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.

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OPINION

Could Respiratory Fluoroquinolones, Levofloxacin and Moxifloxacin, Prove to be Beneficial as an Adjunct Treatment in COVID-19?

Irene Karampela[a,*] and Maria Dalamaga[b,*]

[a]*Second Department of Critical Care, Attikon General University Hospital, Medical School, National and Kapodistrian University of Athens, Chaidari, Athens, Greece*

[b]*Department of Biological Chemistry, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece*

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Since the beginning of the COVID-19 pandemic, researchers have focused on repurposing of existing antibiotics, antivirals and anti-inflammatory drugs to find an effective therapy. Fluoroquinolones are broad spectrum synthetic antimicrobial agents, being chemical derivatives of quinoline, the prodrome of chloroquine. Interestingly, fluoroquinolones may exert antiviral actions against vaccinia virus, papovavirus, CMV, VZV, HSV-1, HSV-2, HCV and HIV. A recent *in silico* study has shown that the fluoroquinolones, ciprofloxacin and moxifloxacin, may inhibit SARS-CoV-2 replication by exhibiting stronger capacity for binding to its main protease than chloroquine and nelfinavir, a protease inhibitor antiretroviral drug. Remarkably, fluoroquinolones have shown multiple immunomodulatory actions leading to an attenuation of the inflammatory response through the inhibition of pro-inflammatory cytokines. Noteworthy, respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute fist line therapeutic agents for the management of severe community-acquired pneumonia. They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and b-lactams. Based on their potential antiviral activity and immunomodulatory properties, the favorable pharmacokinetics and safety profile, we propose the use of respiratory fluoroquinolones as adjuncts in the treatment of SARS-CoV-2 associated pneumonia.

Key Words: COVID-19, Fluoroquinolone, Infection, Levofloxacin, Moxifloxacin, Pneumonia.

The emergence of the coronavirus SARS-CoV-2 evoked an unprecedented threat worldwide. Ever since the start of this pandemic, researchers and clinicians have focused on repurposing of existing antibiotics, antivirals and anti-inflammatory drugs to find an effective therapy to combat COVID-19. However, preliminary clinical trials reported conflicting results regarding the use of the anti-malarial and anti-inflammatory chloroquine and the macrolide azithromycin, while the antiviral remdesivir has not been shown to significantly decrease COVID-19 mortality (1,2).

Fluoroquinolones, a family of 6-fluoro-7-piperazinyl-4-quinolones, are broad spectrum synthetic antimicrobial agents derived from quinolones with the addition of a fluorine atom attached to the central ring (3). They exert their bactericidal effect by targeting the bacterial DNA gyrase (type II topoisomerase) and topoisomerase IV thus inhibiting bacterial DNA synthesis and leading to cleavage of bacterial DNA and rapid bacterial death (4). Fluoroquinolones are active against gram-negative and gram-positive bacteria, anaerobes, mycobacteria and atypical pathogens. Respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute fist line therapeutic agents for the management of severe community-acquired pneumonia, according to treatment guidelines (5).

Fluoroquinolones are chemical derivatives of quinoline, the prodrome of chloroquine (6). Indeed, quinoline and quinolone based compounds are being investigated for their

*These authors contributed equally to this work.

Address reprint requests to: Maria Dalamaga, MD, MSc, MPH, PhD, Associate Professor in Biological, Chemistry-Clinical Biochemistry, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; Phone: (+30) 2107462624; FAX: (+30) 2106082467; E-mail: madalamaga@med.uoa.gr

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antiviral activity against various viruses such as Ebola and Dengue virus (7). Interestingly, fluoroquinolones have also been shown to exert antiviral actions against vaccinia virus, papovavirus, human cytomegalovirus, varicella-zoster virus, herpes simplex virus types 1 and 2, hepatitis C virus and HIV (6,8,9). A recent *in silico* study demonstrated that the fluoroquinolones, ciprofloxacin and moxifloxacin, exert strong capacity for binding to SARS-CoV-2 main protease (M^{pro}), indicating that fluoroquinolones may inhibit SARS-CoV-2 replication (10). Furthermore, fluoroquinolones may bind to the M^{pro} active site more strongly than chloroquine and nelfinavir, a protease inhibitor antiretroviral drug used in the treatment of the AIDS. Additionally, experimental studies have demonstrated that levofloxacin exerts antioxidative and NO regulatory effects in an animal model of H1N1 influenza virus induced lung injury, and significantly improves survival (11). In particular, levofloxacin exhibited scavenging actions against neutrophil-derived hydroxyl radicals and suppressed NO production, leading to decreased markers of oxidative stress and NO metabolites in the lungs of H1N1 influenza virus infected animals. Remarkably, fluoroquinolones exhibit multiple immunomodulatory actions leading to attenuation of inflammatory response through the inhibition of pro-inflammatory cytokines such as IL-1 and TNF-α, as shown in experimental and clinical studies (12). Noteworthy, respiratory fluoroquinolones are characterized by advantageous pharmacokinetic properties, leading to significantly higher concentrations in the lungs compared to serum, as well as an excellent safety profile comparable to other antibiotics used to treat respiratory infections, such as macrolides and b-lactams (13,14).

Considering the potential antiviral activity of respiratory fluoroquinolones against SARS-CoV-2, along with their immunomodulatory properties, their favorable pharmacokinetics and the excellent safety profile, we propose their use as adjuncts in treating patients presenting COVID-19. Therefore, randomized clinical trials of respiratory fluoroquinolones are necessary to explore their potential therapeutic effect as an adjunct in the treatment of SARS-CoV-2 associated pneumonia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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