Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19?

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Keywords: vitamin C, COVID-19, SARS-CoV-2, IL-6, drug discovery

Abstract

SARS-CoV-2 causes the potentially fatal COVID-19 disease. Already during the outbreak of SARS-CoV-1, the use of vitamin C was suggested. Many severe COVID-19 patients have elevated levels of the mediators interleukin-6 and endothelin-1. These mediators may explain the age-dependence of COVID-19 pneumonia, the preponderance of male and obese or hypertensive patients, as well as of persons of colour, and smokers. There is clear evidence that vitamin C can reduce these mediators. Vitamin C is cheap and safe. Hence using a relatively low dose of vitamin C as prophylaxis, and in case of severe COVID-19 disease, an (intravenous) high-dose regimen may be beneficial. Ongoing clinical trials are expected to provide more definitive evidence.
A novel human coronavirus has recently been identified, i.e. SARS-CoV-2, which causes the potentially fatal COVID-19 disease \(^1\). SARS-CoV-2 is only the latest of three human coronavirus strains (the others being: SARS-CoV-1 and MERS-CoV) that can cause severe illness, but it is the first to cause a pandemic \(^2\). Major efforts are under way worldwide in the search for pharmaceutical interventions, but no therapies with proven efficacy to treat COVID-19 are currently available, although (hydroxy-)chloroquine with and without zinc supplementation is being used off-label as prophylaxis or treatment \(^3\)-\(^{11}\). Approximately 5\% of the patients diagnosed with COVID-19 become critically ill and require advanced respiratory support with (non-)invasive mechanical ventilation and added oxygen as the standard of care \(^4\),\(^12\),\(^13\). A recent report suggests that hyperbaric oxygen therapy could be a promising alternative, which is interesting in light of the suggestion that some SARS-CoV-2 proteins may interfere with haemoglobin function \(^14\),\(^15\).

According to the latest intensive care national audit & research center (ICNARC) report on COVID-19 in critical care, approximately 52\% of critically ill patients with confirmed COVID-19 do not survive \(^16\).

Already during the outbreak of SARS-CoV-1 (2003); the use of vitamin C, an essential micronutrient for humans and a free radical scavenger, was suggested as a non-specific treatment for severe viral respiratory tract infections \(^4\),\(^17\),\(^18\). Indeed, it is known that vitamin C supports various cellular functions of both the innate and the adaptive immune system, including modifying susceptibility to various viral infections, and by influencing inflammation \(^19\),\(^20\). Moreover, in chick embryo tracheal organ cultures, vitamin C increased resistance to infection by a coronavirus \(^21\). Additionally, vitamin C treatment restores the stress response and improves the survival of stressed humans \(^22\). However, a recent preliminary open-label study in patients with sepsis and acute respiratory distress syndrome showed that a 96-hour infusion of vitamin C compared to placebo did not significantly improve organ dysfunction scores or change markers of inflammation \(^23\). In contrast, early use of intravenous vitamin C in combination with corticosteroids and thiamine proved effective in preventing progressive organ dysfunction and in reducing the mortality of patients with severe sepsis and septic shock \(^24\). Intravenous hydrocortisone alone, however, did not significantly improve the survival of patients with septic shock compared to high-dose vitamin C, hydrocortisone and thiamine combined \(^25\), suggesting no added value of vitamin C in sepsis, although vitamin C may have beneficial effects in adults and children with pneumonia \(^26\). A Cochrane Systematic Review concludes that vitamin C is safe, inexpensive and has a consistent effect on the duration and severity of the common cold \(^27\),\(^28\). It furthermore concludes that mega-dose
prophylaxis is not rationally justified for community use, although it may be justified at times e.g. in periods of heavy physical exercise.

Evidence is accumulating that many severely ill COVID-19 patients have elevated cytokine levels, including of the multifunctional inflammatory key molecule interleukin-6 (IL-6), resembling the cytokine storm described in SARS and MERS \(^{1,29-34}\). This may indicate that high mortality is due to virus-driven hyperinflammation. Preliminary data suggest that COVID-19 pneumonia is a late-stage complication caused by the hyperactivation of immune effector cells, and treatment with (intravenous) high-dose vitamin C has been proposed to suppress these effectors \(^{35}\). Treatment with vitamin C decreases IL-6 and it blocks \textit{in vivo} the release of IL-6 in the endothelium induced by endothelin-1 (ET-1) in humans \(^{22,36}\). ET-1 is a potent vasoconstrictor peptide, but it is also recognized as a pro-inflammatory cytokine, including in the lung, and increased expression has been associated with pneumonia, pulmonary hypertension, interstitial lung fibrosis and acute respiratory distress syndrome \(^{37-39}\). In severe COVID-19 patients who survive the disease, cytokine levels, including IL-6, gradually return later in the course of the disease to levels comparable to those in mild cases \(^{31}\). Additionally, preliminary data from a Chinese study treating COVID-19 pneumonia with tocilizumab, a humanized recombinant monoclonal antibody blocking the IL-6 receptor, supports the pathogenic role of IL-6, although the treatment itself is controversial (ChiCTR2000029765, chinaXiv:202003.00026v1) \(^{40,41}\). Several clinical studies to test safety, tolerability and efficacy of tocilizumab for COVID-19 pneumonia are under way (NCT04317092, NCT04332913, NCT04320615). Also, a similar study is ongoing with another human monoclonal antibody, sarilumab, that targets the same IL-6 receptor (NCT04315298).

It is clear that older patients have an increased risk to develop (severe forms of) COVID-19 pneumonia \(^{16}\), which is thought to be a late response of the immune system to the viral infection. This may seem counterintuitive since many aspects of the immune response decrease in the elderly. However, both in mice and humans, serum levels of IL-6 increase with age \(^{42-44}\). Overexpression of IL-6 in older mice is harmful, and during systemic inflammation IL-6 strongly increases; moreover, this increase is prolonged with age in multiple tissues (e.g. lungs, heart, and plasma) \(^{45}\). Elevated levels of IL-6 are associated with a higher frequency of multiple organ failure \(^{34,46}\). Genomic analysis revealed that older people mount a stronger immune response, including IL-6, to SARS-CoV-1, and there is no reason to assume this would be different for SARS-CoV-2 \(^{30,47}\).
IL-6 or ET-1 may not only explain the age-dependence of COVID-19 pneumonia, but also the preponderance of male and obese or hypertensive patients, as well as of persons of colour, and smokers. Almost three out of four critically ill COVID-19 patients are male (72.5%; n=2,811) 16. Men have on average higher plasma IL-6 levels than women 43,46,48,49. In addition, under basal conditions, oestradiol induces a decrease, and testosterone an increase in the number of cells secreting ET-1 when stimulated with angiotensin-II 50. Long-term hormone replacement therapy users and premenopausal woman have lower systemic levels of IL-6 than their non-using co-twins or postmenopausal woman, respectively 51. Higher mortality was observed in COVID-19 patients with severe comorbidities 12, such as hypertension, diabetes and obesity. COVID-19 patients receiving angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers for their hypertension had a lower rate of severe disease and a lower level of IL-6 in peripheral blood 52. Adipocytes also produce IL-6 and this may explain why obese individuals have higher endogenous levels of C-reactive protein 49,53. It seems that more non-white than white people become critically ill 16. There is some evidence that ET-1 levels are significantly increased in black men compared to white men 54. Also, COVID-19 patients who smoke seem to be more susceptible, and it is known that ET-1 potentiates smoke-induced acute lung inflammation 55. Finally, there is some preliminary evidence that a need for mechanical ventilation was very strongly associated with elevated IL-6 levels, and that moderately elevated IL-6 levels are sufficient to identify COVID-19 patients at high risk of respiratory failure 1,56.

Given the critical role of IL-6 in severe COVID-19 disease, and the demonstrated ability of vitamin C to prevent the rise of IL-6 in several (pro)inflammatory conditions 57, it is logical to assume that vitamin C may benefit COVID-19 patients. Moreover, since vitamin C inhibits the increase of a range of inflammatory cytokines 20,58, it may be therapeutically superior to blockers of individual cytokine mediators. A randomized placebo-controlled study showed that vitamin C (500 mg twice daily) alleviates the inflammatory status by reducing, amongst others, IL-6 and C-reactive protein in hypertensive and/or diabetic obese patients 59. This suggests that vitamin C may also be of use in severe forms of COVID-19. Vitamin C may also inhibit the ability of neutrophils to form neutrophil extracellular traps, which may contribute to organ damage and mortality in COVID-19 60. Finally, vitamin C may have beneficial effects on the thrombotic or thromboembolic disease commonly found in COVID-19 patients 61-63.

A clinical trial is ongoing in which vitamin C (6 to 12 g /day) is being administered intravenously for moderate and severe cases of COVID-19 pneumonia (NCT04264533). At least 10 new COVID-19
related clinical trials have been started or are announced since February 2020 to investigate the therapeutic effect of vitamin C alone or in combination with one or more other substances e.g. vitamin D, zinc (gluconate), hydroxycholoquine (sulphate), azithromycin.

**Conclusion**

COVID-19 pneumonia and its progression to respiratory failure appear to be driven by an immune hyperreaction in which IL-6 and ET-1 play an important role. Vitamin C can reduce these (and other) inflammatory mediators in various inflammatory conditions, and this is clinically beneficial in (non-COVID-19) hypertensive and/or diabetic obese adult patients. Considering the weight of the evidence, and because vitamin C is cheap and safe, an oral low dose (500 mg/day) may be useful prophylactically, and in case of severe COVID-19 disease, an (intravenous) high-dose regimen may be beneficial. Ongoing clinical trials are expected to provide more definitive evidence.

**Acknowledgements**

We thank Dr. Patrick Van Dijck for proofreading the manuscript and Alan Feyaerts for his suggestions in the creation of this article.

**Contributions**

A.F.F. conceived and coordinated the study; A.F.F. and W.L. contributed to the writing of the manuscript.

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