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LETTER TO THE EDITOR

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Erythropoietin-induced hemoglobin subunit beta may stimulate innate immune RNA virus pattern recognition, suppress reactive oxygen species, reduce ACE2 viral doorway opening, and neutrophil extracellular traps against COVID-19

To the Editor,

I read the case report with respect to a critically ill patient with coronavirus disease 2019 (COVID-19) dramatically recovering following human recombinant erythropoietin (rhEPO).[1]

Subcutaneous rhEPO was given by subcutaneous injections every other day at dose of 300 IU/kg divided into five doses of 4000 IU for a nine-day treatment course.[1]

Possibly hemoglobin (HB), especially subunit beta also contributed to recovery, since HB participates in innate immunity through differentially regulating the retinoic acid inducible gene I (RIG-I) and melanoma differentiation-associated gene 5, which are involved in viral recognition and mobilizing an interferon response. HB also may promote reactive oxygen species upgrading RIG-I with release of interferon,[2] interferon being one of the primary responses of the innate immune system to viruses.

HB alpha and beta chain, is expressed in alveolar type II cells in response to hypoxia as well as other genes associated with HB biosynthesis in erythroid precursors,[3] which could contribute to innate immunity within the lung against viruses.

HB alpha expressed in vascular endothelial (VE) cells also regulates nitric oxide (NO) effect on vascular reactivity.[4]

Erythropoietin is protective of the VE [5] and may protect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the VE since

autopies show endothelitis and direct viral invasion of the VE.[6] Dysfunctional epithelium appears to be a common feature of risk factors for complications or more severe illness in COVID19, such as diabetes, hypertension, cardiovascular disease, male sex, and smoking.[6]

Angiotensin-(1-7), enzymatically produced by ACE2, the receptor for SARS-CoV-2,[7] acting on angiotension II, produces NO from endothelial cells.[8] SARS-CoV-2 binding of ACE2 probably interferes with normal ACE2 function with suppressed endothelial NO synthase results in loss of vasodilation and antithrombotic effects from absence of NO.

Stabilizing endothelium may be as important in treatment of COVID19 as antiviral treatment.[6] Medication, such as statins and ACE inhibitors may be helpful in this regard.[6] rhEPO when it can be administered safely may be important in stabilizing the endothelium

rhEPO can cause problems, such as blood clots and hyperviscosity, if utilized with normal hematocrit levels, so ordinarily it is not utilized except in treatment of anemia, which is its FDA approved indication.

Erythropoietin, originating in the kidneys, may be deficient with kidney disease, which is prevalent in multiorgan failure associated with advanced COVID 19, so replacement of deficiency could be important in maintaining a functional endothelium.

Abnormal blood clotting, and the numerous small vessel thrombosis observed in COVID19 autopsies including viral involvement of the endothelium with endothelitis, indicates involvement of the endothelium, with likely concurrent shedding of the associated glycocalyx.

The effects of erythropoietin on viral invasion may be through innate immunity, mediated through HB, and on protective effects on the VE.

Erythropoietin has limitations on usage, the primary recognized use being in anemia, but it also has pleiotrophic effects on the circulation mediated through the VE, which is vulnerable to SARS-CoV-2 infection, and is likely responsible for the thrombotic complications which are becoming more commonly recognized as the pandemic continues.

A trial is being conducted in France to evaluate endothelial involvement. (assessment of endothelial and hemostatic changes during severe SARS-CoV-2 Infection (COVID-thelium), including syndecan-1, a marker of degradation of glycocalyx, D-dimers plasma levels association with thrombotic events, and Von Willebrandt factor, viscoelastic testing, and vascular endothelial growth factor receptor type 1.

Components of the endothelium and associated glycocalyx will be assessed to determine the degree of involvement and extent of damage to the endothelium in COVID19. NCT04357847.[9]

A trial is also planned for rhEPO treatment of COVID-19 including severely affected patients emphasizing, improving respiration, countering excessive inflammation and neuroprotective aspects on brain and peripheral nervous system.[10]

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