover. Hepcidin is the major regulator of iron hemostasis (44) and its production and serum levels are highly stimulated during infections and inflammatory conditions. Overexpression of hepcidin takes place via the JAK-STAT3 pathway and PRRs signaling in hepatocytes and myeloid leukocytes

(45). This results in reduced availability of iron for erythropoiesis and implicated to anemia associated with inflammation. There are growing evidence, emphasizing on the possible role of iron and iron-induced-ROS and DAMPs in activation of NLRP3 and NF-κB signaling pathway, respectively (46,47).

Throughout the infection processes, the host must limit iron availability to pathogens which utilize free iron to promote their infectivity/pathogenicity. Unfortunately, overexpression of hepcidin induces iron sequestration in mononuclear phagocytes. This favors the growth of those pathogens highly dependent on iron availability and engages with macrophages. When macrophages are iron-loaded, they also express elevated levels of pro-inflammatory cytokines (45).

As mentioned above, EPO is secreted in response to cellular hypoxia, and stimulate erythropoiesis in bone marrow. Its interaction with various organs leads to the production of supportive factors of erythropoiesis. EPO administration may potentiate mobilization of iron stores and its transport to bone marrow and lessen accessible free iron. It thus helps in redistribution of iron for sufficient hemoglobin cycling (48). Some evidence suggest that exogenous EPO administration to healthy volunteers could result in profound decrease in serum hepcidin without significant change in the serum iron level within the first day (49). Furthermore, as mentioned in the preceding texts, EPO effectively inhibits the activation of NF-κB and JAK/STAT3 pathways, which may be induced by DAMPs, iron and iron-induced ROS (27,37,38).

Limitation

Erythropoiesis-stimulating agents look interesting therapeutic options, with positive effects on hematologic indicators and reduced need for blood transfusion. However, there are some growing concerns highlighting the increased risk of thrombotic events, especially venous thromboembolism, in patients during routine implementation of this practice (50). Yet, we should take into account the fact that most reports of thrombosis complications with these products have been described in cancer patients or those with chronic renal failure with prolonged administration of these products. Furthermore, these patients are at higher risk of developing thrombotic events (51,52). Notably, the risk of thrombotic complications was increased, when erythropoiesis-stimulating agents were applied to achieve higher hemoglobin levels more than 12 g/dL (53). Another point to be mentioned is that approximately all of these patients in critical care setting are under thromboprophylaxis with heparin or related products. Therefore, we only recommend these agents in those cases with suspicion of overstimulation of hepcidin, e.g., COVID-19 patients, who receive concomitant thromboprophylaxis with heparin, with hematocrit levels less than 30% and only for 3–5 d to prevent possible thrombotic events.

Conclusion

This article has given an overview of the effects of EPO on ALI/ARDS which has implications to the pathology of COVID-19. Though it has not been tested for its possible efficacy against SARS-CoV-2 infection, based on its effects in similar pathologies, EPO may be considered as an adjuvant therapeutic strategy for the management of ALI/ARDS in patients with COVID-19. Our assessment also calls for experiments that evaluate the direct effect of EPO on SARS-CoV-2 infection (COVID-19).

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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