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Doxycycline and Minocycline Drugs as a Treatment Proposal for Inhibition of ARDS and Inflammatory Cytokine Mediators Caused by COVID19

Mohamed A. Mostafa*

Bachelor of Pharmacy, Microbiology, Immunology and Biochemistry, Mansoura University

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ABSTRACT

The novel coronavirus 2 (COVID 19) is a highly transmittable viral disease aroused in Wuhan, China at the end of 2019 and spreads around the world. The International Committee on Taxonomy of Viruses (ICTV) named it on February 11, 2020, as severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 can infect humans as well likewise as animals and transmit from person to person. The World Health Organization declared that the novel coronavirus 2 pneumonia epidemic and was classified as a public health emergency of international attention on January 30, 2020. When COVID-19 infects the upper and lower respiratory tract it can give rise to mild or acute Respiratory Distress Syndrome (ARDS) with resultant release of cytokines like IL-1B, IL6, IL37, TNF alpha, and CCL2. we evaluated the effectiveness of doxycycline and minocycline as a tetracycline derivative to modulate serum levels of cytokines and we stand out their anti-inflammatory effect that can inhibit inflammation and pro-inflammation response that was caused by COVID-19, providing pertinent strategy.

Keywords: COVID-19, SARS-CoV-2, ARDS, Tetracyclines, Cytokines.

1 Introduction

Tetracyclines are bacteriostatic antibiotics. The mode of action of tetracyclines based on their binding to bacterial 30s ribosomal subunit and inhibitition of protein synthesis. The second generation, Doxycycline and Minocycline are a semi-synthetic tetracycline derivative. They are better in pharmacokinetic activity than the first-generation tetracyclines; it is absorbed totally when it is taken orally. Because of its high lipophilic properties, particularly Minocycline which passes through the blood brain barrier, accumulated in both the CSF and CNS cells [1].

Doxycyline was found to benefit patients with multiple sclerosis, Huntington's disease and rheumatoid arthritis presumably by suppressing microglia activity [2, 3]. This, in turn, lowered levels of several proinflammatory cytokines including tissue necrosis factor (TNF) and interleukin 1 beta (IL-1β) [2, 3].

The effectiveness of doxycycline were studied by J. E. Z. Castro, et al., [4] in the management of cytokines triggered by Dengue virus and modulating serum levels of IL-6, IL-1B, and TNF and cytokine receptor/receptor antagonist TNF-R1 and IL-1RA in hospitalized patients with Dengue virus disease.

Minocycline's antiviral activity has been described initially against HIV [5], the infection in which CD4+ T cells showed increased amounts of IL-1, IL-6, TNF alpha, interferon gamma and low levels of IL-2 levels [6]. and this activity against other viral infections was experimentally estimated later within the

Simian Immunodeficiency virus (SIV), Japanese encephalitis virus (JEV), Human T- lymphocytic virus type-1 (HTLV-1), West Nile virus (WNV), Rabies, Sindbis and Reoviruses.

2 Discussion

Elevated cytokine levels are a hallmark of numerous bacterial and viral infectious diseases including covid 19 Pro-inflammatory cytokines, such as IL-6, IL1-β and TNF, are believed to cause the majority of symptoms, such as fever, malaise, and coagulopathies associated with viral infections [7, 8, 9]. Indeed, the degree of imbalance between such cytokines and their anti-inflammatory counterparts may be the primary prognostic indicator of disease outcome [10, 11]. These finding have led to the development of a broad spectrum of potential therapeutic agents, including monoclonal antibodies and antibiotics, which act to down-regulate various cytokines [12, 13].

Drugs belonging to the tetracycline class of antibiotics possess several advantages including a long history of safe use and low cost as doxycycline and minocycline. As well, they are able to cross the blood-brain barrier easily may prove the treatment of infections including the central nervous system.

In the present study, we investigate the effectiveness of doxycycline and minocycline to modulate the levels of various cytokines and soluble receptor/receptor antagonists in patients with COVID-19.

previously observed that dengue virus infection resulted in a marked increase in serum cytokine and cytokine receptor/antagonist levels [14, 15]. Doxycycline were able to modulate pro-inflammatory cytokines levels. Down-regulation was rapid, being observed within 3 days of treatment and continuing through day 7 [16]. A similar effect was noted for IL-1RA, doxycycline modulated TNF-R1 concentration, inhibit multiplication in tissue culture and was able to interact with the dengue virus E protein showing effective immune-modulator and long plasma half-life [17].

On the other hand, Minocycline binds to and inhibits HIV integrase, and was shown an anti-HIV activity in human CD4+ T cells resulting in reduction in single cycle replication and reactivation, and this was the primary time that minocycline was shown to own a capability to decrease viral expression from resting CD4+ T cells [18].

Minocycline has properties as anti-inflammatory agent because it down regulates CD40L on T cells through CD40/40L pathway [19], anti-apoptic action and immune-modulatory activity [20], and neuro-protective effects [21]. These properties not rely on minocycline's antimicrobial activity because of its ability to inactivate enzymes like caspase-1 and -3, and activating BcL-2 [22, 23]. The same investigators showed that minocycline reduced cytokine secretion such as IL-1, IL-6 and TNF-a leading to inhibition or reduction of cytokine storm [24]. Neuro-protective activities of minocycline may be due to many possible modes of action which involve anti-inflammatory actions, is also due to the inhibition of p38MAPK stimulation in microglia and therefore alleviated cytokines and chemokines release [[25], [26], [27]], anti-apoptotosis [28] by preventing release of cytochrome C and caspase expression [29].

As Mahyar Etminan [30] mentioned in his research letter based on his evidence on believing that tetracyclines (doxycycline or minocycline) may be effective agents in the treatment of COVID-19. As mentioned previously that doxycycline and minocycline are highly lipophilic antibiotics that chelate zinc substances on matrix metallo-proteinases (MMPs) [31]. Coronaviruses depend on host MMPs for survival, cell to cell adhesion, cell infiltration, and replication [32, 33].

Tetracyclines have zinc chelating properties which may also help in preventing COVID-19 infection in humans and reducing the ability of the virus to replicate within the host cells. Also, tetracyclines might be have the ability to inhibit RNA replication on positive-sense single stranded RNA, as COVID-19.

The study showed that the dengue virus could be treated by doxycycline. Also, at normal human temperature and fever conditions, doxycycline significantly inhibited the serine protease of the virus, as well as a decrease in concentration dependent viral Replication [34]. The same investigators also found that the post infection replication was inhibited by doxycycline with decreased ability of the viruses to enter the cultured cells [34].

One more study showed a reduction in retroviral load by 70% when doxycycline used as a remedy for cells at human body temperature [35]. Also, tetracyclines may have the ability to treat COVID-19 infection by means of their well-known anti-inflammatory activities, including down-regulation of the NFKB pathway due to the decrease in inflammatory cytokines levels such as IL1β, TNFα, and IL6 independent of its mechanism as antibiotic [36].

These cytokines are markedly elevated when SARS-CoV is exposed to lung tissue in addition to triggering the pathogenesis of its infection [37]. On the other hand, a novel publication indicated that coronaviruses induce the proliferation of mast cells inside the respiratory submucosa, which led to producing inflammatory agents such as histamine, protease and inflammatory cytokines such as IL-1 and IL-33 [38], which are the major causes of Acute Respiratory Distress Syndrome (ARDS).

Two other studies showed that tetracycline derivatives can induce apoptosis of mast cells and stimulation of protein-kinase C, thus decreasing levels of circulating inflammatory agents [39, 40]. As the outer shell of COVID-19 is lipophilic and tetracyclines are lipophilic in nature, so there are high tissue penetration of tetracyclines to the lungs which may cause the inhibition of viral replication in the lungs, and with their anti-inflammatory effect, tetracyclines could play an essential role as therapeutic medications in COVID-19 treatment. This will lead to decrease death due to septic shock that may be caused by complicated pneumonia or ARDS in hospitalized patients [41].

3 Conclusion

The present study indicates that doxycycline or minocycline may provide a clinical benefit in the treatment of COVID-19 infection by modulating the cytokine cascade, inhibition of lung inflammation and/or ARDS. Doxycycline or minocycline can be potential therapeutic drugs for COVID-19 that is hidout in plain sight. Furthermore tetracyclines are much safer than other drugs that have been used in COVID-19 treatment trials such as antiretroviral drugs or chloroquine derivatives.

4 Recommendation

We hope to consider and investigate the potential therapeutic effectiveness of tetracyclines, particularly doxymycine and minocycline in COVID-19 treatment and management of inflammatory cytokines and ARDS from international research groups and physicians.

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6 Competing Interests

The author declared that no conflict of interest exists in this article.

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