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Research Article

Minocycline in Combination With/Without Azithromycin as a Potential Treatment in Covid-19 Suspected or Infected Patients

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Abstract: The pandemic coronavirus disease which has started in 2019 (COVID-19) in Wuhan China, is the major humanity concern nowadays. COVID-19 causes Acute Respiratory Distress Syndrome (ARDS) after cytokine storm is pursuing and elderly are the most susceptible. Efforts are made to find a vaccination or a treatment for COVID-19 infection. Due to lack of adequate evidence, no anti-SARS-CoV-2 drug or vaccine has been approved officially, yet. Drug repurposing is at the essence of this battle and since Minocycline has a preferable safety profile and high tolerability, it can be a great tool to the treatment regimens applied. Minocycline has demonstrated antiviral and immunomodulatory activity that is independent of its antibacterial activity. Additionally, the proposed combination with Azithromycin enhances the anti-inflammatory effects of Minocycline which is necessary for a fighting off an excessive cytokine storm response. Some researchers reported effective therapeutic options. On the other hands, there use was limited either because of severe side effects or high cost. In this review article we shall go over recent researches that would support the usage of Minocycline in combating the Coronavirus (SARS-CoV-2) outbreak. Further efforts are require to developing the safest and most effective approach to decrease mortality rate in suspected population and severe case.

Keywords: Azithromycin, COVID-19, Immuno-Modulator, Hydroxychloroquine, Minocycline.

INTRODUCTION

In light of the most recent viral outbreak, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the world is at a frantic race to find a treatment for such a rapidly spreading infectious disease. This novel coronavirus disease 2019 (COVID-19) has a higher transmissibility from human to human compared with SARS-CoV-1, that's make it global challenging, despite of its lower pathogenicity compared with SRS-CoV-1. Considering it's already at pandemic status, it comes as no surprise that the number of confirmed cases has reached a staggering 575,444 (as of 28/3/2020) worldwide and is still expected to increase. Because of growing understanding of SARS-CoV-2 in the virology, epidemiology and clinical management strategies and its high transmissibility, researchers study older anti-viral and anti-microbial agents effectiveness instead of developing new ones. However, no anti-SARS-CoV-2 drug or vaccine has been officially approved due to the absence of adequate evidence. As a result, the most viable option showcased to us, during this period, is drug repurposing.

One of the drugs to be repurpose is Minocycline. Minocycline semi-synthetic second generation tetracycline has antibacterial activity and approved for use in gram negative or gram positive infections. It is recommended for anthrax, meningococcal carrier state, respiratory tract infections and many other infections. It is of great interest due to its displayed anti-inflammatory, antioxidant, anti-apoptotic and immune modulatory effects. Additionally, it has been shown to have in-vitro antiviral activity against different viral infections namely: Human Immunodeficiency Virus (HIV), Japanese Encephalopathy Virus (JEV), West Nile Virus (WNV), and the Influenza Virus. Also, Minocycline has been shown to have in-vitro/in-vivo activity against Enterovirus 71 (EV71) brainstem encephalitis (BE) (Dutta, K., & Basu, A. 2011). The second agent is Azithromycin (Azalide/Macrolide family) which has antibacterial and anti-inflammatory effect, used for community acquired pneumonia, upper respiratory tract infection and many other bacterial infections. Even the evidences of using Minocycline and Azithromycin are

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low, Its combination with Azithromycin could be warranted and a further rigorous preclinical models and clinical trials are necessary. In this minireview, we aim to summarize the updated potential advantages of Minocycline with or without Azithromycin compared with Hydroxychloroquine (HCQ) (Gautam,C.S., & Aulakh, R. 2020).

DISCUSSION

The pathogenesis of the coronavirus has yet to be fully understood, with only hypotheses present to give us an idea of what we're dealing with. According to the latest findings, it has been shown that SARS-CoV-2 has lower pathogenicity but higher transmissibility from human to human when compared to its former counterpart SARS-CoV-1. The major concern of SARS-CoV-2 pathogenesis is the severe alveolar damage after alveolar cells type-II preferential attacking which ultimately causing Acute Respiratory Distress Syndrome (ARDS) with varying severities depending primarily on patient's immune competency and cytokine storm status. Considering the possible lympho-depleting effect of the disease at its early stages, will dictate whether a patient's immune system can ward off the virus or not. Moreover causing hyper inflammatory condition of high concentration of cytokines was seen in Intensive Care Unit (ICU) patients' more than non ICU patients. After COVID-19 infection, CD-4 T cells are rapidly activated and produce granulocyte-macrophage colony stimulating factor (GM-CSF) and inflammatory cytokines and higher expression of interleukin 6 (IL-6), tumor necrosis factors (TNF), and interleukin-8 (IL-8) (Lin, L. *et al.,* 2020). The most noticeable manifestations of the COVID-19 is a marked increase in these inflammatory cytokines which can develop into a more severe and deadly case of cytokine storm. Thus, suppression of these pro-inflammatory mediators, or in other words, rebalancing the imbalance between the pro-inflammatory and anti-inflammatory mediators can be a viable options for mitigating this cytokine storm (Li, H. *et al.,* 2020).

With that being said, Minocycline's high safety index alongside its proven long-term tolerability both make it a good candidate for repurposing. Additionally, it has better a pharmacokinetic profile than the first-generation tetracyclines and it is completely absorbed when it's taken in its oral formulation allowing it to be almost completely bioavailable. Of its most common side effects nausea, vertigo, and mild dizziness are, luckily, all completely reversible upon discontinuation of the drug. Minocycline despite its antibacterial activity, it has been used in viral infection for its pleiotropic effect. Its antiviral properties were first highlighted in 1990 by Lemaitre *et al.,* for its protection against human immunodeficiency virus (HIV) in human acute lymphoblastic T-cell leukemia (CEM) cells. They were able to display that Minocycline prevented the HIV mediated cytopathic effects, in vitro, 7-14 days post infection. Later on, it was further reported to have significant anti-inflammatory and neuroprotective activity in a simian immunodeficiency virus (SIV) model of HIV associated central nervous system (CNS) disease. Such effects are due to various modes of action of Minocycline from suppression of cellular activation of CD4+ T-cells to inhibition of activation of apoptosis signal-regulating kinase-1 (ASK1). Neuroprotective and anti-inflammatory effect on microglia of minocycline made it effective for dementia caused by Acquired Immunodeficiency Syndrome (AIDS). Suppression of lymphocyte and macrophages HIV and SIV retroviruses replication in vivo, was also reported (Nagarakanti, S., & Bishburg, E. 2015).

Apart from its efficacy against retroviruses, Minocycline is also effective against flaviviral infections. A study published in 2007 claimed that minocycline significantly inhibited West Nile virus replication in cultured human neuronal cells and subsequently prevented virus-induced apoptosis. Its antioxidant properties are underlined in an in-vitro study conducted on neuro-blastoma cells infected with the Japanese Encephalopathy Virus (JEV) where Minocycline was shown to significantly reduce the oxidative stress caused by the infection. The pleiotropic effects of Minocycline like neuroprotection, anti-inflammation, and protection against oxidative stress are independent of its antibacterial action. When considering the reasoning behind using Minocycline for the treatment of the Coronavirus, the intended mechanism of action is to suppress the excessive inflammatory response that is taking place. Recent data has shown that ICU patients had higher cytokine levels when compared to non-ICU patients infected with the coronavirus. They also had higher percentages of GM-CSF, IL-6, and $CD4^+$ T-cells. Such findings lead us in the direction of associating cytokine levels with disease severity.

A study titled anti-inflammatory and antiviral effects of Minocycline in Enterovirus 71 infections (EV71) concluded that minocycline can be considered as novel approach in treating or controlling enterovirus neurological complications. In this study, Minocycline reduced cytopathic effects (CPEs), viral protein expressions, viral titers, the levels of interleukin IL-6 and IL-8 and relative mRNA expressions of IL-12p40, IL-1β, and TNF. Double dose minocycline was also used to see if the response was dose dependent and, accordingly, the results were further resulted in reduction of clinical scores, mortality rate, viral titers in brain tissues, and inhibition of both IL-6 and GM-CSF (Liao, Y.-T. *et al.,* 2019). Also, Respiratory Syncytial Virus (RSV) infection which is one of the most common causes of lower respiratory tract infection that lead to morbidities and mortalities especially in geriatric and pediatric population. A recent explorative and observational study for Minocycline against RSV

concluded that Minocycline has decreased infection related cytopathic effects and can hinder RSV infection (Bawage, S. S. *et al.,* 2019). Minocycline has off-label use in rheumatoid arthritis. A randomized, double blinded trial of minocycline 100mg two times daily versus hydroxychloroquine 200mg twice daily. The trial included 60 adults having recent rheumatoid arthritis. After the 2 year trial researchers concluded that minocycline was more effective than hydroxychloroquine for patients with early disease. Discontinuation of use because of adverse effects was 3 patients from minocycline group due to finger nail discoloration, dizziness and rash. On the other side 2 patients from hydroxychloroquine group due to gastrointestinal distress and rash.

As for the combination of Minocycline and Azithromycin, the rationale behind it includes Azithromycin's additional anti-inflammatory effect that would favor its usage in infections with an inflammatory component. Hence, why it's so frequently used in controlling lung disease in cystic fibrosis patients. Interestingly, Azithromycin was also found to have antiviral effects, unlike its other macrolide counterparts. It effectively inhibited rhinoviruses by upregulating the type I interferon (IFN-I) responses in bronchial epithelial cells. In one study Azithromycin was tested against the influenza A virus (H1N1) pdm09 to test its antiviral activity and elucidate its mode of action. Azithromycin was found to hinder the virus' internalization into cells by endocytosis. This effect could be associated to its direct interaction with the virus' cell surface, as opposed to interacting with the receptors found on the hosts cells (Zeng, S. *et al.,* 2019; Tran, D. H. *et al.,* 2019; & Menzel, M. *et al.,* 2016). Similarly, pre-treating the cells with Azithromycin before cellular infection greatly reduced progeny virus production after 48 hours of culturing. This could aid for its utilization prior to infection, prophylactically. Furthermore, when tested against the Zika Virus Azithromycin successfully showed that it can upregulate the host's natural IFN-I/III responses against the infection and lead to its subsequent suppression.

Lastly, its noteworthy to mention that Azithromycin also possesses an advantageous pharmacokinetic and safety profile that would support its usage with Minocycline. Such a combination doesn't pose a risk of QT interval prolongation unlike the proposed combination of Hydroxychloroquine and Azithromycin. Bearing in mind that the greater majority severely ill patients, infected with coronavirus, are the elderly (65 years and older) we aim to use a drug combination that doesn't further compromise their health status.

CONCLUSION

In summary, development of new drugs requires time, effort and high expenses on average 10-15 years and approximately 2 billion American dollar. It is rational to try already existing medications with recorded antiviral and anti-inflammatory effects. And taking into consideration that most susceptible population for COVID-19 infections are elderly. Most of them having cardiovascular diseases, diabetes mellitus, hypertension and already having myocardial infections and retinopathies and multiple medication use for various comorbidities which requires careful use of HCQ and Azithromycin combination use. There is a great deal of research that has highlighted the promising proposition of using Minocycline as an antiviral agent. It has shown through various mechanisms its ability to exert anti-inflammatory, ant apoptotic, antioxidant, and immune modulatory effects on the immune system. Accordingly, the combination of Minocycline and Azithromycin could be the safer and more tolerable solution to combating such a virus. However, more insightful work is required to prove its potential effectiveness against the Coronavirus, especially during critical times like the one we're in.

Clinical Relevancy Statement

Reviewing the history of minocycline use in viral infections leads to prediction of a potential mechanism of Minocycline targeting coronavirus infection and coronavirus related health complications. Using medications with anti-inflammatory properties in addition to antimicrobial properties are thought to be beneficial in supporting patient immunity and decrease pro inflammatory mediators' levels that may worsen the coronavirus infection severity.

Conflicts of interest: None declared.

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REFERENCES

1. Bawage, S. S., Tiwari, P. M., Pillai, S., Dennis, V. A., & Singh, S. R. (2019). Antibiotic Minocycline Prevents Respiratory Syncytial Virus Infection. *Viruses*, *11*(8), 739.
2. Dutta, K., & Basu, A. (2011). Use of minocycline in viral infections. *Indian Journal of Medical Research*, *133*(5), 467–470. https://doi.org/10.1128/AAC.00483-20
3. Gautam,C.S., & Aulakh, R. (2020). Potential Armamentarium To Contain Covid-19 Pandemic In Developing Countries: Be Prepared And Act

Timely! Acta Scientific Paediatrics, 3(4 April 2020), 4.

4. Li, C., Zu, S., Deng, Y.-Q., Li, D., Parvatiyar, K., Quanquin, N., … Cheng, G. (2019). Azithromycin Protects against Zika Virus Infection by Upregulating Virus-Induced Type I and III Interferon Responses. *Antimicrobial Agents and Chemotherapy*, *63*(12). doi: 10.1128/aac.00394-19.
5. Li, H., Zhou, Y., Zhang, M., Wang, H., Zhao, Q., & Liu, J. (2020). Updated approaches against SARS-CoV-2. Antimicrobial Agents and Chemotherapy.
6. Liao, Y.-T., Wang, S.-M., & Chen, S.-H. (2019). Anti-inflammatory and antiviral effects of minocycline in enterovirus 71 infections. *Biomedicine & Pharmacotherapy*, *118*, 109271. doi: 10.1016/j.biopha.2019.109271.
7. Lin, L., Lu, L., Cao, W., & Li, T. (2020). Hypothesis for potential pathogenesis of SARS-CoV-2 infection——a review of immune changes in patients with viral pneumonia. *Emerging Microbes & Infections*, 1–14. doi: 10.1080/22221751.2020.1746199.
8. Menzel, M., Akbarshahi, H., Bjermer, L., & Uller, L. (2016). Azithromycin induces anti-viral effects in cultured bronchial epithelial cells from COPD patients. *Scientific Reports*, *6*(1). doi: 10.1038/srep28698
9. Nagarakanti, S., & Bishburg, E. (2015). Is Minocycline an Antiviral Agent? A Review of Current Literature. Basic & Clinical Pharmacology & Toxicology, 118(1), 4–8. doi: 10.1111/bcpt.12444
10. Tran, D. H., Sugamata, R., Hirose, T., Suzuki, S., Noguchi, Y., Sugawara, A., … Suzuki, K. (2019). Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process. *The Journal of Antibiotics*, *72*(10), 759–768. doi: 10.1038/s41429-019-0204-x
11. Zeng, S., Meng, X., Huang, Q., Lei, N., Zeng, L., Jiang, X., & Guo, X. (2019). Spiramycin and azithromycin, safe for administration to children, exert antiviral activity against enterovirus A71 in vitro and in vivo. *International Journal of Antimicrobial Agents*, *53*(4), 362–369. doi: 10.1016/j.ijantimicag.2018.12.009.