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Hyperferritinemia in patients with COVID-19: An opportunity for iron chelation?

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Abstract

Studies from China on COVID-19 revealed that nonsurvivors had cytokine storm with high IL-6 and hyperferritinemia. Iron liberated from necrotic cells may catalyze free radical production and amplify lipid peroxidation causing membrane dysfunction and multiorgan failure. Consequently, iron chelators have been successfully utilized in various experimental and clinical models of cytokine storm and multiorgan damage, such as in ischemia-reperfusion injury, sepsis, and infections. Since viral replication may be influenced by iron accumulation, iron chelation has been proven beneficial in a variety of viral infections, such as HIV-1, hepatitis B virus, Mengovirus, Marburg hemorrhagic fever, Enterovirus 71, and West Nile virus. In this commentary, we elaborate on the idea of considering iron chelation as a therapeutic modality in patients with severe COVID-19 infection. For critically ill patients in the ICU, intravenous deferoxamine would provide sufficient and rapid iron chelation to ameliorate cytokine storm, whereas in less severe cases an oral chelator could prevent the development of excessive inflammatory response.

KEYWORDS

COVID-19, cytokine storm, iron chelation, SARS-CoV-2

Studies emerging from China suggest that many patients who die of COVID-19 have an excessive immune response, the so called cytokine storm, characterized by high fever, cytopenias (especially lymphopenia), pulmonary involvement (mainly ARDS), and elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), interleukin-6, and ferritin. When Zhou et al compared all adult hospitalized patients with COVID-19 who had been discharged or died, they found that nonsurvivors had lower lymphocyte counts and higher Interleukin-6 and ferritin levels.[1] This dismal complication of severe COVID-19 infection bears a resemblance to the cytokine storms observed in several other inflammatory conditions, including severe viral infections, sepsis, and the systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome, macrophage activation syndrome, graft-versus-host disease and hemophagocytic lymphohistiocytosis.[2] Regardless of the initial triggering factor, the vigorous immune system activation increases the expression of dozens of inflammatory mediators, including the pro-inflammatory cytokines tumor necrosis factor-alpha, interleukin-1 and interleukin-6. These cytokines signal the immune cells, such as T-cells and macrophages, to produce more cytokines. This vicious circle cause significant damage to body tissues and leads to multiorgan failure and death. Recently, to get cytokine storm under control, a number of specific anticytokine approaches have been proposed, including drugs targeting interleukin-1, interleukin-6, interleukin-18, and interferon-gamma.

Pro-inflammatory cytokines also trigger an increase in hepcidin, which promotes sequestration of iron by ferritin. In fact, hyperferritinemia has been typically found in all these conditions, calling attention to the possible pathogenetic role of iron in the cascade of destruction. Extracellular ferritin could also directly contribute to the development of the cytokine storm as a pro-inflammatory mediator.[3] Iron is both necessary to the body and potentially toxic. It is necessary for cellular respiration and oxygen transport and is potentially toxic for its ability to catalyze the conversion of hydrogen peroxide into free radicals. To prevent such damage, all life forms that use iron bind the iron atoms to proteins. Ferritin is the major intracellular iron storage protein in all organisms, and its structural properties are largely conserved through species. However, when iron is massively liberated from necrotic tissues and damaged mitochondria promotes the Fenton reaction, which generates hydroxyl radical, the most potent among various reactive oxygen species and stimulates lipid peroxidation, a chain reaction that accelerates damage to the cellular membranes and causes cellular death.[4] For that reason, we and others have supported the notion that in addition to clearing pro-inflammatory stimuli, treatments targeting iron, such as exogenously administered iron chelators, may be beneficial for all forms of excessive inflammation. Besides their chronic use for the treatment of iron overload due to frequent blood transfusions, such as in patients with thalassemia major, myelodysplastic syndromes etc., iron chelators have been successfully used in a variety of acute insults, including ischemia-reperfusion injury, hemorrhagic shock, sepsis and SIRS, cancer, multiple trauma, organ necrosis, and a range of viral and parasitic infections (Table 1).

Examples from our own experience include experimental studies with pigs developing severe SIRS after acute hepatic ischemia, where deferoxamine (DFO) infusion at a dose of 150 mg/kg completely blocked IL-6 production, delayed SIRS and circulatory collapse, and conferred protection to brain, lungs, and kidneys.[14-16] On clinical grounds, we found that an infusion of DFO at a dose 50 mg/kg for 8 hours in patients undergoing coronary artery bypass grafting (CABG), blocked lipid peroxidation and prevented myocardial stunning after termination of cardiopulmonary bypass.[9] Others have also showed that elimination of iron by chelators improved outcome in different hyperferritinemic situations. For example, the oral iron chelator deferasirox improved survival outcomes and restored graft-versus-leukemia effect in patients with hyperferritinemia after allogeneic stem cell transplantation in acute myeloid leukemia.[21] In addition, DFO has been tried against a range of viral and parasitic infections since replication may be influenced by iron accumulation (Table 1). Bayraktar et al[8] showed that administration of DFO at a dose of 80 mg/kg over three consecutive days enhanced the response rate to interferon-alpha treatment of chronic viral hepatitis B. Costagliola et al found that iron chelation lowered the progression of HIV disease in thalassemia major patients.[7] Of particular interest, iron chelation has been also found to be advantageous in experiments with Mengovirus, Marburg hemorrhagic fever, Enterovirus 71, and West Nile virus.[10,11,17,19]

Although every viral disease and epidemic is different, the experience of the beneficial effects of iron chelation against other viruses and inflammatory conditions with SIRS and hyperferritinemia provides important historical precedents that are both reassuring and useful, as humanity now confronts the COVID-19 epidemic. One of the most important mechanisms underlying the deterioration after COVID-19 infection is the cytokine storm, an uncontrolled inflammatory response associated with the induction of multiple cytokines and chemokines. Therapies with pro-inflammatory blockers, stem cells and transfusion of convalescent plasma have all been applied to patients with severe COVID-19 disease, in order to counteract the cytokine storm and its dismal consequences. However, at the time of this writing no proven treatment for COVID-19 infection exists and scientists around the world have been desperately testing an array of therapeutic modalities to find novel therapies for those patients with severe disease.

Despite the effective use of iron chelators in various inflammatory conditions, as reviewed above, iron chelation has not been translated into clinical practice as yet. Since there are no effective treatments for COVID-19, we propose an urgent open-label trial with iron chelators in patients with severe COVID-19 infection and hyperferritinemia, in an effort to prevent or ameliorate cytokine storm and possibly improve their survival. For iron chelation to be effective in the acute setting of severe COVID-19 infection a sufficient dose must be administered, as early as possible. It is of paramount significance, however, to carefully address a number of issues before administration of iron chelation therapy. When would be the best timing for this therapy to begin? Which would be the chelator and the best route of administration? What is the optimal dosage and what are the expected side effects? Patients with severe COVID-19 should be screened for hyperinflammation using readily available laboratory tests (eg, oxygen requirement $\geq$60%, increasing ferritin levels $\geq$ 1000 ng/mL and CRP values $>$ 10-fold over baseline, and decreasing platelets $< 100\,000 \times 10^9$/L and lymphocyte counts $< 1000 \times 10^9$/L). Worsening of these parameters indicates progressive severity of COVID-19 infection and predicts that more aggressive critical care will be needed. For those patients at the beginning of severe COVID-19 infection, an oral iron chelator could be administered for 10-14 days. For example, the oral iron chelator deferasirox at a dose of 20-40 mg/kg has been given once daily and proven sufficient to reduce iron burden in adult and pediatric patients.

TABLE 1 Clinical and experimental studies showing beneficial effects of iron chelation in various settings, including ischemia-reperfusion injury, sepsis, SIRS, and multiple viral infections

Author/Year	Setting	Intervention	Outcome
Clinical studies			
Menasche[5]	CPB	DFO infusion 30 mg/kg × 4 hours and 250 mg/L in cardioplegic solution	Prevents lipid peroxidation
Ferreira[6]	CABG	1000 mg/L DFO in cardioplegic solution	Prevents OFR Preserves myocardial cells
Costagliola[7]	HIV-1 disease in thalassemia major patients	DFO mean daily dose 40 mg/kg	Lowers the progression of HIV disease
Bayraktar[8]	Chronic hepatitis B	Weekly DFO infusion 80 mg/kg	Enhanced the rate of response to IFN-α
Paraskevaidis[9]	CABG	50 mg/kg DFO infusion for 8 hours	Prevents lipid peroxidation and cardiac stunning
Cho[21]	Allogeneic stem cell transplantation in acute myeloid leukemia	Deferasirox at a dose of 10-20 mg/kg/d	Improved survival outcomes and restoration of graft-versus-leukemia effect
Experimental studies			
Mulvey[10]	Mengo picornavirus- infected cells	DFO in cell culture	Blocks free iron in Mengo virus-infected cells
Ignat'ev[11]	Marburg hemorrhagic fever	DFO in infected guinea pigs	Moderate response
Ritter[12]	Septic rats	DFO 20 mg/kg plus NAC SQ	Improved survival
Avantes[13]	*Trypanosoma cruzi* in mice	DFO (5 mg/animal/day)	Decreased mortality and parasitemia
Arkadopoulos[14]	Pigs with SIRS after hepatic necrosis	DFO 150 mg/kg as infusion	Decreased intracranial pressure and improved survival
Kostopanagiotou[15]	Pigs with SIRS after hepatic necrosis	DFO 150 mg/kg as infusion	Attenuated lung injury
Vlahakos[16]	Pigs with SIRS after hepatic necrosis	DFO 150 mg/kg as infusion	Blocked IL-6 production and conferred renoprotection
Yang[17]	Enterovirus 71-infected mice	DFO 10 mg/kg	Reduced mortality
Wang[18]	Endotoxemic mice	DFO 100 mg/kg	Suppressed endotoxic shock and improved survival
Duchemin[19]	Infection of mosquito cells with West Nile virus	DFO-treated mosquitoes	Reduced viral titers

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DFO, deferoxamine; NAC, N-acetylcysteine; OFR, oxygen free radicals; SIRS, systemic inflammatory response syndrome; SQ, subcutaneously.

Minor side effects have been reported including transient gastrointestinal disturbances (nausea, vomiting, diarrhea, and abdominal pain), diffuse maculopapular skin rash, and increased alanine aminotransferase (ALT) and serum creatinine. More severe side effects including Fanconi syndrome and auditory and ocular toxicities have been associated with chronic therapies.[22] For those critically ill patients admitted to ICU, daily intravenous DFO infusions could be given. Deferoxamine is a readily available and well tolerated medication for subcutaneous or intravenous administration in patients with transfusional iron overload for almost half a century. For chronic use it has been given at a dose of 40-50 mg/kg/day for 5-7 days per week.[20] However, for acute iron intoxication in adults a much higher dose (up to 6 g per day) has been given. We and others have used IV DFO at a dose ranging from 50 to 100 mg/kg in clinical studies on diverse settings, without observing any acute infusional toxicity, other than local reactions at the infusion site. Side effects attributed to chronic therapy of DFO have included ophthalmologic and audiologic complications, renal toxicity and some bacterial infections, in particular with *Yersinia enterocolitica*.[23] The primary end points should contain need and duration of ventilation and ECMO, ICU length of stay, hospital length of stay, and in-hospital mortality. The secondary end points could include the median duration of fever (before presentation and during hospitalization) and other symptoms, PaO_2/FiO_2, Acute Physiology and Chronic Health Evaluation (APACHE) II, a series of clinical and laboratory data collected and recorded daily, and other COVID-19 complications such as cardiac involvement or thrombotic events. In accordance to our proposition, other investigators have recently suggested that depriving iron supply may represent a promising adjuvant therapeutic modality against a number of viruses, including COVID-19.[24,25]

In summary, there are compelling data from experimental animal models and clinical studies regarding the role of iron chelation in preventing excessive inflammatory response and tissue damage by blocking free iron and preventing the oxygen radical formation and lipid peroxidation. In addition to the efforts to block certain cytokines to ameliorate cytokine storm in patients with severe COVID-19 infection, we elaborate on the idea of considering iron chelation as an additional therapeutic modality in patients with severe COVID-19 infection. For critically ill patients in the ICU, intravenous deferoxamine would provide sufficient and rapid iron chelation to ameliorate cytokine storm, whereas in less severe cases an oral chelator could prevent the development of excessive inflammatory response. Further larger adequately powered double-blind randomized trials will be required before the administration of iron chelators to patients with severe COVID-19 infection is routinely advocated.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

VDV, concept and drafting of article; KPM, concept and critical revision of the article; NAP, concept and critical revision; DVV, concept and drafting of article. All authors approved the article.

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