Cytokine release syndrome (CRS) and nicotine in COVID-19 patients: trying to calm the storm

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Summary

SARS-CoV-2 is a new coronavirus that has caused a worldwide pandemic. It causes a severe acute respiratory syndrome (COVID-19), fatal in many cases, characterized by a cytokine release syndrome (CRS). Great efforts are currently being made to block the signal transduction pathway of pro-inflammatory cytokines in order to control this "cytokine storm" and rescue severe patients. Consequently, possible treatments for cytokine-mediated hyperinflammation, preferably within approved safe therapies, are urgently being searched to reduce rising mortality. One approach to inhibit proinflammatory cytokine release is to activate the cholinergic anti-inflammatory pathway through nicotinic acetylcholine receptors (α7nAchR). Nicotine, an exogenous α7nAchR agonist, is clinically used in ulcerative colitis to counteract inflammation. We have found epidemiological evidence, based on recent clinical SARS-CoV-2 studies in China, that suggest that smokers are statistically less likely to be hospitalized. In conclusion, we hypothesize that nicotine could constitute a novel potential CRS therapy in severe SARS-CoV-2 patients.

Introduction

SARS-CoV-2 is a new coronavirus that originated in Wuhan (Hubei Province, China) in December 2019 and it has already spread into a pandemic spreading worldwide[1]. It causes a severe acute respiratory syndrome[2]. SARS-CoV-2 is the third coronavirus outbreak during the current century after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[3].

SARS-CoV-2 causes varying illness degrees. Fever and cough are dominant symptoms, but severe disease also occurs. Then, when COVID-19 patients' aggravation is presented, lungs hyperinflammation may appear due to virus-activated "cytokine storm" or cytokine release syndrome (CRS)[4]. Among different cytokines increased in such exacerbated response[5], mainly Interleukin-6 (IL-6) in serum is expected to predict the severity of SARS-CoV-2 pneumonia, as suppression of pro-inflammatory IL-6 have been shown to have a therapeutic effect in many inflammatory diseases, including viral infections[6].

In severe cases, SARS-CoV-2 has been shown to activate both, innate and adaptive immune system in the alveolar tissue, inducing the release of many cytokines and subsequent cytokine release syndrome[7]. During this response, levels of pro-inflammatory cytokines (include TNFα, interleukin (IL)-1b, IL-6, and IL-8) are increased[5] which is also an important cause of death[8]. Therefore, one may think that controlling such crucial inflammatory factors could be a successful approach to reduce mortality in severe patients.

Could the cytokine storm be controlled by a physiological protective anti-inflammatory mechanism?

It has been demonstrated the existence of a cholinergic anti-inflammatory pathway that modulates inflammatory responses during systemic inflammation[9]. α7–nicotinic acetylcholine receptor (α7nAChR) are known to be expressed on macrophages and to be essential for attenuating the inflammatory response by their activation during systemic inflammation[10]. The underlying mechanism conveys that activation of α7nAChR on infiltrated inflammatory cells, including macrophages and neutrophils, induces suppression of NF-kB activation[11] and secretion of pro-

inflammatory cytokines and chemokines from inflammatory cells including alveolar macrophages[12]. Interestingly, it has been already reported that nicotine, a α7nAChR agonist, exerts an anti-inflammatory effect in a murine model of acute lung injury[13]. In fact, in other inflammatory diseases as ulcerative Colitis (UC), smoking or treatment with nicotine has demonstrated to significantly decrease the risk of developing the disease[14].

The nicotine-COVID19 hypothesis

In this scenario, we hypothesize that nicotine could ameliorate the cytokine storm and severe related inflammatory response through α7nAChR-mediated cholinergic anti-inflammatory pathway. Nicotine is an accessible, existing and approved treatment, with described side effects, that could likely reduce the rising mortality in the short term.

Support for the hypothesis

Paradoxically, it is well stablished that smokers have a significantly increased risk of chronic respiratory disease and acute respiratory infections. Current smokers have a higher risk of developing influenza compared to non-smokers[15]. Smoking is also significantly associated with MERS-CoV[16], and there is no clear evidence for SARS-CoV-2[17].

As in China, among men, 54.0% are current smokers while among women, only 2.6%[18], it should be expected that the number of current smokers hospitalized with SARS-CoV-2 should be in a similar or larger percentage, with male predominance. However surprisingly, the number of hospitalized smoking patients in the Chinese outbreak is much lower than expected[19–23]. In Table 1 we show results of comparing, both separately and using a combined approach, proportions of hospitalized smokers with SARS-CoV-2 in five different studies. Combined total current smokers was 159 compared to 526·0 expected considering male/female current smokers' ratio in China. We perform χ^2 test or Fisher's exact test to compare differences between observed and expected current smoker, for all the studies individually and combining all data, and we found significant differences in all cases ($p < 0{\cdot}001$).

On the other hand, there are different formulations for nicotine administration: gums, patches, inhalators, nasal and oral sprays, sublingual tablets and electronic cigarettes. Apart from the electronic cigarettes that are quite new, the previous are considered relatively safe as most side effects are mild[24]. For instance, in the clinical practice transdermal nicotine is administered at high tolerated dosage for controlling clinical manifestations of chronic UC. For acute SARS-CoV-2 treatment to ameliorate hyperinflammation, nicotine dosage and pharmaceutical form could be chosen according to previous experience with UC[14,25].

To our knowledge, no clinical trials of nicotine in COVID19 patients are currently being run. The most promising trial under run is the one using Tocilizumab, a blocker of IL-6 receptor for the treatment of cytokine storm[6], so it is expected to be an effective drug of severe patients.

Conclusions

It has been observed that the number of current smokers hospitalized in the SARS-CoV-2 outbreak in China is lower than expected if compared to the prevalence of smoking in this country. It has been described that due to a cytokine storm, many patients aggravate, showing severe inflation in the lungs. Our proposal may be easily tested in the short term, as it takes advantage of the existence of a cholinergic anti-inflammatory pathway that physiologically modulates inflammatory responses during systemic inflammation effect. Then, controlling the cytokine storm using nicotinic administration could be expected to become a new method for the treatment of severe patients, as it has already been proved in UC patients.

Just very recently a group of recognized experts in the field recommended the "identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality"[8]. Current treatment with Tocilizumab seems to be useful to control cytokines storm. However, very strict criteria for its clinical use limits its availability, mainly due to price and adverse effects. Our proposal suggest that the treatment with nicotine by using any of the pharmaceutical forms available in the market could reduce the lung inflammatory response by controlling the cytokines storm and thus, the number of patients in need of hospitalization for aggravation in the SARS-CoV-2 outbreak.

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Contributors

JGR and AN designed the study and collected data. JGR, LJD, JDNL, and AN wrote the manuscript. All authors analysed and interpreted the data.

Competing Interests statement

The authors declare no conflict of interest.

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Table 1. Comparison of hospitalized current smokers in the Chinese COVID19 outbreak. The combined analysis is the result of the summation of all individual studies.

	N (male/female)	current smokers	expected current smokers (male/female)	Sig.
Zhou et al., 2020	191 (119, 72)	11	66·2 (64·3, 1·9)	p<0·0001
Guan et al., 2020	1096 (637, 459)	137	355·9 (344·0, 11·9)	p<0·0001
Huang et al., 2020	41 (30, 11)	3	16·5 (16·2, 0·3)	p=0·0006
Zhang et al., 2020	140 (69, 71)	2	39·2 (37·3 ,1·9)	p<0·0001
Mo et al., 2020	155 (86, 69)	6	48·2 (46·4, 1·8)	p<0·0001
Combined	1623 (941, 682)	159	526·0 (508·2, 17·8)	p<0·0001