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Commentary: Could iron chelators prove to be useful as an adjunct to COVID-19 Treatment Regimens?

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ABSTRACT

The pandemic of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a significant threat to global health. Currently, no specific prophylactic and therapeutic treatment is available. No evidence from randomized clinical trials (RCTs) that a treatment may ameliorate the clinical outcome of patients with COVID-19 exists with the only exception of preliminary evidence from remdesivir trials. Here, we present evidence from the literature and a compelling hypothesis on the potential immunomodulatory, iron chelating and anti-oxidant effects of iron chelators in the treatment of COVID-19 and its complications. Interestingly, iron chelation has been shown *in vitro* to suppress endothelial inflammation in viral infection, which is the main pathophysiologic mechanism behind systemic organ involvement induced by SARS-CoV-2, by inhibiting IL-6 synthesis through decreasing NF-kB.

Iron chelators exhibit iron chelating, antiviral and immunomodulatory effects *in vitro* and *in vivo*, particularly against RNA viruses. These agents could attenuate ARDS and help control SARS-CoV-2 *via* multiple mechanisms including: 1) inhibition of viral replication; 2) decrease of iron availability; 3) upregulation of B cells; 4) improvement of the neutralizing anti-viral antibody titer; 5) inhibition of endothelial inflammation and 6) prevention of pulmonary fibrosis and lung decline *via* reduction of pulmonary iron accumulation. Both retrospective analyses of data in electronic health records, as well as proof of concept studies in humans and large RCTs are needed to fully elucidate the efficacy and safety of iron chelating agents in the therapeutic armamentarium of COVID-19, probably as an adjunctive treatment.

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a significant threat to global health [1–3]. After a median incubation period of approximately 5 days (range: 2–14 days) [4], the majority of cases present mild symptoms, mainly from the respiratory tract, while some progress to viral pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure or death. While ARDS is associated with a high mortality rate of 30–40% [5,6], evidence suggests that COVID-19 related ARDS may have a worse outcome [7–9].

Currently, no specific prophylactic and therapeutic treatment is available. No evidence from randomized clinical trials (RCTs) that a treatment may ameliorate the clinical outcome of patients with COVID-19 exists [10] with the only exception of preliminary evidence from remdesivir trials [11]. Here, we present evidence from the literature and a compelling hypothesis on the potential immunomodulatory, iron chelating and anti-oxidant effects of iron chelators in the treatment of COVID-19 and its complications.

SARS-CoV-2 is a *Betacoronavirus* originating from bat-derived coronaviruses with transmission through an unknown intermediate mammal host to humans and presenting many similarities with SARS-Co-V [1,2]. SARS-CoV-2 targets epithelial cells through the S protein which attaches to the angiotensin-converting enzyme 2 (ACE2) receptor [12].

SARS-CoV-2 primarily affects the tissues expressing elevated levels of ACE2 including the lung, heart, kidney, the gastrointestinal tract, as well as the endothelium with systemic manifestations [13–15]. Diffuse endothelial inflammation with systemic involvement of microcirculation leading to thrombosis, tissue edema and organ ischemia has been demonstrated in histological analyses of various organs in patients suffering from COVID-19 [16]. Potential mechanisms of the systemic clinical findings of COVID-19 include: 1) the multi-tissue expression of ACE2

Abbreviation: ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DFO, deferoxamine; DNA, deoxyribonucleic acid; IL, interleukin; FDA, Food and Drug Administration; ICU, intensive care unit; NF-kB, nuclear factor kB; RCT, randomized clinical trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor-α.

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receptors; 2) the pronounced systemic increase of inflammatory cytokines and mediators, which may be even characterized as a "cytokine storm" [17]; 3) diffuse endotheliitis [16]; and 4) the dysregulated iron homeostasis resulting in oxidative stress and inflammatory response.

Dysregulation of iron homeostasis with higher iron levels may promote the course of viral infections [18–20], being associated with a range of respiratory diseases, including ARDS and pulmonary fibrosis [21]. Experimental and clinical data have indicated that excessive oxidative and nitrosative stress may contribute to the pathogenesis of ARDS. Furthermore, altered plasma and lung iron levels, as well as related parameters are associated with ARDS pathogenesis [22–24]. Evaluating serum ferritin levels in patients at risk may help predict the development of ARDS and, thereby, improve treatment [25]. Interestingly, based on a pre-print of *in silico* analysis performed on published biological protein sequences, it was shown that protein sequences of SARS-CoV-2 may form a complex with porphyrin, as well as affect the heme on the 1-β chain of hemoglobin resulting in the dissociation of the iron [26].

Iron chelators (Deferoxamine, Deferiprone and Deferasirox), particularly deferoxamine (DFO), have been approved by the FDA for the treatment of iron overload [27,28]. Besides iron chelation, DFO may inhibit pathogens, including bacteria, viruses and fungi, due to its immunomodulatory properties in various infected animal models [29]. Due to their antiviral and immunomodulatory effects *in vitro* and *in vivo* [29], we hypothesize that iron chelators may possess beneficial immunomodulatory and antiviral actions against SARS-CoV-2. Indeed, DFO treatment has been shown to decrease the mortality and relieve the symptoms of Enterovirus 71-infected mice [29]. More importantly, B cell levels of the infected mice were upregulated while the neutralizing antibody titer was also improved [29]. COVID-19 is characterized by lymphopenia [30–32]. We hypothesize that iron chelators may improve both lymphopenia observed in COVID-19 by upregulating lymphocytes, particularly B cells, as well as the neutralizing antibody titers against SARS-CoV-2.

More importantly, we would speculate that iron chelators may decrease SARS-CoV-2 replication *via* decreasing iron availability which plays an important role in viral replication, as shown in a number of RNA viruses. Iron chelators have been shown to inhibit human immunodeficiency virus type 1 (HIV-1) replication. The expression of the p24 antigen in human monocyte-derived macrophages and peripheral blood lymphocytes was reduced by all three iron chelators through the decrease of cellular proliferation, highlighting an additional benefit in antiretroviral combination therapy [33]. Moreover, iron availability plays an important role in viral replication in RNA viruses as shown in West Nile virus infection in its mosquito vector, HIV and Hepatitis C Virus (HCV) [33–35]. Based on mechanistic studies, iron may affect HCV replication *via* its effect on a number of host genes which are pivotal in replication [34]. Saliva from mosquitoes treated with DFO resulted in decreased viral titers of West Nile virus compared with untreated controls, indicating low viral transmission capacity [36]. Interestingly, the treatment with DFO infusions ameliorates the response rate to interferon-α treatment of chronic viral hepatitis B, resulting in histological improvement and loss of hepatitis B virus DNA [37].

It could also be reasonable to speculate that iron chelators may prevent the development of pulmonary fibrosis and lung function decline following COVID-19 infection. Increased iron levels and/or dysregulated iron homeostasis occur in several lung diseases, including pulmonary fibrosis [21]. More than 20% of survivors of the 2003 outbreak of SARS developed residual pulmonary fibrosis one year after infection [38–40]. Of note, fibrotic changes have also been reported in more than 17% of patients during the acute phase of COVID-19 [41]. In animal models, fibrosis and lung function decline are associated with pulmonary iron accumulation in bleomycin-induced pulmonary fibrosis [21]. Furthermore, iron accumulation is elevated in lung sections from patients with idiopathic pulmonary fibrosis where human lung fibroblasts exhibit higher proliferation and cytokine and extracellular matrix responses when exposed to higher iron levels. In experimental pulmonary fibrosis, intranasal treatment with the iron chelator DFO has been shown to prevent pulmonary fibrosis and decline in lung function presenting also immunomodulatory properties [21].

Iron is also implicated in endothelial inflammation induced by viral infections through induction of reactive oxygen species leading to nuclear factor kB (NF-kB) activation and subsequent upregulation of pro-inflammatory mediators such as IL-1β, IL-6 and TNF-α. Iron chelation by DFO has been shown to suppress endothelial inflammation induced by influenza A infection *in vitro* by inhibiting IL-6 synthesis through decreasing NF-kB [42]. Emerging evidence suggests that endothelial inflammation is the main pathophysiologic mechanism behind the multiorgan involvement and failure induced by SARS-CoV-2 infection. Therefore, we believe that iron chelating agents might prove useful to ameliorate the systemic manifestations of COVID-19.

In conclusion, iron chelating agents exhibit iron chelating, antiviral and immunomodulatory effects *in vitro* and *in vivo* [29], particularly against RNA viruses. These agents could attenuate ARDS and help control SARS-CoV-2 *via* multiple mechanisms including: 1) inhibition of viral replication; 2) decrease of iron availability; 3) upregulation of B cells; 4) improvement of the neutralizing anti-viral antibody titer; 5) inhibition of endothelial inflammation and 6) prevention of pulmonary fibrosis and lung decline *via* reduction of pulmonary iron accumulation. To do so, both retrospective analyses of data in electronic health records, as well as proof of concept studies in humans and, at a later stage, large RCTs are needed to fully elucidate the efficacy and safety of iron chelating agents in the therapeutic armamentarium of COVID-19, probably as an adjunctive treatment.

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Author contributions

Maria Dalamaga conceived the idea, designed the commentary and its sections, performed literature search, wrote, edited and reviewed the manuscript.

Irene Karampela performed literature search, wrote section on acute respiratory distress syndrome and edited the manuscript.

Christos S Mantzoros supervised, edited and reviewed the manuscript.

Declaration of competing interest

No conflict of interest to disclose.

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