Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Nutrition 79–80 (2020) 110948

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Hypothesis

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

Adam F. Feyaerts Ph.D. [a,b,c,*], Walter Luyten Ph.D., M.D. [d]

[a] VIB Center for Microbiology, KU Leuven, Leuven, Belgium
[b] Laboratory of Molecular Cell Biology, KU Leuven, Leuven, Belgium
[c] Department of Technology, UCLL, Leuven, Belgium
[d] Department of Biology, KU Leuven, Leuven, Belgium

ARTICLE INFO

Article History:
Received 26 April 2020
Received in revised form 14 June 2020
Accepted 4 July 2020

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

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.

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

*Corresponding author. Tel.: 0479334963.
E-mail address: adamfeyaerts@gmail.be (A.F. Feyaerts).

https://doi.org/10.1016/j.nut.2020.110948
0899-9007/

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 woman have lower systemic levels of IL-6 than their nonusing cotwins or postmenopausal woman, 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.

Acknowledgments

The authors thank Dr. Patrick Van Dijck for proofreading the manuscript and Alan Feyaerts for his suggestions in the creation of this article. The authors thank a reviewer for pointing out the increased bowel tolerance for oral vitamin C in ill patients described by Cathcart, and for providing additional useful literature references.

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.

References

[1] Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020;71:769–77.
[2] Gabutti G, d'Anchera E, Sandri F, Savio M, Stefanati A. Coronavirus: Update related to the current outbreak of COVID-19. Infect Dis Ther 2020;9:1–13.
[3] Prajapat M, Sarma P, Shekhar N, Avti P, Sinha S, Kaur H, et al. Drug targets for corona virus: A systematic review. Indian J Pharmacol 2020;52:56–65.
[4] Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med 2020;46:315–28.
[5] Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res 2020;177:104762.
[6] Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents 2020;55:105923.
[7] Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. PloS One 2014;9:e109180.
[8] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72–3.
[9] te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6:e1001176.
[10] Scholz M, Derwand R. Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19? Med Hypotheses 2020;142:109815.
[11] U.S. Food and Drug Administration. Fact sheet for health care providers Emergency Use Authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Available at: https://www.fda.gov/media/136537/download. Accessed April 19, 2020.
[12] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.
[13] Brochard L. Mechanical ventilation: Invasive versus noninvasive. Eur Respir J 2003;(Suppl 47). 31s–7.
[14] Liu W., Li H.COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. 2020. Preprint: 10.26434/chemrxiv.11938173.v6
[15] International Hyperbarics Association, Naval Specialty Medical Center Program Team. Demonstration report on inclusion of hyperbaric oxygen therapy in treatment of COVID-19 severe cases. Available at: https://www.ihausa.org/Hyperbaric_oxygen_therapy_in_the_treatment_ofCOVID-19_Severe_Cases.pdf Accessed April 17. 2020.
[16] Intensive Care National Audit & Research Centre. ICNARC report on COVID-19 in critical care. Available at: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports. Accessed June 5, 2020.
[17] Hemila H. Vitamin C and infections. Nutrients 2017;9:339.
[18] Hemila H. Vitamin C and SARS coronavirus. J Antimicrob Chemother 2003;52:1049–50.
[19] Hemila H. Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J 1997;16:836–7.
[20] Ang A, Pullar JM, Currie MJ, Vissers MCM. Vitamin C and immune cell function in inflammation and cancer. Biochem Soc Trans 2018;46:1147–59.
[21] Carr AC, Maggini S. Vitamin C and immune function. Nutrients 2017;9:1211.
[22] Atherton JG, Kratzing CC, Fisher A. The effect of ascorbic acid on infection chick-embryo ciliated tracheal organ cultures by coronavirus. Arch Virol 1978;56:195–9.
[23] Marik PE. Vitamin C: An essential "stress hormone" during sepsis. J Thorac Disease 2020;12:S84–8.
[24] Fowler AA 3rd, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI randomized clinical trial. JAMA 2019;322:1261–70.
[25] Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. Chest 2017;151:1229–38.
[26] Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: The VITAMINS randomized clinical trial. JAMA 2020;323:423–31.
[27] Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-Working in harmony to reduce the risk of infection. Nutrients 2020;12:236.
[28] Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: A meta-analysis. Nutrients 2019;11:708.
[29] Hemila H, Chalker E. Vitamin C for preventing and treating the common cold. The Cochrane Database Syst Rev 2013:CD000980.
[30] Douglas RM, Hemila H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2007:CD000980.
[31] Brandt C, Pedersen BK. The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. J Biomed Biotechnol 2010;2010:520258.
[32] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
[33] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. MedRxiv 2020;55:102763.
[34] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol 2020;214:108393.
[35] Gao Y, Li T, Han M, Li X, Wu D, Xu Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92:791–6.
[36] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020:102452.
[37] Erol A. High-dose intravenous vitamin C treatment for COVID-19. Silivri-Istanbul, Turkey: Erol Project Development House for the Disorders of Energy Megabolism; 2020.
[38] Bohm F, Settergren M, Pernow J. Vitamin C blocks vascular dysfunction and release of interleukin-6 induced by endothelin-1 in humans in vivo. Atherosclerosis 2007;190:408–15.
[39] Freeman BD, Machado FS, Tanowitz HB, Desruisseaux MS. Endothelin-1 and its role in the pathogenesis of infectious diseases. Life Sci 2014;118:110–9.
[40] Teder P, Noble PW. A cytokine reborn? Endothelin-1 in pulmonary inflammation and fibrosis. Am J Respir Cell Mol Biol 2000;23:7–10.
[41] Silver RM. Endothelin and scleroderma lung disease. Rheumatology (Oxford) 2008;47:v25–6.
[42] Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Immunotherapy 2020;12:269–73.
[43] Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Available at: http://www.chinaxiv.org/abs/202003.00026. Accessed April 17, 2020.
[44] Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. medRxiv 2020. 2005.2029.20117358.
[45] Intensive Care National Audit & Research Centre. ICNARC report on COVID-19 in critical care. Available at: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports. Accessed April 10, 2020.
[46] Raynor J, Karns R, Almanan M, Li KP, Divanovic S, Chougnet CA, et al. IL-6 and ICOS antagonize bim and promote regulatory T cell accrual with age. J Immunol 2015;195:944–52.

[47] Young DG, Skibinski G, Mason JI, James K. The influence of age and gender on serum dehydroepiandrosterone sulphate (DHEA-S), IL-6, IL-6 soluble receptor (IL-6 sR) and transforming growth factor beta 1 (TGF-beta1) levels in normal healthy blood donors. Clin Exp Immunol 1999;117:476–81.
[48] Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A 2003;100:9090–5.
[49] Starr ME, Evers BM, Saito H. Age-associated increase in cytokine production during systemic inflammation: Adipose tissue as a major source of IL-6. J Gerontol A Biol Sci Med Sci 2009;64:723–30.
[50] Sperry JL, Friese RS, Frankel HL, West MA, Cuschieri J, Moore EE, et al. Male gender is associated with excessive IL-6 expression following severe injury. J Trauma 2008;64:572–8. discussion 578–9.
[51] Baas T, Roberts A, Teal TH, Vogel L, Chen J, Tumpey TM, et al. Genomic analysis reveals age-dependent innate immune responses to severe acute respiratory syndrome coronavirus. J Virol 2008;82:9465–76.
[52] Wei J, Xu H, Davies JL, Hemmings GP. Increase of plasma IL-6 concentration with age in healthy subjects. Life Sci 1992;51:1953–6.
[53] Starr ME, Saito M, Evers BM, Saito H. Age-associated increase in cytokine production during systemic inflammation-II: The role of IL-1beta in age-dependent IL-6 upregulation in adipose tissue. J Gerontol A Biol Sci Med Sci 2015;70:1508–15.
[54] Pearson LJ, Yandle TG, Nicholls MG, Evans JJ. Regulation of endothelin-1 release from human endothelial cells by sex steroids and angiotensin-II. Peptides 2008;29:1057–61.
[55] Ahtiainen M, Pöllänen E, Ronkainen PHA, Alen M, Puolakka J, Kaprio J, et al. Age and estrogen-based hormone therapy affect systemic and local IL-6 and IGF-1 pathways in women. Age (Dordr) 2012;34:1249–60.
[56] Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020;9:757–60.
[57] Bastard JP, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentrations in obese subjects. Circulation 1999;99:2221–2.
[58] Evans RR, Phillips BG, Singh G, Bauman JL, Gulati A. Racial and gender differences in endothelin-1. Am J Cardiol 1996;78:486–8.
[59] Bhavsar TM, Liu X, Cerreta JM, Liu M, Cantor JO. Endothelin-1 potentiates smoke-induced acute lung inflammation. Exp Lung Res 2008;34:707–16.
[60] Herold T, Jurinovic V, Arnreich C, Hellmuth JC, von Bergwelt-Baildon M, Klein M, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv 2020. 2004.2001.20047381.
[61] Canali R, Natarelli L, Leoni G, Azzini E, Comitato R, Sancak O, et al. Vitamin C supplementation modulates gene expression in peripheral blood mononuclear cells specifically upon an inflammatory stimulus: A pilot study in healthy subjects. Genes Nutr 2014;9:390.
[62] Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience 2020;14:1022.
[63] Boretti A, Banik BK. Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome. PharmaNutrition 2020;12:100190.
[64] Ellulu MS, Rahmat A, Patimah I, Khaza'ai H, Abed Y. Effect of vitamin C on inflammation and metabolic markers in hypertensive and/or diabetic obese adults: A randomized controlled trial. Drug Des Devel Ther 2015;9:3405–12.
[65] Hernández A, Papadakos PJ, Torres A, González DA, Vives M, Ferrando C, et al. Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19. Rev Esp Anestesiol Reanim 2020;67:245–52.
[66] Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med 2020;217:e20200652.
[67] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020;75:2950–73.
[68] Sathler PC, Lourenço AL, Saito MS, Arêas APG, Rodrigues CR, Cabral LM, et al. The antihemostatic profile of vitamin C: Mechanisms that underlie the technical application of a physiological molecule. Arch Biol Sci 2016;68:325–31.
[69] Parahuleva MS, Jung J, Burgazli M, Erdogan A, Parviz B, Hölschermann H. Vitamin C suppresses lipopolysaccharide-induced procoagulant response of human monocyte-derived macrophages. Eur Rev Med Pharmacol Sci 2016;20:2174–82.
[70] U.S. National Library of Medicine. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/results?term=vitamin+c+AND+COVID-19&Search=Search. Accessed April 17, 2020.
[71] Wang F, He MM, Wang ZX, Li S, Jin Y, Ren C, et al. Phase I study of high-dose ascorbic acid with mFOLFOX6 or FOLFIRI in patients with metastatic colorectal cancer or gastric cancer. BMC Cancer 2019;19:460.
[72] PDQ Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ high-dose vitamin C. Bethesda, MD: National Cancer Institute; 2020.
[73] Cathcart RF, Vitamin C. titrating to bowel tolerance, anascorbemia, and acute induced scurvy. Med Hypotheses 1981;7:1359–76.
[74] Power BM, Forbes AM, van Heerden PV, Ilett KF. Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet 1998;34:25–56.