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Doxycycline Combination for Fastest Treatment in COVID-19

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Abstract:

The pandemic of coronavirus disease (COVID-19) has massively spread across 210 countries & territories around the globe. The agent causing the infection identified to be a beta coronavirus; was first named as Novel coronavirus (2019-nCoV). The International Committee of taxonomy of viruses then changed the name to SARSCoV- 2, connoting the coronavirus causing severe acute respiratory syndrome-2Currently; there is a race against time to identify prophylactic and therapeutic treatments against COVID-19. Until these treatments are developed, tested, and mass produced, it might be prudent to look into existing therapies that could be effective against this virus. Best on research paper, tetracycline may be effective against in the treatment of COVID-19 are highly lipophilic antibiotics Chelate with Zinc compound on matrix metalloproteinases (MMPs).

The pandemic of coronavirus disease (COVID-19) has massively spread across 210 countries & territories around the globe. The agent causing the infection identified to be a beta coronavirus; was first named as Novel coronavirus (2019-nCoV). The International Committee of taxonomy of viruses then changed the name to SARSCoV- 2, connoting the coronavirus causing severe acute respiratory syndrome-2. Respiratory failure had been certainly the major cause of death in previous viral pandemics, from the Spanish flu in 1918 to the MERS-CoV in 2012, likewise is the case in the new COVID-19.

Keywords: *Bifidobacterium bifidum; Lactobacillus; antibiotic resistance; genome analysis; lactic acid bacteria; tetracycline resistance;*

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Introduction:

Infection with novel SARS-CoV-2 carries significant morbidity and mortality in patients with pulmonary compromise, such as lung cancer, autoimmune disease, and pneumonia. For early stages of mild to moderate disease, care is entirely supportive. Antiviral drugs such as remdesivir may be of some benefit but are reserved for severe cases given limited availability and potential toxicity. Repurposing of safer, established medications that may have antiviral activity is a possible approach for treatment of earlier-stage disease. **(1)**. *Tetracycline and its derivatives (e.g. doxycycline andminocycline) are non-traditional antibiotics with a well-established safety profile, potential efficacy against viral pathogens such as dengue fever and chikungunya, and may regulate pathways important in initial infection, replication, and systemic response to SARS-CoV-2. We present a series of four high-risk, symptomatic, COVID-19 patients, with known pulmonary disease, treated with doxycycline with subsequent rapid clinical improvement. No safety issues were noted with use of doxycycline. Doxycycline is an attractive candidate as a repurposed drug in the treatment of COVID-19infection, with an established safety profile, strong preclinical rationale, and compelling initial clinical experience described here. The reviews of this paper are available via the supplemental material section.*

The dynamic study is based on three properties of tetracycline (a) Tetracycline are known as chelate zinc from metalloproteases (MMPs) **(2)**. *The chelating activity may help to inhibit covid infection by blocking replication in host cell. In dengue virus tetracycline also inhibit the replication of positive polarity of single stranded-RNA. Tetracycline also modulates innate immunity (Anti-inflammatory activity) which is related with inflammatory skin diseases* **(3)**. *Tetracycline also control cytokinin storm by COVID-19. Tetracycline as lipophilic nature also work by pulmonary penetration. Doxycycline long history of safety, duration of treatment & low cost. For doxycycline main adverse effect events expected Skin disorder & immune system disorder.*

Doxycycline In Prospective study for Viral Protein Inhibition:

Method of Study: *This is a prospective, phase III, randomised, double-blind, placebo-controlled, multi-centre, national study to evaluate the use of doxycycline on patients with at less one risk of worsening COVID-19 disease.*

Method of Clinical study: *After increasing rate of Pulmonary infection, patients are hospitalizing with severe pulmonary infection in COVId-19 at 25% after hypothesis use of doxycycline the rate would decrease 12%.*

Objective of Clinical study: *Decrease rate of patients requiring hospitalization & decrease mechanical ventilator assistance*

Anti-inflammatory & Immunomodulatory properties, Doxycycline is also considered to be cardioprotective. Myocardial injury during perfusion, matrix mettaloprotiase-2(MMP2) are released. Doxycycline's inhibition of MMP-2 pathway support to rescue left ventricular function [4]*. As a result, in patient with acute ST segment elevation myocardial infraction & left ventricular dysfunction. Doxycycline could reduce undesirable left ventricular remodelling* [5]*.*

Coronaviruses are also known to rely heavily on host MMPs for survival, cell infiltration, cell-to-cell adhesion, and replication, many of which have zinc as part of their MMP complex [6]*.*

Coverage Of Doxycycline in Dengue Virus:

At normal human body temperature and fever conditions, doxycycline significantly inhibited the virus own serine protease as well as noting concentration dependent viral replication [7]*. Doxycycline inhibited post infection replication in addition reducing the virus ability to enter the cultured cell. Another study shows that retroviral load was decreased by 70% when cell was treated with doxycycline at human body temperature* [8]*.*

Followed by Clinical Study Doxycycline in High Risk COVID-19 Patients: New York Study:

The study population included 89 high-risk patients diagnosed with COVID-19. These patients were residents of long-term care facilities, with a median age of 78years (43- 101 years), who developed a sudden onset of fever, cough, shortness of breath (SOB), and hypoxia.

Majority of these patients had co-morbidities: 70% had hypertension, 34% had diabetes, 46% had coronary artery disease (CAD), 26% had congestive heart failure, and 42% were obese.

All patients diagnosed with COVID-19 received Doxycycline and regular standard of care. Doxycycline was administered 100 mg orally or intravenously for seven days along with the regular standard of care.

The results were indicative of significantly improved clinical outcomes: Eighty-five percent (85%) of patients showed clinical recovery that was defined as resolution off ever (average 3.7 days), resolution of SOB (average 4.2 days), and improvement of oxygen saturation/pulse oximetry (POX) with an average of 84% before treatment and average of 95% after treatment. [9].

Within 10 days of symptom onset, 3% of patients (n=3) required transfer to hospital due to clinical deterioration and death occurred in 11% (n=10) of patients.

Early treatment with Doxycycline in high-risk patients with moderate to severeCOVID-19 infections in non-hospital settings, such as long-term care facilities (LTCFs), led to early clinical recovery, reduced hospitalization, and mortality [10].

Anti-inflammatory & Immunomodulatory Therapy:

Doxycycline is also considered to be cardioprotective. Following myocardial injury duringre perfusion, matrix metalloproteinases-2 (MMP-2) are released. Doxycycline's inhibition of this MMP-2 pathway supports to rescue left ventricular function [11]. *As a result, in patients with acute ST-segment elevation myocardial infarction (STEMI) and left ventricular dysfunction, Doxycycline could reduce undesirable left ventricular remodelling* [12]. *These cardioprotective characteristics of Doxycycline may help to improve clinical recovery in COVID-19 patients with acute myocardial injury.*

Antiviral Activity -To Multiple virus & Through Multiple Pathway:

In Vitro study antiviral activity of Doxycycline against SARS-COV: 2 [13]. *The mechanism of antiviral activity by tetracycline group derivatives seems to be secondary transcriptional upregulation of intercellular Zinc-Finger antiviral protein (ZAP) an encoding host cells* [14]. *ZAP also bind to specific targeted RNA & repress RNA translation. Experimental studies have used tetracycline.*

Experimental studies have used tetracyclines to induce the overexpression of host ZAP in HEK293 (Human Embryonic Kidney Cell 293) [15]

Global Recommendations for Doxycycline

NICE UK guideline - Antibiotics for pneumonia in adults in hospital duringCOVID-19 [16]*. Doxycycline is considered one of the empirical choices of oral antibiotics:*

Lactic Acid Bacillus:

Lactic acid bacillus can act as reservoir of antibiotic resistance gene that can ultimately transferred to pathogen. Minimum Inhibitory Concentration (MIC) is compromised by 16 antibiotics to 25 LAB isolates of five lactobacillus. A TET (W) gene susceptible by PCR analysis in 2 Bifidobacterium bifidum strains although they have been proved by tetracycline suspectable. No new genes were identified in the genome of lactobacillus species sequenced after using tetracycline. After changing strain in presence of tetracycline [17]*. Lactic acid bacillus interference with viral entry or viral replication in the intestine. This mechanism may have role in reducing dissemination of coronavirus via gut-lung axis. As reports from China indicate that COVID-19 might be associated with intestinal dysbiosis causing inflammation and poorer response to pathogens (*[18]*, the case exists for probiotic strains that restore gut homeostasis* [19] *It is feasible that orally administered probiotic strains could further influence this gut-lung axis, as some can migrate from the gut to distant site*

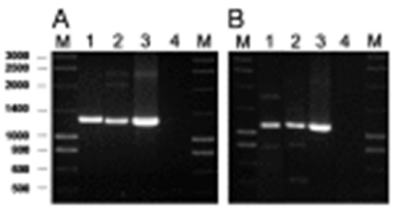

Fig: PCR Amplification of tetracycline resistant genes by suspectable Lactobacillus strains

Conclusion:

Coronavirus disease 2019 (COVID-19) continues to remain a significant public health challenge, and the current antiviral arsenal for its treatment is limited, with questionable efficacy. While efforts are underway for the discovery of new effective agents, validation of their actual potential may take quite some time. Therefore, the repurposing of existing drugs for new indications is the need of the hour, as we see it happening globally. Along with this endeavour, Doxycycline emerges as an antimicrobial agent possessing antiviral and anti-inflammatory activities; which by dampening the critical cytokine storm has the potential to prevent lung damage. Along with its cost-effectiveness, acceptable tolerance and ease of availability, Doxycycline, as a prominent consideration in patients with COVID-19

seem a rational as well as a realistic one. Coronaviruses are also known to rely heavily on host MMPs for survival, cell infiltration, cell-to-cell adhesion, and replication, many of which have zinc as part of their MMP complex. Probiotic orally administered influence gut-ling axis, stop dysbiosis which may alter immune function & secondary bacterial or viral infection. It is a well treatment options may have tremendous impact on lowering the burden disease, minimizing the chance of developing disrupted immune manifestations & reduce hospital stay. A number of brands already have been used in clinical trial for fighting with 2nd variation of corona virus. In Future Some upcoming marketed brand will be used further infected population for further 3rd stage or more wave. so, such therapies may be considered as perfect combination in COVID-19 preliminary infection.

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