Review Article

The potential role of Fluoroquinolones in the management of Covid-19 a rapid review

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ABSTRACT

COVID-19 is a pandemic viral pneumonia caused by β-coronavirus SARS-CoV-2. It is associated with many complications including extreme systemic inflammatory response which eventually causes acute respiratory distress syndrome (ARDS), hypercoagulability, cytokine storm, failure of vital organs, and a high incidence of death. Bacterial secondary infection is possibly involved, in such cases, the role of antibiotics is justified. However, some antibiotics may have a role beyond the management of secondary infection. The current review discussed the potential antiviral effects of certain Fluoroquinolones (FQs) against SARS CoV-2 viruses. Several mechanisms such as targeting Main proteases and acting as zinc ionophore are discussed. Also explained their unique features, good access to lung tissues for suppression of inflammatory response via modulation of matrix metallopeptidases (MMPs) are explored. Their role in secondary infections, pharmacokinetics, and safety issues was briefly explored. The promising favorable features of FQs along with their efficacy in the management of secondary infections, highlights the need to consider these important antibiotics for more research as well as clinical trials in the management of COVID-19.

Keywords: FQ, Covid-19, Viral pneumonia, SARS-COV-2, ARDS, Matrix metallopeptidases

Introduction

COVID-19 is a complicated infectious viral pneumonia caused by β-coronavirus SARS-CoV-2 [1-3]. There are many risk factors for Severe illness & complications including advanced age, comorbidities such as heart disease, hypertension, prior stroke, diabetes, etc [4, 5]. Complications also include ARDS [6]. The most frequently observed histopathologic changes linked to critical cases of COVID-19 was Diffuse Alveolar Damage (DAD), with the focal organization, intra-alveolar fibrinous exudates containing inflammatory cells, hyaline membrane formation, proliferating fibroblasts surrounded by neutrophils, and dilated pulmonary capillaries with micro thrombus formation [7-10].

Moreover, complications may include hypoxia and coagulation disorders [11, 12]. Data were accumulated which documented the association between the novel virus infection and "cytokine storm" [13-15] which eventually cause acute respiratory distress syndrome (ARDS); organ failure, and high incidence of death [6].

SARS-CoV-2 genomics and drug targets

SARS-CoV-2 has a single- positive-sense stranded RNA associated with a nucleoprotein protein **(Figure 1)**. In all coronaviruses, the genomic proteins are Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) [16]. Many target sites for drugs against the virus were suggested [17]. Most repurposed drugs act against the virus by one or more of the following: (1) inhibition of viral binding to its host cell receptors, (2) preventing membrane fusion, (3) prevent viral endocytosis, and release of viral RNA, (4) suppressing replication and translation by interfering with many of viral-specific protease/helicase [17-26].

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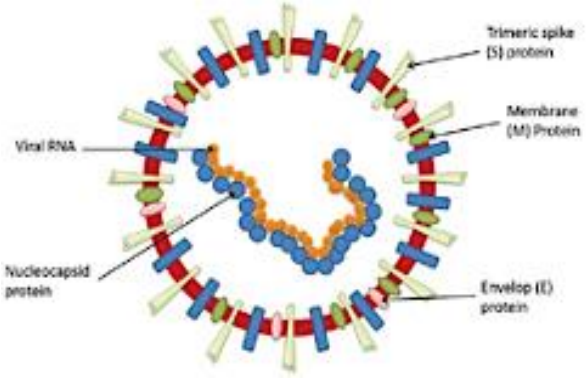

Figure 1. Simplified genomic structure of SARS-CoV-2

Secondary infection among hospitalized COVID-19 patients

Bacterial co-infection was recognized with previous pandemic viral pneumonia and possibly raise disease-associated mortality [27, 28].

Data are accumulated regarding secondary infections in covid-19 patients [29-40]. These findings can be summarized as follows:

- Severely ill hospitalized patients, especially those admitted to ICU commonly suffer secondary bacterial lung infections. The fungal or secondary viral infection is less common.
- Prolonged disease/intubation was associated with nosocomial infection with Gram-negative multidrug-resistant bacteria.
- Incidence of secondary infection among the elderly and those with chronic diseases such as chronic obstructive pulmonary disease (COPD) [41].
- Co-infection with various viruses was also possible; e.g. influenza A virus [42] and Cytomegalovirus [43].

Limited publications suggested the role of FQs in COVID-19 [44], therefore this review aimed to highlight the potential benefit of judicious use of these antibiotics in this pandemic disease.

COVID 19 and expanding use of antibiotics

Repurposing of available FDA approved drugs seemed a realistic approach for the management of the novel virus [45, 46]. These drugs were usually suggested by computational approaches [47]. A list of these drugs was published [3, 48- 51]. Many are candidates for further *in vivo* testing or clinical trials [52]. One drug may have multiple targets and additional effects. Among these repurposed drugs are antibiotics especially those with documented efficacy against secondary infections for example macrolides, tetracycline, fluoroquinolones (FQs) among others [53-56].

Materials and Methods

PubMed, Google Scholar, search. using appropriate Keywords, e.g., COVID-19, SARS-CoV-2, FQ, more detailed pharmacology of these drugs was retrieved from web-based drug information resources and textbooks

Fluoroquinolones (FQs)

Overview

Quinolones and FQs are bactericidal, broad-spectrum antibiotics indicated for the management of, respiratory tract infections (RTI) among many other indications [57, 58]. FQs inhibit bacterial DNA synthesis [59]. Currently, four generations of FQs are available, all are active against many gram-negative bacteria. The 4th generation e.g. gatifloxacin, clinafloxacin retains the gram-positive and gram-negative bactericidal activity and inhibits anaerobic bacteria [57].

Role in the management of pneumonia?

FQs have a clear role in the management of pneumonia. Levofloxacin and Oseltamivir were successfully used to treat Severe Pneumonia [58]. The 4th generation gatifloxacin, moxifloxacin showed broad activity against Gram-positive organisms, as *S. pneumoniae* and *Enterobacteriaceae*, atypical and anaerobic, also showed a lower incidence of resistance and longer half-life allowing once-daily dosing [59]. However, several reports highlighted the important rational use of FQs should be implemented to minimize the development of bacterial resistance [60, 61].

Antiviral activity of FQs

FQs were demonstrated to be active against certain viruses in cultured mammalian cells. Ofloxacin had inhibitory activity against the vaccinia virus (VV) and it prevents the pox tail lesion formation in mice infected with VV [62]. Moreover, FQ derivatives inhibited the replication of HIV-1, HIV-2 [63], and African swine [64]. The efficacy of some FQs e.g. ciprofloxacin was reported for Hepatitis C Virus (HCV) and the BK polyomavirus (BKV) [65, 66], Ofloxacin was active against rhinovirus (RV) [67].

Suggested mechanism for antiviral activity

Among the identified drug target for coronaviruses is the main protease (M^{pro}, or $3CL^{pro}$) [68] and papain-like protease(s) (PL^{pro}), which are essential contributors in the viral replication cycle. These enzymes are not available in human cells so that drugs targeting these enzymes will be specific with a minor impact on human cells. Silico studies demonstrated that FQ (e.g. moxifloxacin), binds to and inhibits SARS-CoV-2 M^{pro}, consequently prevent its replication [69]. Interestingly the interaction of FQs with M^{pro} suggested being stronger compared to other protease inhibitors namely nelfinavir and chloroquine.

An illustration of this suggested mechanism is presented in **(Figure 2)**. In the same context, ofloxacin was observed to

inhibit topoisomerases/helicases in the vaccinia virus [62]. It also inhibited reverse transcriptase in human immunodeficiency virus (HIV) activity [70-73].

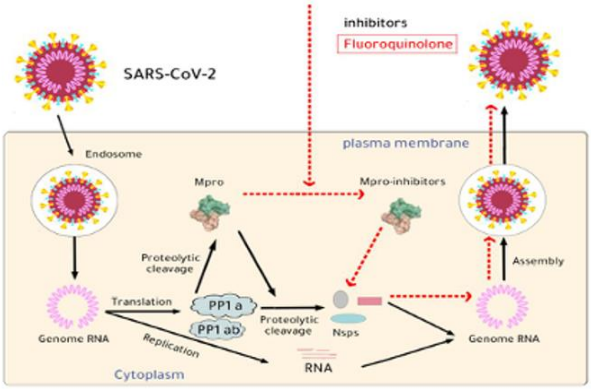

Figure 2. Proposed Cellular Effect of FQ on SARS-CoV-2

Immune modulation/ anti-inflammatory effect

Umbro *et al*. (2013) demonstrated the benefits of ciprofloxacin in kidney transplant patients in preventing acute rejection and attributed these findings to the activity of the drug against BKV [73]. Also, Enoki *et al*. (2015) reported that levofloxacin attenuated various acute inflammatory conditions associated with viral pneumonia [74]. Poor distribution of the HCQ due to lung pathological changes was suggested as a reason for lower efficacy in severe cases of covid-19 [75]. Recall that viral lung infections, induce a state of oxidative stress due to reactive oxygen species (ROS) and nitric oxide (NO) [75]. FQs show anti-oxidant activity against these events and suppress lung inflammation associated with pneumonia [76]. Fluoroquinolones suppress the production of pro-inflammatory cytokine Il-1 and TNF [77]. Phase 3 clinical trial proved its efficacy of IL-1 antagonist in the management of sepsis [78].

The diagram **(Figure 2)** shows, the viral entry, the release of its RNA from endosomes, FQs, accumulate intracellularly bind to Mpro and inhibit its activity, Mpro is involved in the production of Nsps which are essential for viral replication and assembly. Adapted from Mengist 2020 [79].

Favorable PK characteristics of FQs allowing efficacy in respiratory infections

FQ shows excellent access to lung tissue, including bronchial mucosa, so that its level excessed that, in serum at a steady state [80]. An in vitro study showed that ciprofloxacin is actively transported across bronchial lung epithelial cells [81].

This was confirmed clinically in mechanically ventilated severely ill Patients with COPD. The drug demonstrated excellent penetration into bronchial secretions, In all patients, the target level (AUC0–24/MIC ≥125) was achieved [82]. Moreover, a prospective open-label study documented the favorable pharmacokinetics and pharmacodynamics of moxifloxacin in COPD patients [83].

FQ as zinc ionophore

Ciprofloxacin can form a complex with Zn(II), **(Figure 3)** with enhanced antibacterial activity against bacteria compared to the parent noncomplex drug. This was explained because the fact chelation of the Zn ion reduces its polarity thus increases its lipophilicity and permeation through the membranes [84].

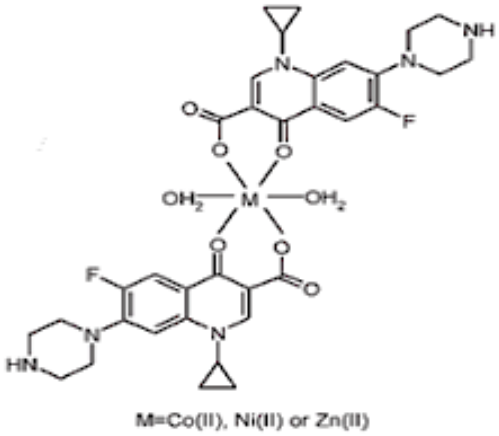

Figure 3. Ciprofloxacin Zinc complex

Recalling the role of zinc supplement against Covid-19 due to its potential immune stimulation, broad-spectrum antiviral activity [85-87]. It is supposed to enhance both innate and humoral immunity, especially in immunocompromised geriatric patients. Zinc shows the synergistic effect with some antiviral drugs. It may diminish the RNA-synthesis in coronavirus. Taken together, we speculate that FQ is likely to have (Zinc ionophore action), zinc supplement may enhance their activity against covid-19.

Safety concern of FQs

The pharmacology of FQs is detailed in several textbooks and web-based drug information resources [88]. Fluoroquinolones, like most antibiotics, have a long list of adverse effects, drug interactions, and contraindications that should be considered before their use [89]. The safety concern of FQs was a subject of several reviews [90]. A Systematic Review and Meta-Analysis of Randomized Controlled Trials revealed FQs are associated with more CNS- and GI-related adverse effects compared with other types of antibiotics [91]. However, regarding the management of life-threatening infections, it is logical to judge the risk to benefit ratio. Although potential FQs related disability was associated with their chronic use (120 days) [92]. This concern is not likely to be relevant in the management of Covid-19 associated pneumonia. The Risk of Fluoroquinolone-induced Tendinopathy and Tendon Rupture was also reported [93].

Cardiac toxicity of FQs

Meta-analysis studies showed a positive association between FQs and the development of an aortic aneurysm. Some risk factors that appear to be related to these effects include prolonged FQ treatment and aging [94, 95]. FQs prolong the QT interval by blocking voltage-gated potassium channels, especially the rapid component of the delayed rectifier potassium current I(Kr), expressed by HERG (the human ether-a-go-go-related gene). Moxifloxacin carries the greatest risk. Ciprofloxacin has the lowest risk of QT prolongation. All FQs should also be used with caution in patients at risk for QT prolongation. The overall risk of fatal arrhythmia TdP is low, which can be minimized by a proper management plan including identifying high-risk patients and avoiding concomitant drugs with synergistic cardiotoxic effects [96, 97].

Drug interaction

There are significant interactions between FQs and multivalent cations (calcium, aluminum, zinc) [98]. FQs can increase the level of warfarin, cyclosporine, sirolimus, and digoxin [99]. However, in a clinical setting, the extent of drug interaction may vary under fast and fed conditions [100].

Conclusion

It is imperative to suggest that FQs may have potential antiviral effects and can be effective in some patients affected by SARS CoV-2 viruses. It is suggested that these infected patients could be stratified according to certain criteria such as cardiac, diabetic, and old age patients, etc. Accordingly, various types of patients could benefit from the use of FQs in the present pandemic.

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