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ROLE OF DOXYCYCLINE IN COVID-19- A REVIEW

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ABSTRACT The novel SARS-coV-2 is a potential threat and health hazard mostly for people already suffering from pulmonary infections such as lung cancer, any autoimmune disorders, etc. This poses a threat in every phase of the infection. Treatment with some antiviral agents such as remdesivir may prove to be useful but their increased level of toxicity makes them quite unfavourable. Use of drugs like doxycycline which have gone through the process of providing timely treatment and better results in diseases such as chikungunya and dengue, than resorting to only anti-viral drugs, has proven to be more helpful.

KEYWORDS : COVID-19, SARS-coV-2, Respiratory distress, Doxycycline, Coronavirus

INTRODUCTION:

SARS-coV-2 is a new-found strain of coronavirus that has taken the world by absolute storm. While most are advised to seek treatment in the comfort of their homes, ie, self-quarantine, some patients who already harbour respiratory diseases are hospitalised.[1]

The most important aspect of study of drugs for COVID-19 is repurposing of existing drugs. Doxycycline is a derivative of tetracycline and can be easily used in therapy of COVID-19. Tetracycline and its derivatives have anti-viral properties. They also have anti-inflammatory properties which makes it ideal to ameliorate symptoms of the infection.[2]

Doxycycline is mainly usage at dosage 100 mg twice daily for bacterial or derma logical conditions. [3]According to clinical studies, Doxycycline is very effective in treatment of Chikungunya and Dengue fever. Also, it affects various steps involved in pathway of replication of COVID-19 virus. Tetracyclines have pleiotropic features which result from non-conventional pathways.

Epidemiology:

A water-soluble tetracycline antibiotic is Doxycycline hyclate. It prevents the growth of gram negative as well as positive bacteria. It treats acne, malaria, can be used for prophylaxis and treatment. It is especially useful in treated outbreaks like mycoplasma and cholera.

Since there is no definitive therapy right now for COVID-19, older drugs which have already proven to be useful are being repurposed. They are not only being effectively used to treat the symptoms of COVID-19, but also for the purpose of study and advancement for clinical trials and potential therapy of the infection. [3]

The novel SARS-coV-2 presents itself in three phases: the initial phase comprising only mild symptoms, the pulmonary phase which deals with predominance of symptoms related to the lungs and also with adaptive immunity, and lastly, phase 3 which is the hyperinflammatory phase of the disease which can lead to a variety of conditions, the most fatal being multi-organ failure. [4]

Doxycycline as Proven Therapy:

Doxycycline has been resorted to as a drug of choice for therapy of COVID-19 due to its already established efficacy in chikungunya and dengue. [5]

Certain case studies have also shown improvement of symptoms in COVID-19 positive patients. A 48-year old woman with this virus, already harbouring adenocarcinoma of the lung, was put on Doxycycline which improved her symptoms in a week.

An 88 year old man with an array of diseases such as sick sinus syndrome, mild obstructive lung disease, was tested positive for coronavirus. He was put on Ceftriaxone and Azithromycin as therapy. Soon, ceftriaxone was not continued further and Doxycycline was used instead of Azithromycin. Significant improved results were seen after 14 days of therapy. [1]

Dosage:

A standard dose of Doxycycline- 100 mg twice daily was employed in the above mentioned cases. [6]

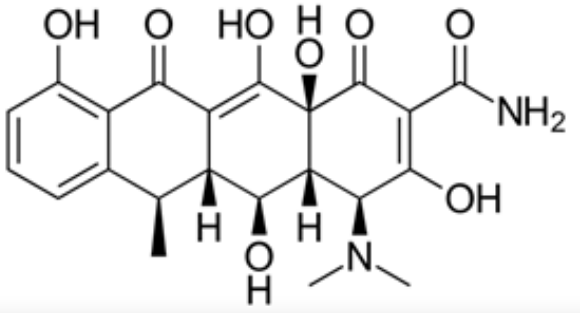
The important point to note about Doxycycline to differentiate it from other tetracycline derivates is it's dual action of cellular cytotoxicity and anti-inflammatory effects.

General Dosage:

Initial: 200 mg/day twice daily oral/intravenously on day 1 (IV given once/day)[6]

Maintenance: 100-200 mg/day once/day or can be divided once every 12 hours orally/IV.

Mechanism Of Action:



Chemical Structure [7] *Doxycycline* $C_{22}H_{24}N_2O_8$

Doxycycline acts against SARS-coV-2 in a variety of ways which makes it suitable as therapy for COVID-19. One of the ways in which it acts is the inhibition of MMP-9 (a metalloproteinase) which is significant for viral entry. [7]It also has been found to inhibit IL-6 which is also a regulator of "cytokine storm" along with MMP-9 (metalloproteinase-9). It is linked to viral pneumonitis. [8]

It also causes apoptosis of epithelial cells which are aged or "senescent." Since it is also an established ionophore, it increases the concentration of zinc in the cells which is ideal to inhibit replication of the viral strain. Trascriptional upregulation of ZAP (zinc finger antiviral protein) occurs which inhibits viral translation. Increased concentrateon and amount of Zinc is also a factor which plays into the inhibition of the viral attack. [9]It also has an inhibitory effect on (Nuclear Factor) NF-kB and DPP4 (Dipeptidyl-peptidase 4) required for viral entry. [10]CD147/EMMPRIN (extracellular matrix metalloproteinase inducer) is also inhibited by Doxycycline, or rather its low dose. T-lymphocytes are then unable to accept the entry of the

virus. [11]CD147 is also referred to as Basigin or EMMPRIN. The structure of SARS-CoV-2 SP is almost same as of SARS-CoV SP, both bind with ACE2, hence they invade host cells. An anti-CD147 humanized antibody, Meplazumab was used to demonstrate this invasion. [11]

On structural analysis, it was found that Doxycycline inhibits PLpro and 3C-like main protease which are both necessary for viral replication. That basically indicates that when COVID-19 attacks the cell, it releases certain proteins NSP (nonstructural proteins)—1,2 and 3 which are absolutely mandatory for the replication of the virus.[12]Inhibition of NSPs (nonstructural proteins) causes a break in the life cycle of the virus.

Special Population:

Pregnancy:

It is contraindicated due to teratogenic property. It also decreases bone growth in fetus. There is a high chance of major congenital abnormalities, neural tube defects and more. Since this study was based on other derivatives of tetracycline and not specifically doxycycline, the results have still been applied to doxycycline without any evidence of teratogenic effects as such. [13]

It also has been linked to retarded bone growth. When doxycycline usage was studied in animals, it was notrelated to incidence of any anomalies of the skeleton until doses were increases to 17 times of the normal dosage. [13] **Paediatric:**Usually, Doxycycline is used in younger patients with regards to acne, chancroid. But it does produce effects like discolouration of teeth to a yellow colour. It can also cause enamel hypoplasia. Chelation of tetracycline with calcium orthophosphate forms a complex which irreversibly incorporates into the teethin the duration of the stage of tooth development which is calcification. **Geriatric:** As elderly patients might already harbour certain kidney and liver diseases, the treatment should proceed with caution. [13]

Pharmacokinetics:

Doxycycline is usually given orally. It is completely absorbed. Peak levels reached were 2.6 mcg/mL at 2 hours. It is concentrated in bile. Metabolism occurs in the liver. It is excreted in urine. [14]

Adverse Effects:

Gastrointestinal effects like nausea and vomiting may occur. Dermatological side effects are common. Abnormal weight gain is noted. Gut flora may also be altered. [15]

Future Considerations:

A large-scale cohort study is very necessary to establish the efficacy of Doxycycline in patients with COVID-19. This is based on multiple case studies which proceed in the direction of improvement of symptoms after administration of Doxycycline.

DISCUSSION:

Some of the case studies mentioned above as well as those that have been done previously, clearly indicate a direct correlation between the administration of Doxycycline and reduction of symptoms of coronavirus. [16]Since Doxycycline is both anti-microbial as well as anti-inflammatory in its properties, combination therapy must be proposed. It is also a safe drug with low toxicity, in addition to being easily accessible to the public, which makes it ideal to be included in future use as a therapeutic agent with regard to reduction of symptoms of COVID-19. [17]

The effectiveness of Doxycycline may be related to it's effect against the pathways of viral replication. Although it has not shown direct and specific action against SARS-coV-2, Doxycycline has a mechanism of action wherein in acts on CD147/EMMPRIN (extracellular matrix metalloproteinase inducer) and DPP4 (Dipeptidyl-peptidase 4) to inhibit viral replication due to which the symptoms reduce greatly. [11]

It also prevents the cytokine storm by inhibition of IL-6 and MMP-9 which are major regulators of the cytokine storm. [18]

As denoted by earlier studies on Doxycycline in comparison to other drugs such as Ivermectin and some other drugs which have come to use and popularised in regards to COVID-19 recently, it is more cost-effective. The duration of hospitalisation is also lesser in the Doxycycline group. [19]

CONCLUSION:

As a whole, the role of Doxycycline in the reduction of symptoms of COVID-19 has been time and time again proven to be useful and combination therapy might be very helpful. Further studies must be done and clinical trials must also be taken into consideration, owing to the proof of its efficacy.

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