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Applied nutritional investigation

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

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 causes the potentially fatal coronavirus disease 2019 (COVID-19). Already during the outbreak of the severe acute respiratory syndrome coronavirus 1, the use of vitamin C was suggested. Many patients with severe COVID-19 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 color and smokers. There is clear evidence that vitamin C in high doses can reduce these mediators. Vitamin C is cheap and safe. Hence, using a relatively low dose of vitamin C as prophylaxis, and in cases of severe COVID-19, an (intravenous) high-dose regimen may be beneficial. Ongoing clinical trials are expected to provide more definitive evidence.

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Introduction

A novel human coronavirus has recently been identified, the severe acute respiratory syndrome (SARS) coronavirus (CoV) 2, which causes the potentially fatal coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-2 is only the latest of three human coronavirus strains (the other two are SARS-CoV-1 and Middle East respiratory syndrome-CoV) that can cause severe illness, but 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 used off-label as prophylaxis or treatment [3–11]. Approximately 5% of 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 therapy, which is interesting in light of the suggestion that some SARS-CoV-2 proteins may interfere with hemoglobin function [14,15]. According to the latest Intensive Care National Audit and Research Center report from June 5, 2020 on COVID-19 in critical care, approximately 42%

(n = 3615) of critically ill patients with confirmed COVID-19 do not survive [16].

More than 100 animal studies have indicated that a daily dose of a few grams of vitamin C may alleviate or prevent infections [17]. Already during the outbreak of SARS-CoV-1 in 2003, the use of vitamin C, an essential micronutrient for humans and free radical scavenger, was suggested as a nonspecific treatment for severe viral respiratory tract infections [4,18,19]. Indeed, vitamin C is known to support various cellular functions of both the innate and adaptive immune systems, including modifying susceptibility to various viral infections, and by influencing inflammation [20,21]. Moreover, in chick embryo tracheal organ cultures, vitamin C increased resistance to infection by a coronavirus [22]. Additionally, vitamin C treatment restores the stress response and improves the survival of stressed humans [23]. However, a recent preliminary open-label study of patients with sepsis and acute respiratory distress syndrome showed that a 96-h infusion of high-dose vitamin C compared with placebo did not significantly improve organ dysfunction scores or change markers of inflammation [24]. In contrast, early use of intravenous vitamin C in combination with corticosteroid agents and thiamine proved effective in preventing progressive organ dysfunction and reducing the mortality of patients with severe sepsis and septic shock [25]. However, intravenous hydrocortisone alone had a similar effect on the survival of patients with septic shock as the combination of high-dose vitamin C, hydrocortisone, and thiamine [26], which suggests little added

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value of vitamin C in sepsis. However, vitamin C may have beneficial effects in adults and children with pneumonia [27], as well as patients in intensive care units [28]. A Cochrane systematic review concludes that 1 to 2 g vitamin C per day is safe, inexpensive, and has a consistent effect on the duration and severity of the common cold [29,30]. Furthermore, the study concludes that mega-dose prophylaxis is not rationally justified for community use, but may be justified at times (e.g., in periods of heavy physical exercise).

Evidence is accumulating that many patients who are severely ill with COVID-19 have elevated cytokine levels, including the multifunctional inflammatory key molecule interleukin (IL) 6, resembling the cytokine storm described in SARS and the Middle East respiratory syndrome [1,31–36]. 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 [37]. Treatment with vitamin C decreases IL-6 and blocks *in vivo* the release of IL-6 in the endothelium induced by endothelin-1 (ET-1) in humans [23,38]. ET-1 is a potent vasoconstrictor peptide, but also recognized as a proinflammatory cytokine, including in the lungs, and its increased expression has been associated with pneumonia, pulmonary hypertension, interstitial lung fibrosis, and acute respiratory distress syndrome [39–41]. In patients with severe COVID-19 who survive, cytokine levels, including IL-6, gradually return later in the course of the disease to levels comparable with those in mild cases [33]. Additionally, preliminary data from Chinese and U.S. studies treating COVID-19 pneumonia and mechanically ventilated patients, respectively, with tocilizumab (a humanized recombinant monoclonal antibody blocking the IL-6 receptor) support the pathogenic role of IL-6, although the treatment itself is controversial (ChiCTR2000029765, chinaXiv:202003.0002v1) [42–44]. Several clinical studies to test the 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).

Clearly, older patients have an increased risk to develop (severe forms of) COVID-19 pneumonia [45], 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 [46–48]. 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., the lungs, heart, and plasma) [49]. Elevated levels of IL-6 are associated with a higher frequency of multiple organ failure [36,50]. Gene expression analyses 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 [32,51].

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 persons of color and smokers. Almost three out of four patients critically ill with COVID-19 are male (70.8%; $n = 6814$) [16]. Men have on average higher plasma IL-6 levels than women [47,50,52,53]. In addition, under basal conditions, estradiol induces a decrease and testosterone an increase in the number of cells secreting ET-1 when stimulated with angiotensin-II [54]. Long-term hormone replacement therapy users and premenopausal women have lower systemic levels of IL-6 than their nonusing cotwins or postmenopausal women, respectively [55]. Higher mortality was observed in patients with COVID-

19 and severe comorbidities [12], such as hypertension, diabetes, and obesity. Patients with COVID-19 who receive angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers for their hypertension had a lower rate of severe disease and lower level of IL-6 in the peripheral blood [56]. Adipocytes also produce IL-6 and may explain why obese individuals have higher endogenous levels of C-reactive protein [53,57]. More nonwhite than white people become critically ill [45]. There is some evidence that ET-1 levels are significantly increased in black compared with white men [58]. Also, patients with COVID-19 who smoke seem to be more susceptible, and ET-1 is known to potentiate smoke-induced acute lung inflammation [59]. 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 patients with COVID-19 at a high risk of respiratory failure [1,60].

Given the critical role of IL-6 in severe COVID-19 and the demonstrated ability of vitamin C to prevent the increase of IL-6 in several (pro)inflammatory conditions [61], vitamin C can logically be assumed to benefit patients with COVID-19. Moreover, since vitamin C inhibits the increase of a range of inflammatory cytokines [21,62,63], the vitamin 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, among others, IL-6 and C-reactive protein in hypertensive and/or diabetic obese patients [64]. This suggests that vitamin C may also be of use in severe forms of COVID-19 [65]. 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 [66]. Finally, vitamin C may have beneficial effects on the thrombotic or thromboembolic disease commonly found in patients with COVID-19 [67–69].

More than 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], hydroxychloroquine [sulphate], and azithromycin) [70]. For example, a clinical trial is ongoing in which vitamin C (6 to 12 g/d) is administered intravenously for moderate and severe cases of COVID-19 pneumonia (NCT04264533). How the dose ranges were established in these different studies is not always clear. However, a recent review suggests that (much) higher intravenous vitamin C doses may be necessary for the reduction of cytokine storms in acute respiratory distress syndrome [63]. Even very high doses of intravenous vitamin C have been shown to be safe. No serious adverse reactions occurred in patients receiving chemotherapy with concomitant intravenous doses of up to 1.5 g/kg vitamin C at an infusion rate of up to 1 g/min, and no maximum-tolerated dose was reached [71,72]. High doses of vitamin C are generally assumed to be administered intravenously because they are poorly tolerated orally. However, Cathcart argued that bowel tolerance for vitamin C increased with the severity of illness in many patients, so that oral doses of up to 200 g/d could be tolerated by some patients [73]. This administration route may be preferable for patients treated at home or in facilities where intravenous administration may be difficult. For intensive care patients, intravenous administration may be preferred because virtually all have intravenous lines, and many cannot swallow or have gastrointestinal problems that interfere with drug absorption [74].

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 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 (1–2 g/d) may be useful prophylactically, and in cases of severe COVID-19, a (very) high-dose regimen may be beneficial. Ongoing clinical trials are expected to provide more definitive evidence.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit Author Statement

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

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