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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REVIEW ARTICLE

Pharmacological basis for the potential role of Azithromycin and Doxycycline in management of COVID-19

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Abstract A novel corona virus SARS-CoV-2 has led to an outbreak of the highly infectious pandemic COVID-19 complicated viral pneumonia. Patients with risk factors frequently develop secondary infections where the role of appropriate antibiotics is mandatory. However, the efforts of drug repurposing lead to recognizing the role of certain antibiotics beyond the management of infection. The current review provided the detailed antiviral, immunomodulatory effect, unique pharmacokinetic profile of two antibiotics namely azithromycin (AZ) and doxycycline (DOX). It summarizes current clinical trials and concerns regarding safety issues of these drugs.

Azithromycin (AZ) has amazing lung tissue access, wide range antibacterial efficacy, conceivable antiviral action against COVID-19. It also showed efficacy when combined with other antiviral drugs in limited clinical trials, but many clinicians raise concerns regarding cardiovascular risk in susceptible patients. DOX has a considerable role in the management of pneumonia, it has some advantages including cardiac safety, very good access to lung tissue, potential antiviral, and immunomodulation impact by several mechanisms. The pharmacological profiles of both drugs are heightening considering these medications for further studies in the management of COVID-19.

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Contents

1. Introduction

1.1. COVID-19

Covid-19 is a pandemic disease with high mortality which is caused by the rapid spread of the Severe Acute Respiratory Syndrome SARS-COV-2 (Organization, 2020, Taskforce, 2020). It appeared for the first time in Wuhan, China, in December 2019, WHO later announced that the disease had become a global pandemic (Sohrabi et al., 2020, Huang et al., 2020). When this research was prepared in early July 2020, about half a million deaths were reported; out of approximately11 million confirmed cases of COVID-19 worldwide (CSSE, 2020). The median time to dyspnea is about 5–8 days, to develop acute respiratory distress syndrome (ARDS) 8–12 days, and 10–12 days for ICU admission. Some patients deteriorate within a few days after the onset of the symptoms (Zhou et al., 2020, Yang et al., 2020).

1.2. Complications

Complications commonly involve vital organs and various systems as the intracellular entry of SARS-CoV-2 is mediated by its binding to specific receptors, namely the angiotensin-converting enzyme 2 receptors. These receptors are widely distributed in lung tissues (type II alveolar cells), many other vital organs, endothelial cells, monocytes, and macrophages (Qi et al., 2020). There was a clear association between SARS-COV 2 infection and the development of "cytokine storm" (Henderson et al., 2020, Mahmudpour et al., 2020, Huang et al., 2020, Channappanavar and Perlman, 2017), a major cause of acute respiratory distress syndrome (ARDS); multiple organ failure and death (Xu et al., 2020). The novel virus, in severe cases, induces hyperproduction of cytokines, then immune cells start to attack healthy tissues. Blood vessels leak, severe hypotension, clots form, and multiple organ failure can ensue (Mehta et al., 2020).

1.3. Secondary infection

Viral pneumonia increases the risk of bacterial co-infection which raises the severity and mortality of the disease (Morris et al., 2017). Zhou et al. 2020 reported that about 50% of patients who are died after hospitalization due to COVID-19 had secondary bacterial infections. Studies indicated that 10–30% of hospitalized patients with severe COVID-19 commonly suffer secondary infections. The highest incidence of these infections was demonstrated among those admitted to the intensive care unit (ICU). Patients with severe disease are more predisposed (maybe five-time greater) to secondary bacterial/fungal infections. Nosocomial infection with Gram-negative multidrug-resistant was more frequent among ICU patients with prolonged disease/intubation. Elderly (Lim et al., 2020), and those with chronic diseases such as chronic obstructive pulmonary disease (COPD) are more predisposed to respiratory co-infections (Cox et al., 2020). Some publications reported co-infection with various viruses among critically ill COVID-19 patients for example influenza A virus (Hashemi et al., 2020), and Cytomegalovirus (D'Ardes et al., 2020).

1.4. Risk factors for severe illness

Severely ill COVID-19 patients usually have many other complications. The severity of COVID-19 can range from mild to critical that require ICU (Wu and McGoogan, 2020). The main risk factors for the complications were aging, cardiovascular disease. Diabetes and obesity. Specific risk factors have also been reported that include, pregnancy, chronic respiratory diseases, heart, liver, kidneys, chronic neurological conditions, diabetes, blood disorders, suppressed immunity due to HIV, obesity(body mass index (BMI) 40 or more, smoking, alcoholism, and drug abuse (Lewis, 2020, D'Antiga, 2020, Simonnet et al., 2020, Vetter et al., 2020, N.I.H., 2020).

1.5. Role of antibiotics in COVID-19

European Respiratory Society (ERS, 2020); China (Jin et al., 2020); Germany (Kluge et al., 2020). Indian MOH (MoHFW-Guidlines -India, 2020).Turkish (Kodaz, 2020) and Egyptian (MOHP.EG, 2020) guidelines described the importance of antibiotics in the management of secondary infection associated with COVID-19. Some other guidelines didn't mention the role of antibiotics, examples include web-published guidelines Australia (Taskforce, 2020) and the Saudi Arabia Ministry of Health (KSA, 2020).

This review aims to recall experience regarding the role of antibiotics in previous viral pneumonia pandemics and to provide a pharmacological basis of the potential role of specified antibiotics Doxycycline (DOX) and Azithromycin (AZ) to improve clinical outcomes of management of COVID -19. We did a focused search on PubMed, Google Scholar, and other web-based resources, the search was restricted to full access, English articles. We used keywords and advanced search, e.g., COVID-19, SARS-CoV-2, Viral pneumonia, Antibiotics, antiviral drugs, immunomodulation, secondary infection, Macrolide, Azithromycin, Tetracycline, and Doxycycline.

2. Azithromycin (AZ)

2.1. Overview

Azithromycin (AZ) belongs to the azalide group, a macrolide antibiotic. It decreases protein production, which leads to bacterial growth stoppage. This happens by interfering with their protein synthesis. It inhibits mRNA translation through binding to the 50S subunit of the bacterial ribosome, without affecting the nucleic acid synthesis (FDA, February 2016). AZ is an FDA approved drug for the management of infections. It has a relatively low cost, available in almost all countries. Recently it was repurposed for management of COVID-19. Debates exist about its efficacy and safety, especially when concomitantly used with hydroxychloroquine (HCQ) or chloroquine (CQ). The following sections aim to clarify these issues from pharmacology perspectives

2.2. Antiviral effect of AZ

AZ's antiviral activity has been shown *in vitro* on a large panel of viruses: Ebola, Zika, respiratory syncytial virus, influenza H1N1 (FDA, February 2016). RIG-I like receptors are a family of RNA helicases that function as cytoplasmic sensors of pathogen-associated molecular patterns. They mediate the production of interferons and cytokines response to viral infection (Oshiumi et al., 2010). In cultured bronchial epithelial cells from COPD patients, AZ was demonstrated to induces RIG-I like receptors in a concentration-dependent manner and increases expression of type I and III interferons (Menzel et al., 2016).

AZ had been recognized as one of the repurposed drugs to be investigated in the management of COVID-19. An *in-vitro* study finds the effect of AZ alone against SARS-CoV-2, while other studies found that effect only when combined with hydroxychloroquine (Gbinigie and Frie, 2020).

Touret and co-workers determined the *in vitro* EC50 of AZ against the SARS virus, as 2.12 μM and EC90 as 8.65 μM following a 72 h incubation period post-infection. In another *in vitro* study, after a 60 h incubation period, the combined use of HCQ 2 μM plus AZM 10 μM showed complete inhibition of viral replication (Touret et al., 2020).

2.3. Demonstration of antiviral / immunomodulation effect in human

In 2010, Aline Schögler and Brigitte S. Kopf et al. discovered the antiviral effect of AZ on rhinoviruses (RVs) in pulmonary exacerbations contributed to cystic fibrosis (CF) morbidity. AZ reduces the replication of RV, possibly through the antiviral response amplification facilitated by the IFN pathway (Schögler et al., 2015).

There are survival benefits when ceftriaxone-plus-AZ therapy might be through modulation of immune checkpoints in a mouse model of pneumococcal pneumonia (Yoshioka et al., 2016, Touret et al., 2020, FDA, February 2016).

AZ has been used as adjunctive therapy for an antibacterial coverage and potential immunomodulatory with an anti-inflammatory effect in treating some viral RTI (e.g., influenza) (Ishaqui et al., 2020, Schögler et al., 2015, Grayson et al., 2017, Lee et al., 2017), and in the management of some respiratory conditions like bronchiolitis, bronchiectasis, COPD exacerbations, cystic fibrosis, and ARDS (Zhang et al., 2019, Kawamura et al., 2018).

2.4. Anti-inflammatory and immunomodulatory effects

AZ has immunomodulatory and anti-inflammatory effects, including the effect of the proinflammatory cytokine Macrolides are important treatment options in treating many chronic inflammatory diseases due to their immune effects. The non-microbial effects of macrolides are extensive, ranging from changes in cell number and function to increased and organized cytokine production to the expression of adhesion molecules (A low number of neutrophils and inhibition of neutrophil function leads to a decrease in the concentrations of elastase and IL-8 neutrophils, which ultimately reduces tissue injury. Macrolides also modulate the function of monocytes and macrophages. (Bermejo-Martin et al., 2009, Zhang et al., 2019, Kawamura et al., 2018, Kuo et al., 2019, Abrams and Raissy, 2019, Arabi et al., 2019, Ishaqui et al., 2020, Schögler et al., 2015, Grayson et al., 2017). Clinical trial immunomodulatory experience with macrolides in respiratory disorders are shown in Tabel 1.

Table 1 Clinical trial immunomodulatory experience with macrolides in respiratory disorders.

Indication	Immunological markers effects	Type of study, drugs (duration)	Reference
Bronchial asthma	No significant variation in sputum eosinophil and neutrophil count	Placebo controlled RCT, AZM (12 weeks)	(Cameron et al., 2013)
Bronchial asthma	↓ sputum levels of IL-4, IL-5, IFN-γ	Placebo controlled RCT, AZM (12 weeks)	(Jian et al., 2009)
Bronchial asthma	↓ BAL neutrophil count	Placebo controlled RCT, AZM (6 weeks)	(Piacentini et al., 2007)
Bronchial asthma	↓ Nasopharyngeal TNF-α, IL-1 & IL-10	Placebo controlled RCT, CAM (0.7 weeks)	(Fonseca-Aten et al., 2006)
Bronchial asthma	↓ Sputum eosinophil count & ECP ↓ Blood eosinophil count & ECP	Placebo controlled RCT, CAM (8 weeks)	(Amayasu et al., 2000)
Bronchial asthma	↓ BAL TNF-alpha, IL-5 & IL-12 ↓ Airway tissue TNF-α, IL-5 & IL-12	Placebo controlled RCT, CAM (6 weeks)	(Kraft et al., 2002)
Bronchial asthma	↓ Sputum neutrophil count, neutrophil elastase, IL-8 ↓ MMP-9 (NS)	Placebo controlled RCT, CAM (8 weeks)	(Simpson et al., 2008)
Bronchial asthma	↓ sputum neutrophil count, neutrophil elastase, MMP-9 & IL-8	Placebo controlled RCT, CAM (8 weeks)	(Wang et al., 2012)
Bronchial asthma	↓ sputum and blood eosinophil count, ECP	Placebo controlled RCT, RXM (12 weeks)	(Shoji et al., 1999)
Chronic Obstructive Pulmonary Disease	↑ Blood neutrophil oxidative burst ↓ blood leukocyte count, thrombocyte count, IL-8, E-selectin, CRP, lactoferrin, serum amyloid A. No change in blood TNF-α, IL-6, GM-CSF No change in sputum neutrophil and eosinophil counts	Placebo controlled RCT, AZM (0.4 weeks)	(Parnham et al., 2005)
Chronic Obstructive Pulmonary Disease	↓ sputum neutrophil chemotaxis (NS) No change in total cell count, neutrophil count, IL-8, leukotriene B4, TNF-α, neutrophil elastase	Placebo controlled RCT, CAM (12 weeks)	(Banerjee et al., 2004)
Chronic Obstructive Pulmonary Disease	↓ sputum total cell count, neutrophil count, neutrophil elastase	Placebo controlled RCT, ERM (24 weeks)	(He et al., 2010)
Cystic fibrosis	↓ blood neutrophil count, MPO, high-sensitivity C reactive protein, serum amyloid A, Calprotection	RCT, AZM (4 weeks)	(Ratjen et al., 2012)
Cystic fibrosis	Statistically insignificant ↓ sputum IL-8, neutrophil elastase	RCT, AZM (24 weeks)	(Equi et al., 2002)
Cystic fibrosis	Statistically insignificant ↓ BAL neutrophil elastase, neutrophil count and ↑ macrophage count	RCT, CAM (12 weeks)	(Doğru et al., 2009)
Cystic fibrosis	↓ sputum IL-8, IL-4, TNF-α, neutrophil elastase An insignificant ↓ sputum INF-γ ↓ blood IL-4, IL-8 & TNF-α	Placebo controlled study, CAM (52 weeks)	(Pukhalsky et al., 2004)

2.5. AZ as a repurposed drug for the management of COVID-19

A clinical trial with a limited number of patients demonstrated a higher clearance of the novel virus when the patients treated with AZ and hydroxychloroquine compared to hydroxychloroquine alone (Diana et al., 2020). These findings were subjected to debates and will be more discussed later.

2.6. Pharmacokinetics

The bioavailability of AZ is 37% after a single oral dose (500 mg), and the peak serum concentration is 0.4 mg/L. Intestinal absorption of macrolide is believed to be mediated by P-glycoprotein (ABCB1) efflux transporters, encoded by the ABCB1 gene. Its distribution is much higher in tissues than serum or plasma with 31.1 L/kg leading to a relatively high volume of distribution. Lungs, prostate, and tonsils show a high rate of AZ uptake. AZ is concentrated within polymorphonucleocytes and macrophages, which allows an effective activity against Chlamydia trachomatis. The major route of elimination is by biliary excretion, primarily unchanged. The terminal half-life is about 68 h (DRUGBank, 2020, A5395, 2020).

2.7. Accumulation in lysosomes of immune and lung cells

The broad tissue absorption of AZ is attributed to the cellular absorption of this primary antibiotic in the relatively acidic lysosomes as a result of ion trapping and to an energy-dependent pathway associated with the nucleoside transport system. The results of laboratory studies show that AZ concentrates rapidly within cells where the ratio of intracellular to extracellular drug concentration exceeds 30 after one hour, and up to 200 ratios have been reported after 24 h (AHFS, 2020b).

A PK study in a patient who is going to lung transplantation revealed that after a dose of 500 mg/day, the peak levels of plasma and lung (Cmax) were 0.18 mg/ml, 8.93 mg/kg of lung tissue, and the time to reach these levels (Tmax) was 12 Hour (plasma), 60 h (lung). This means that the lung concentration was about 45 times compared to the serum level, and the consistency of the stable lung concentration was delayed (Danesi et al., 2003).

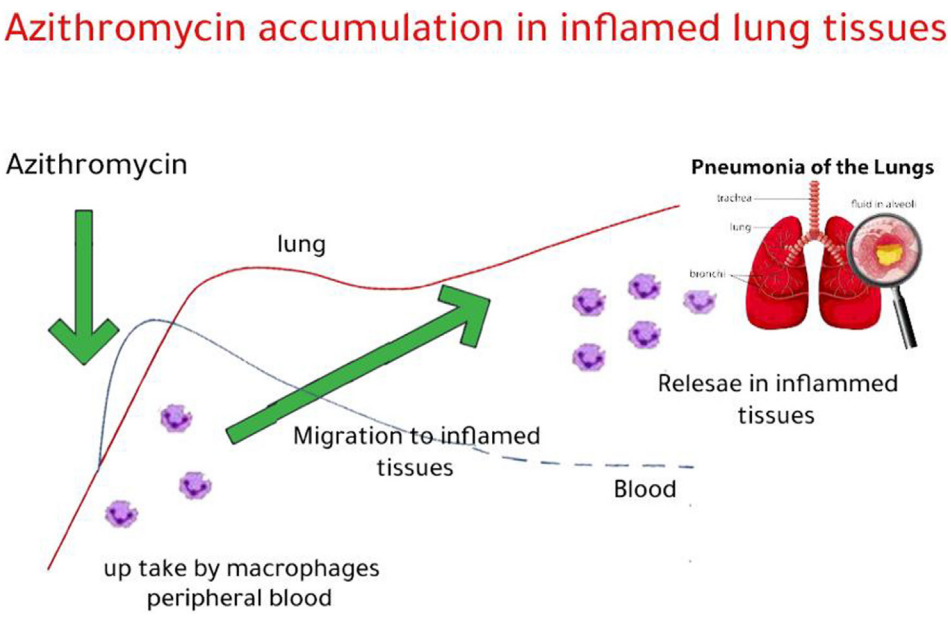

Fig. 1 Illustration of accumulation of AZ in inflamed lung tissues adapted from data in these publications (Schentag and Ballow, 1991; Frank et al., 1992; Hall et al., 2002; Parnham et al., 2014).

AZ has unique pharmacokinetic properties that have a positive effect on its high effectiveness in lung infections, as it has shown a predominant outflow in tissues, especially those inflamed or infected. Fig. 1 illustrated accumulation within phagocytic cells that mostly migrate to the site of infection/inflammation (Schentag and Ballow, 1991, Frank et al., 1992, Hall et al., 2002, Parnham et al., 2014). *In vitro* studies have shown that accumulation of AZ in phagocytes is an unstable process compared to other macrolides (Bosnar et al., 2005).

2.8. Safety issues

Regarding patients with no history of cardiac disease, AZ rarely causes a life-threatening arrhythmia due to QT prolongation through the blockage of the rapid delayed rectifier potassium current (IKr). It seems that the combination of hydroxychloroquine and AZ is more harmful than their single-use. The American College of Cardiology recommends a QT monitoring to stop AZ use (if used) and/or decrease the dose of hydroxychloroquine in the case of QT prolongation (Diana et al., 2020). The National Institute of Health (NIH) and the Infectious Diseases Society of America (IDSA) recommends against the use of the combination regimen, except in the context of a clinical trial (Health., 15 May 2020, America, 2020 Apr 22). As both drugs are linked to the QT prolongation, caution is needed when considering the use of them in patients with COVID-19, especially in patients with a high risk of QT prolongation, outpatients who may not have close monitoring, or who are receiving other medications associated with arrhythmias. The risk and benefit ratio must be carefully monitored if the regimen of AZ and hydroxychloroquine is used (Health., 15 May 2020, America, 2020 Apr 22, Giudicessi et al., 2020, Mercuro et al., 2020, Bessière et al., 2020, Bonow et al., 2020, Ramireddy et al., 2020).

A Retrospective Analysis of 1061 cases in Marseille, France, was observed. The results show safe outcomes when AZ and hydroxychloroquine are administered before any complications of COVID-19 with a very low fatality rate (Million et al., 2020). There are still ongoing trials to study the effect of both drugs. Additional data is needed with controlled clinical trials before any conclusions can be made.

Given all the favorable features of AZ, antiviral activity, broad-spectrum antibacterial activity, immunomodulation epically lung inflammation, unique PK features, access to lung tissues is very high, effective, targeting lysosomes, potential synergistic effect with other repurposed antiviral drugs, the risk for cardiac toxicity can be minimized by the adequate exclusion of patients with risk factors and monitoring. All these features make this low cost, available, a good candidate for further studies.

3. Doxycycline (DOX)

3.1. Overview

Doxycycline (DOX) is a broad-spectrum synthetic derivative of tetracycline, a bacteriostatic antibiotic drug. Its works by inhibiting protein synthesis by reversibly binding to 30 s subunit at A site blocking the binding of aminoacyl t-RNA to mRNA to inhibiting the addition of new amino acid to growing peptide chain leading to inhibition of the translation process. Regarding its administration, due to it has a long duration of action allowing once-daily dosing. DOX has good access to most tissues, so it is active against many gram-positive and negative bacteria such as Homophiles influenza. It has been the drug of choice in infection caused by Mycoplasma Pneumonia (Chopra, 2001). Beyond its effect in pneumonia, it has antiviral and immunomodulation effect that makes it an interesting drug to be considered in COVID-19, these topics will be discussed in the next sections.

3.2. Antiviral effect of DOX

Studies have demonstrated significant inhibitory effects of DOX against anti-retroviral viruses (Sturtz, 1998), and the multiplication of the dengue virus in infected cell lines (Rothan et al., 2014, Yang et al., 2007). DOX also controlled the chikungunya virus infection (CHIKV) by inhibiting the protease cysteine in Vero cells and showed a significant decrease in the CHIKV blood titer in mice (Rothan et al., 2015).

The antiviral mechanism of tetracycline derivatives may be secondary to the transcriptional regulation of zinc-finger antiviral protein (ZAP), which is a coding gene in host cells (Tang et al., 2017). ZAP can also bind to targeted viral mRNAs and suppress the translation of RNAs (Guo et al., 2004, Zhu et al., 2012).

Experimental studies have shown that tetracycline can lead to the excessive expression of the ZAP host in HEK293, rat, and monkey cell lines (Ferro cells), which have contributed to the inhibition of RNA viruses such as dengue, Ebola, HIV, Zika, and influenza (Müller et al., 2007, Li et al., 2019).

Studies have indicated that treatment with DOX reduces acute lung infection in mice infected with the virulent H3N2 virus (Ng HH, 2012). Interestingly, the synergistic effects of DOX with oseltamivir provided the basis for effective intervention against swine flu infection (Quispe-Laime et al., 2010). DOX has been shown to reduce acute lung injury (ALI), in mice infected with the highly pathogenic H3n2 influenza virus: the study revealed that Dox acts as an inhibitor of metallic matrix proteins (MMPs), T1-α levels (membranous protein of the first epithelial type) and thrombomodulin (protein) Blanket) The activity of MMP-2 and MMP-9 in Bronchoalveolar fluid significantly decreased after DOX treatment studies, showing a significant decrease in lung damage. These results have documented that DOX may be beneficial in improving ALI during influenza pneumonia (Ng HH, 2012).

3.3. Anti-inflammatory and immunomodulatory effect

Fas/Fas ligand (FasL)-mediated apoptosis plays an important role in maintaining T lymphocyte homeostasis and modulating the immune response. DOX showed the ability to inhibit Jurkat T lymphocyte: "immortalized line of human T lymphocyte cells that are used to study acute T cell" proliferation and induces their apoptosis. The DOX-induced increase of apoptosis in these cells is consistent with the increase of FasL expression. These results suggest that DOX may downregulate the inflammatory process in certain diseases by eliminating activated T lymphocytes through Fas/FasL-mediated apoptosis (Metlay et al., 2019).

Regarding the immunomodulatory activity of DOX in leptospira-infected macrophages and *in vivo*. DOX downregulated IL-1β by suppressing NLRP3 inflammasome activation. This suppression effect was not only limited to leptospira stimulation but also included a conventional NLRP3 inflammasome agonist, LPS, and ATP. Using mice and hamsters, DOX suppressed leptospira-induced IL-1β by suppressing MAPK, NF-κB, and NLRP3 inflammasome activation (Metlay et al., 2019).

As the efficacy of DOX against leptospirosis is acceptable, the inhibition of IL-1β levels may be a new treatment strategy against leptospirosis (Metlay et al., 2019).

Minocycline showed anti-inflammatory effects and viral replication suppression in cells infected with Enterovirus 71 infection, it reduces the level of IL-6 and IL-8, and relative mRNA expression of TNF-α. In a murine model, its inhibited IL-6 and granulocyte colony-stimulating factor in plasma and TNF-α in the cerebellum (Metlay et al., 2019).

Recent computational methods study identified DOX among the drugs that could potentially be used to inhibit SARS-CoV-2 papain-like protease (Metlay et al., 2019).

3.4. Demonstration of antiviral / immunomodulation effect in human

A clinical study showed DOX is more effective compared to tetracycline to modulate serum levels of IL-6, IL-1B, and TNF and cytokine receptor/receptor antagonist TNF-R1 and IL-1RA in patients with dengue fever (DF) or dengue hemorrhagic fever (DHF).

Severe inflammatory condition plays a major role in causing dengue and hemorrhagic fever, leading to a cytokine storm (M Fredeking, 2015), DOX treatment reduces pro-inflammatory cytokines, including IL-6 and tumor necrosis factor (TNF) -α, in patients with Dengue hemorrhagic fever, and the death rate was 46% lower in the treatment group than DUX (11.2%) than in the untreated group (20.9%) (M Fredeking, 2015). DOX was more effective than tetracycline in reducing these pro-inflammatory cytokines (Castro et al., 2011a).

Minocycline demonstrated anti-inflammatory and viral reproductive effects in cells affected by Enterovirus 71 infection, as it lowers the IL-6 and IL-8 levels, and the mRNA relative expression of TNF-α (Liao et al., 2019).

3.5. Potential utility of DOX against COVID-19

The pathogenic properties of COVID-19 closely resemble those of SARS-CoV infection, which cause lung tissue remodeling through urokinase pathways, coagulation, and wound healing and through extracellular matrix proteins, including MMPs (Gralinski and Baric, 2015) which is involved in remodeling. Lung and extracellular matrix destruction, lead to damage to the endothelial basal plate and increased vascular permeability (Gralinski et al., 2013).

More importantly, mechanical ventilation, which has an essential role in the management of ARDS, is associated with another lung injury by activating MMPs, which leads to a lung injury caused by ventilation (Castro et al., 2011b).

As mentioned earlier, DOX has a protective role in virus-induced lung infection as an inhibitor of MMPs and is a family of more than 24 proteins in which it relies on zinc (Doroszko et al., 2010). Therefore, this effect is due to the ability of tetracycline derivatives to catalyze the $Zn2+$ catalytic ion, which is necessary for MMP activity, regardless of its antimicrobial properties (Castro et al., 2011b). Among tetracycline derivatives, DOX is the most potent inhibitor of MMP, even at a dose without antimicrobial effect (25 mg) (Castro et al., 2011b). Since pulmonary immunodeficiency infection / acute respiratory distress syndrome is evident in patients with severe COVID-19, MMPs inhibition may help repair damaged lung tissue and promote recovery (W ang et al., 2020).

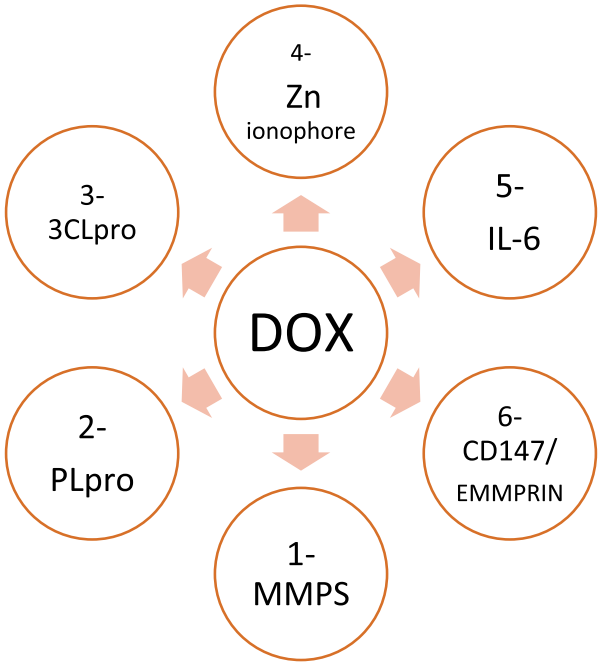

Fig. 2 Purposed multiple effects of doxycycline against SARS-COV-2 and/or attenuation of its complications (Kong et al., 2015, Phillips et al., 2017; Wu et al., 2020; Griffin et al., 2010; te Velthuis et al., 2010; Sargiacomo et al., 2020; Wang et al., 2020).

3.6. PK and safety profile

DOX is inexpensive and widely available, it is safe to endure and is an attractive option for treating COVID-19 in addition to providing coverage against uncommon bacterial pneumonia such as mycoplasma pneumonia and Legionella pneumonia. DOX is a semisynthetic antibiotic of tetracycline derived from oxytetracycline. Doxycycline enters the cell by hydrophilic pores in the outer cell membrane and the active pH-dependent transport system in the inner cytoplasmic membrane (Holmes and Charles, 2009). If given IV, the risk of thrombophlebitis should be considered. Moreover, to reduce the risk of esophageal irritation and ulcers, DOX should be administered with a sufficient amount of fluids and should not be given at bedtime. To reduce the risk of photosensitivity caused by DOX, patients should be directed to avoid direct sun exposure for a long time. The usual dose of DOX can be used in patients with impaired kidney function (Holmes and Charles, 2009).

Approximately 90–100% of the oral dose of DOX structure is absorbed from the digestive system in fasting adults with normal kidney function, peak serum concentrations of DOX are achieved within 1.5–4 h, with average 1.5–2.1 μg/ml. The serum half-life is about 15–16 h after one dose and about 22 h after multiple doses in patients with normal kidney function, while in patients with severe renal impairment, the serum half-life is about 18–26 h after one dose, and 20–30 h after multiple doses. The serum half-life is not changed in patients undergoing dialysis. Approximately 20–26% of a single oral dose or IV dose of DOX is excreted in the urine and 20–40% is excreted in the stool within 48 h as an active drug. It is used with caution in patients with renal or hepatic impairment but usually, there is no need to adjust the dose when reconstituted and diluted with 0.9% sodium chloride or 5% dextrose, it is stable for 48 h at 25 °C during infusion. DOX hyclate IV should protect it from direct sunlight (Riond and Riviere, 1988, Holmes and Charles, 2009, AHFS, 2020a).

In light of these potential benefits, we propose the use of DOX for further concern in the management of COVID-19, particularly patients with cardiac comorbidities. Fig. 2 provided a summary of DOX multiple mechanisms against SARS-COV-2.

3.7. Summary of multiple mechanisms of DOX against COVID-19

Summary of Multiple mechanisms of DOX against COVID-19 was as the following:

(1) DOX inhibits metalloproteinases (MMPs), this effect likely prevents viral entry into host cells and effectively attenuate viral-mediated acute respiratory distress syndrome (ARDS) (Kong et al., 2015, Phillips et al., 2017).
(2) DOX inhibits papain-like proteinase (PLpro) that mediates the generation of non-structural proteins (NSPs 1–3) by cleavage of the replicase polyprotein. These NSPS have a crucial role in viral replication (Wu et al., 2020).
(3) DOX by inhibiting 3C-like main protease (3CLpro) also has a role in the formation of more NSPs (4–16) / maturation, all are essential in the virus replication (Wu et al., 2020)
(4) DOX is suggested to act as an ionophore that, increasing Zin intracellular concentrations, which has a role suppressing viral replication in addition to other roles in enhancing the immune system (Griffin et al., 2010, te Velthuis et al., 2010).
(5) DOX inhibits the critical inflammatory mediator of the senescence-associated secretory phenotype (SASP), namely IL-6 that responsible for most serious complications of viral infection (Sargiacomo et al., 2020).
(6) Low-dose of DOX inhibits expression of CD147/EMMPRIN that may have a role in the viral entry into T lymphocytes (Wang et al., 2020).

4. Conclusion

AZ has excellent lung tissue targeting, broad-spectrum antibacterial effect, possible antiviral activity against COVID-19. It demonstrated efficacy in limited clinical trials, however, there is a concern for cardiac toxicity. DOX is considered in the management of pneumonia also has many features, epically cardiac safety besides excellent access to lung tissue, potential antiviral, and immunomodulation effect. All these features make these drugs a good candidate to be considered for farther research and clinical trials for the management of COVID-19.

Declaration of Competing Interest

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.

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