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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.

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Based on a pre-print of 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 decreasing iron availability which 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 κB (NF-κB) 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-κB [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.

References

[1] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–9.
[2] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
[3] Coronavirus update (live): 3,138,097 cases and 217,968 deaths from COVID-19 virus outbreak. Worldometer. Available from: .www.worldometers.info. [Retrieved 28 April 2020].
[4] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. Mar 10, 2020. https://doi.org/10.7326/M20-0504.
[5] Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33.
[6] Belani C, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(8):788–800 [Erratum in: JAMA 2016; 316(3):350].
[7] Yang Y, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81 [S2213-2600 (20)30079-5. Erratum in: Lancet Respir Med. 2020;8(4):e26].
[8] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. April 22, 2020. https://doi.org/10.1001/jama.2020.6775.

[9] Grasselli G, Zangrillo A, Zanetti A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. April 06, 2020. https://doi.org/10.1001/jama.2020.5394.

[10] Sanders JM, Monogue ML, Lodowski DT, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. April 13, 2020. https://doi.org/10.1001/jama.2020.6019.

[11] https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-

[12] Wessling-Resnick M. Iron homeostasis and the in

[13] Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–7.

[14] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. Apr 10, 2020 [pii: jccl.ahead-of-print/cclm-2020-0369/cclm-2020-0369.xml].

[15] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall BS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.

[16] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020;395(10234):417–8 [S0140-6736(20)30937-5].

[17] Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020;9(1):687–90.

[18] Drakenstijn H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6:541–52.

[19] Moalem S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. Biometals. 2004;17:135–9.

[20] Westling-Renström M. Iron homeostasis and the inflammatory response. Annu Rev Nutr. 2010;30:105–22.

[21] Ali MK, Kim Ry, Brown AC, Donovan C, Vanka RS, Mayall JR, et al. Critical role for iron accumulation in the pathogenesis of fibrotic lung disease. J Pathol. Feb 21, 2020. https://doi.org/10.1002/path.5401.

[22] Neves J, Leitz D, Kraut S, Brandenberger C, Agraval R, Weissmann N, et al. Disruption of the hepcidin/ferroportin regulatory system causes pulmonary iron overload and restrictive lung disease. ElBioMedicine. 2017;20:230–9.

[23] Toblli JF, Caq G, Gian JF, Dominici FP, Angerosa M. Markers of oxidative/nitrative stress and inflammation in lung tissue of rats exposed to different intravenous iron compounds. Drug Devel Delve Ther. 2017;11:12251–63.

[24] Lagan AI, Quinlan CJ, Mumbey S, Melley DD, Goldstraw P, Bellinger GJ, et al. Variation in iron homeostasis genes between patients with ARDS and healthy control subjects. Chest. 2008;133(6):1302–11.

[25] Connolly KC, Moss M, Parsons PE, Moore EE, Moore PA, Giclas PC, et al. Serum ferritin as a predictor of the acute respiratory distress syndrome. Am J Respir Crit Care Med. 1997;155(1):21–5.

[26] Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv. 2020. https://doi.org/10.26434/chemrxiv.15938173/v1.

[27] Mobarra N, Shaniaki M, Ehtesbani H, Salmahi M, Saebi M, et al. A review on iron chelators in treatment of iron overload syndromes. Int J Hematol Oncol Stem Cell Res. 2016;10(4):239–47.

[28] Meyer D. Iron chelation as therapy for HIV and Mycobacterium tuberculosis co-infection under conditions of iron overload. Curr Pharm Des. 2006;12:1941–7.

[29] Williams A, Meyer D. Desferrioxamine as immunomodulatory agent during microorganism infection. Curr Pharm Des. 2009;15:1261–8.

[30] Yang Y, Ma J, Xie J, Bai L, Guan F, Zhang T, et al. Desferrioxamine compensates for decreases in B cell counts and reduces mortality in enterovirus 71-infected mice. Mar Drugs. 2014;12(7):4086–95.

[31] Chan JF, Aitaj A, Yuan S, Poon VK, Chan CC, Lee AC, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis. Mar 26, 2020. https://doi.org/10.1093/cid/ciaa325 [pii: ciaa325].

[32] Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sargentianis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol. Apr 13, 2020. https://doi.org/10.1002/ajh.25829.

[33] Georgiou NA, van der Bruggen T, Oudshoorn M, Nottet HS, Marx JJ, van Asbeck BS. Inhibition of human immunodeficiency virus type 1 replication in human mononuclear blood cells by the iron chelators deferoxamine, deferoxipine, and blesinoxycin. J Infect Dis. Feb 2000;181(2):484–90.

[34] Bartolomei G, Cevik RE, Marcello A. Modulation of hepatitis C virus replication by iron and hepcidin in HuH hepatocytes. J Gen Virol. 2011;92(Pt 9):2072–81.

[35] Theurl I, Zoller H, Obrist P, Datz C, Bachmann F, Elliott RM, et al. Iron regulates hepatitis C virus translation via stimulation of expression of translation initiation factor 4. J Infect Dis. 2004;190(4):819–25.

[36] Duchemin J, Paradkar PN. Iron availability affects West Nile virus infection in its mosquito vector. Virol J. 2017;14:103.

[37] Rayakratt Y, Koseoglu T, Sonner C, Kayhan B, Temizer A, Uzunalimoglu B, et al. The use of deferoxamine infusions to enhance the response rate to interferon-alpha treatment of chronic viral hepatitis B. J Viral Hepat. 1996;3(3):129–35.

[38] Hui DS, Wong KT, Ko PW, Tam LS, Chan DP, Woo J, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest. 2005;128(4):2247–61.

[39] Xie L, Liu Y, Fan B, Xiao Y, Tian Q, Chen L, et al. Dynamic charges of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. Respir Res. 2005;6:5.

[40] Venkataramanan T, Frieman MB. The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis. Antiviral Res. 2017;143:142–50.

[41] Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. Eur Radiol. Feb 13, 2020. https://doi.org/10.1007/s00330-020-06731-x.

[42] Visseren F, Verkerk MS, van der Bruggen T, Marx JJ, van Asbeck BS, Diepersloot RJ. Iron chelation and hydroxy radical scavenging reduce the inflammatory response of endothelial cells after infection with Chlamydia pneumoniae or influenza A. Eur J Clin Invest. 2002;32(Suppl. 1):84–90.