Research Article

The role of blood disorders in the manifestation of ARDS in COVID 19 and EPO as a potential therapeutic agent

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Blood disorders caused by SARS-CoV-2 that may lead to hypoxaemia and subsequently to ARDS in COVID-19 patients as well as possible therapeutic effects of erythropoietin in order to restore oxygenation are analyzed.

The pulmonary inefficiency observed in COVID-19 patients may not be caused by cell damage in the lungs alone, this is suggested by the atypical presentation of ARDS (1).

While there is an increased concentration of ACE2 receptors in alveolar cells, the most probable point of entry for the virus, there are cases where patients are unable to breathe while there isn't substantial damage to the lungs and under mechanical ventilation (2). The lack of oxygenation in these conditions suggests that SARS-CoV-2 may affect oxygenation via paths not directly correlated with pulmonary function.

The main cytokines which are elevated in severe patients with a SARS-CoV-2 infection are IL-1 , IL-6 , INF-γ and TNF-α (2,3), these cytokines are known to cause blood disorders, IL-1 reduces RBC count by neocytolysis (4), TNF-α and IL-1 inhibit erythropoietin (EPO) production by reactive oxygen species (5) , INF-γ downregulates EPO receptor expression and causes apoptosis of erythrocyte progenitor cells (6) and IL-6 impairs hemoglobin production and erythroid cell maturation (7).

The elevated red blood cell width distribution - RBCW (dyserythropoiesis) found in severe COVID-19 patients is also found in malaria patients reportedly caused by the need to upregulate erythrocyte production by the bone marrow (8) since RBCs are constantly attacked in a malaria infection.

A molecular docking study of various SARS-CoV-2 glycoproteins and hemoglobin reveals that SARS2-CoV-2 glycoproteins bind to components of the hemoglobin conglomerate inhibiting the proper folding of hemoglobin, thus hemoglobin is dissociated and release heme and iron ions in the blood stream further increasing the hypoxia of the patients by inhibiting the body's ability to carry oxygen (9). Chloroquine was shown to disrupt SARS-CoV-2 and hermoglobin interaction. Free heme from hemoglobin is cytotoxic and in the presence of TNF increases cell damage (10) while excess Fe2+ iron forms reactive oxygen species (ROS) which are cytotoxic (11,12), further reduce EPO production and hamper erythropoiesis (13). During a COVID-19 infection the high oxidative environment can damage the RBC membrane increasing the lysis of RBCs (14). RBCs act as dynamic reservoirs of cytokines and

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hemoglobin (13), the lysis of RBCs leads to an increase of inflammatory cytokines, free heme and free iron. RBCs can cross the capillary endothelium in the lungs and have been found in the alveoli of patients with ARDS (14,15) so there may be an increase of cytokines, heme and iron ions near alveolar cells due to this action. An increased level of ferritin in severe patients reveals the body's response in order to reduce iron ion concentration since ferritin can store excess iron ions in a safe form (3). Hepcidin upregulation is common after viral infection thus there is a decrease in iron dietary uptake and an increase of storage of iron in macrophages (16). EPO administration lowers hepcidin directly and indirectly through decreasing IL-6 (since IL-6 downregulats ferroportin an inhibitor of hepcidin), releases iron from macrophages and increases iron uptake from the bone marrow which leads to an increase in RBC production (17). A distant similarity between hepcidin and SARS-CoV-2 glycoproteins has been found (18) which may also be a factor for reduced RBC and hemoglobin count.

SARS-CoV-1 directy increases the activation/phosphorylation of p38 MAPK and the downstream targets in the p38 MAPK pathway (19), phosphorylation of p38 MAPK increases apoptosis of erythroid progenitors while inhibition of the p38 MAPK increases erythroid and myeloid cell concentration in a dose-dependent manner (20). Some cytokines namely IL-6 and TNF-α may also be increased after phosphorylation of p38 MAPK (21).

The papain like protease of SARS-CoV-1 is shown to upregulate the expression of the transforming growth factor beta 1 (TGF-β1) and pro-fibrotic genes via ubiquitin proteasome, ERK1/2 and p38 MAPK mediated pathways (22), TGF-β1 inhibits erythropoiesis by blocking proliferation and accelerating differentiation of erythroid progenitors (23).

The SARS-CoV-1 spike glycoprotein activates the nf-κB pathway (24), nf-κB activation supresses erythroid-specific genes (25) while exogenous administration of EPO inhibits NF-κB and regulates and promotes the anti-inflammatory balance (26).

A BLAST comparison reveals that the membrane glycoproteins of SARS-CoV-1 and SARS-CoV-2 have a 90.52% similarity so there is a high possibility that most of the target molecules as well as the affected signaling pathways for the membrane glycoproteins are the same for both viruses.

The above factors all affect oxygenation and hypoxia may lead to a positive feedback loop via ACE2 and furin upregulation and an increase of the number of the infected cells hence an increase of the inflammatory factors which increase hypoxia. The ACE2 receptor is known to play an integral role in SARS-CoV-2 infection since it the allows the docking of the virus and entry of the viral RNA in cells (27). Although HIF-1 (Hypoxia Inducible Factor-1) which is increased in response to hypoxia and is responsible for EPO production is usually increased after a SARS-CoV-1 infection (28) there is a delay between the onset of severe hypoxia and ACE2 downregulation with ACE2 levels increasing above baseline for 48 hours before falling back to normal and reduced after enough Ang II is accumulated (29,30). An increase of the proprotein furin is associated with the increase of HIF-1 (31), SARS-CoV-2 has a furin cleavage site on the S1/S2 spike proteins junction which faciliates cell-cell fusion and possibly viral entry (32,33) increasing furin concentration should increase the rate of cell infection. According to the above there

should be an an increase of furin concentration once hypoxaemia sets on, upregulation of ACE2 for 48 hours and downregulation of ACE2 for the rest of the duration of hypoxaemia, the above agrees with experimental data redarding COVID-19 and ACE2 (34).

A hypoxia induced cytokine feedback loop due to blood disorders in COVID-19 can cause a buildup of inflammatory cytokines (IL-1, TNF) and increase the concentration of hyalyronic acid (HA) in the lungs, HA is a powerful humectant which can absorb water many times it's weight and inhibit pulmonary oxygen transfer (35). Thus, there is a secondary path in which the pulmonary function can be impaired in COVID-19 patients. Hyaluronidase has been suggested to reduce HA concentration in the lungs of SARS-CoV-2 patients.

Aftter prolongerd hypoxia HIF-1 is reduced while HIF-2 is increased (36), HIF-1 reduces the expression of IL-8 while HIF-2 increases IL-8 (37), elevated IL-8 is found in severe COVID-19 patients (38) and IL-8 is associated with cystic fibrosis and lung damage (39).

Further evidence supporting the role of hypoxia is the increase of myoglobin in severe patients (40), hypoxia increases myoglobin production in the heart even without physical excercise (41).

There may be a correlation between the reduced disease severity in younger ages and reduction of erythropoietic activity with age progression since older ages have reduced growth hormone compared to younger individuals which through IGF-1 reduces apoptosis of erythroid cells and increases the activity of EPO, the HIF-1 response decreases with the progression of age and there exists a correlation between age, inflammation and high IL-6 levels (42).

Various suggestions to lower TNF-a in order to treat SARS-CoV-1 patients have been made (43). Erythropoietin and TNF-a are shown to have a reverse depedency factor and exogenous administration of EPO can lower TNF-a levels (44).

T lymphocyte cell activity and count is very important in the body's ability to fight the SARS-CoV-2 infection suggested by the low T cell count found in severe patients (45). IFN-γ and exogenous EPO are shown to restrain T cell activitation via arginine catabolism while administration of methylarginine can restore the above T cell activity (46,47). SARS-CoV-2 glycoproteins bind to human CD26 and possibly reduce CD26 concentration (48), CD26 is known to participate in T cell activation (49). Exogenous EPO releases immature and mature B and T cells from the bone marrow in the first 24 hours from administration thereby increases the T cell count (50).

Recombinant EPO has recently been used to treat COVID-19 patients with very encouraging results (51). EPO along with methylarginine, chloroquine or other antiviral agents may have therapeutic effects for the patients.

EPO acts by modulating the immune response (suppressing memory T cell and promoting regulatory T cell response) (52), increasing T-cell count (50), decreasing inflammatory cytokines such as TNF-α (44). IL-8 (26) and IL-6 (17). EPO has anti-inflammatory and anti-apoptotic effects for many cell types (53) and increases viable RBC and hemoglobin production which can help restore oxygenation.

Some studies mention the action of nicotinic choligenic receptors in COVID-19 since SARS-CoV-2 appears to have similar genetic sequences as snake venom derived toxins (54) which act as agonists of hematopoietic α7-nACh receptors, are known to reduce available acetylcholine which can reduce the activation of platelets (55) and with this action achieve a thrombogenic effect. Since snake venom derived toxins act on both nicotinic cholirgenic and muscarinic cholirgenic receptors there is a high possibility that SARS-CoV-2 has an inhibiting action for muscarinic cholirgenic receptors which can reduce the self-renewal of erythroid progenitors (55).

There have recently been reported incidences of thrombotic complications in severe COVID-19 patients (56) although D-dimer a blood clot degradation product was known to be correlated with patient severity and was proposed as a severity market since the start of the pandemic (57). It was shown before that SARS-CoV-2 can cause the release of iron ions in the blood stream, when blood coagulation occurs under physiological conditions thrombin converts plasma fibrinogen into an insoluble clot however in the presence of Fe3+ iron produced by the dissociation of hemoglobin, hydroxyl radicals are produced that cause the polymerization of fibrinogen into a highly hydrophobic matrix which when fused with RBCs resists the fibrinolytic degradation of regular blood clots (58). Although antioxidants such as ascorbic acid can reduce certain oxidative reactions, they can have a catalyzing effect in hydroxyl radical formation (59) which is dentrimentral in thrombotic complications, however oxidizing substances can assist in the decomposition of hydroxyl radicals. This may sound paradoxical since ascorbic acid can reduce oxidative damage which occurs during a SARS-CoV-2 infection and is generally recommended as supplementation to combat COVID-19 but may prove damaging to patients with thromboembolic predisposition.

Membrane stabilizers can enhance the stability of RBCs reducing RBC lysis and subsequent increase of cytokines, free heme and free iron (60) however specific action of membrane stabilizers has not been elucidated in COVID-19 patients.

The elevated chemokines in SARS-CoV-1 infection are MCP-1 (monocyte chemoattractant protein 1), MIP-1α (monocyte chemoattractant protein 1α) and RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted) (3,61). RANTES suppression is normally found in typical ARDS (62). The Monocyte Migration Inhibitory Factor (MIF) is decreased in SARS-CoV-1 infection (63), SARS-CoV-1 Nucleocapsid N-glycoprotein has a specific binding to human MIF protein (64). Hypoxia stimulates MIF production via a HIF-1 dependent pathway (65) and MIF is normally increased in typical ARDS (66,67). These findings suggest that SARS-CoV-2 similarly to SARS-CoV-1 may exhibit abnormal concentrations for RANTES and MIF which are not found in typical ARDS. Increase in RANTES and decrease in MIF concentration can paradoxically increase the erythropoietic response (68) however this antagonistic effect is not sufficient to normalize blood oxygenation.

Another path in which SARS-CoV-2 may infect cells is through endocytosis utilizing lipid rafts that are present on cell membranes (69), lipid rafts form aggregates in response to cytokines or integrins to optimize signal transduction while erythropoietin causes the EPO-R receptor to translocate to lipid drafts and increase lipid draft coalesence (70) however whether EPO increases or reduces viral infection through lipid rafts is unknown.

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