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OPINION ARTICLE

Chronic Use of Azithromycin Might Explain the Low Prevalence of COVID-19 in Cystic Fibrosis Patients

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Severe Acute Respiratory Syndrome – Coronavirus 2 (SARS-CoV-2) is the virus responsible for the pandemic that in the first months of 2020 caused worldwide more than 8 millions of infected subjects and 436,000 deaths.

It has been reported that only few individuals affected by cystic fibrosis (CF) developed the clinical manifestations of the often dramatic SARS-CoV-2 related disease, now known as Coronavirus Disease 19 (COVID-19).

In Europe, (data updated at 10 June 2020), only 90 cases of COVID-19 in CF patients have been reported, with 6 subjects requiring admission into intensive care unit (ICU) and 3 deaths. Clinical data are now available for 42 hospitalized patients: 32 of them presented with "mild", 7 with "severe" and 3 with "critical" COVID-19. In more than 70% of CF patients the SARS-CoV-2 infection impaired the pulmonary function, while 42% of them remained totally asymptomatic (https://www.ecfs.eu/news/covid-cf-project-europe).

From the epidemiological point of view, these numbers seem to be very impressive, if we consider that in Europe it has been estimated to live 48,000 CF patients (https://www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report2017_v1.3.pdf) and that the rate of infection by Coronavirus ranged from 29/100,000 (in Greece) to 393/100,000 (in Italy) and 522/100,000 in Spain (https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea).

Also the outcome of COVID-19 in CF population seems to be favorable, if we consider that in the general population 10% of infected individuals during pandemic required hospitalization in ICU [1].

Dr. Colombo reported that, at the 31st March 2020, in Lombardia (Italy) Coronavirus was documented in 10 CF patients out of 42,161 infected people, so confirming the low rate of infection or at least of COVID-19 clinical manifestations in CF population [2]. Different possible explanations for this phenomenon have been hypothesized: 1) The younger age of CF patients, 2) The immediate minimization of social contacts, and 3) The probable protective role of some drugs that CF patients commonly receive, such as azithromycin. This third option might be particularly relevant, considering that it is well known that azithromycin is a "senolytic" drug and that the senescence has been reported to be fundamental in COVID-19 also [3]. In CF, azithromycin is usually employed because its ability of increasing FEV1 [4] and of playing an anti-inflammatory action [5].

In COVID-19, its role has been recently debated: indeed, it has been initially reported that this antibiotics induced a rapid viral load negativization when used in combination with hydroxychloroquine [6], but a recent review showed conflicting results, either *in vitro* or *in vivo*, even if in a small series a superior viral clearance in patients treated with azithromycin and hydroxychloroquine, compared with hydroxychloroquine alone, has been reported [7].

During the first phase of attack, SARS-CoV-2 seems to fight the host both by blocking autophagy, the first line of host anti-viral defense [8], and by increasing the cellular senescence [3]. During infection, one of viral proteins, the open reading frame 9b (Orf-9b), goes to

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localize itself inside the host cells mitochondria where it blocks the interferon-dependent anti-viral action by the proteasome-dependent degradation of the mitochondrial Dynamin-1 like (DRP1) protein. The consequences of this viral activity are several mitochondrial abnormalities and dysfunctions, such as hyperfusion, with the final acquisition for the infected host cells of the senescent phenotype. Once senescent, the infected cells start to widespread the new viruses by producing high amounts of extra-cellular vesicles, such as exosomes, that can reach different sites and further damage different tissues. At the same time, senescent cells overproduce pro-inflammatory cytokines, chemokines and growth factors, responsible for the COVID-19 onset [3]. Indeed, patients with COVID-19 show lymphopenia, elevated levels of pro-inflammatory cytokines (TNF alpha, IL2, IL6, IL17, macrophage inflammatory protein 1 alpha), atrophy of spleen and lung infiltration characterized by a high number of macrophages. This population would be responsible for the "primary" cytokine storm, whilst the "secondary" one might be provoked by the activated T lymphocytes [9].

Recently, our group reported the important role of neutrophils that would be able to form neutrophil extracellular traps (NETs) that may actively contribute to hyper-inflammation and thrombotic events that in COVID-19 are frequently reported [10]. Interestingly, it has been demonstrated that pre-incubation of neutrophils isolated from healthy donors with increasing concentrations of azithromycin significantly decreased the release of NETs [11]. Considering that in CF neutrophils can extrude large amounts of nuclear material through NETs into the airways of patients, so contributing to the lung damage [12], the "anti-NET" activity of azithromycin might once again make these antibiotics an effective bullet against COVID-19 and CF.

In conclusion, SARS-CoV-2, blocking autophagy (especially by using the CD26 receptor), and inducing high rate of senescence, is able to fast replicate before the onset of host's immune response onset. Azithromycin, that already plaid an anti-viral action against Zika and influenza H1N1 viruses [13], by its "senolytic" and "anti-NET" actions, might play a defensive role also against SARS-CoV-2, so probably at least in part contribute to explain the low incidence of COVID-19 in CF population.

Declaration of Competing Interest

I declare that I have no known competing financial interests or personal relationships that could have influenced what reported in this paper.

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This manuscript is dedicated to G.T, L.T, G.T, O.T.

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