Efficacy of Doxycycline in treating COVID-19 Positive Patients: A Case Series

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Research article

Keywords: Doxycycline, COVID-19, Treatment

Posted Date: January 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-141875/v1

Abstract

Background

Given the high morbidity and mortality caused by Coronavrus Disease 2019 (COVID-19), scientific research is necessary to achieve a proper treatment regimen. Since doxycycline is effective in reducing inflammatory factors, including IL-6 and TNF-alpha that play an important role in initiating cytokine storms and probably causing death in patients with COVID-19, its use is associated with low side effects, can be used orally, and is well tolerated, the present study was attempted to evaluate the efficacy of doxycycline in the treatment of inpatients and outpatients with COVID-19.

Methods

This descriptive and prospective study was performed on inpatients and outpatients with COVID-19 from September 14, 2020, to September 28, 2020. The patients were diagnosed with COVID-19 based on polymerase chain reaction test (PCR) from nasopharyngeal secretions or computerized tomography scan (CT). Patients who met the inclusion criteria received doxycycline at a dose of 100 mg every 12 hours for 7 days and then were evaluated on the baseline day and on days 3, 7, and 14 after admission for cough, Shortness of breath (SOB), temperature and oxygen saturation (O2 sat).

Results

Out of 21 patients, 11 patients were male and 10 patients were female. Three patients had diabetes, hypertension, and lymphoma. Only 2 patients were admitted to intensive care unit (ICU), and no patients died. Cough, SOB, temperature, and O2 sat improved in both of outpatients and inpatients compared to baseline. In general, the results showed that doxycycline was more effective in improving cough, SOB, temperature, and O2 sat in outpatients than inpatients. No side effects were reported by the patients.

Conclusion

It can be concluded that doxycycline with the dose and duration prescribed in our study could play an effective role in the treatment of patients with COVID-19. Its use improved patients' cough, SOB, temperature, and O2 sat.

Background

The new coronavirus has emerged since late 2019 and spread rapidly around the world, turning to a pandemic. Medical scientists and researchers are trying to find effective drugs to treat this disease (1). Coronaviruses are named positive-sense RNA viruses because of having crown-like spikes on their surfaces. Coronaviruses are a large family of viruses belonging to the genus Nidovirales, family

Coronaviridae (2, 3). On January 2nd, 2020, 41 patients were diagnosed with Coronavrus Disease 2019 (COVID-19) COVID-19 infection based on laboratory tests. Less than half of them had underlying diseases, such as diabetes, hypertension, and cardiovascular disease (4). In patients with COVID-19, the number of leukocytes in the respiratory system is abnormally high. The main pathogenesis of COVID-19 is severe pneumonia, RNAaemia, incidence of ground-glass opacities, and acute heart injury. Significantly high blood levels of cytokines and chemokines are seen in patients with COVID-19, including IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ IP10, MCP1 , MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some severe cases admitted to the intensive care unit have been shown to have high levels of proinflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, leading to increased disease severity (4). Tetracyclines are lipophilic compounds and have good tissue penetration; hence, there are a good concentration of this drug in the skin, nails, scalp, conjunctiva, tears, milk, saliva, and intracellular fluid (5). They are broad-spectrum bacteriostatic compounds and have activity against gram-positive, gram-negative bacteria, intracellular organisms, atypical organisms (e.g. Chlamydia and Mycoplasma *Virginia)* and protozoan parasites (6, 7). The mechanism of action of doxycycline is to inhibit bacterial protein synthesis through the irreversible binding of 30S and possibly S50 ribosomes as well as alterations in the cytoplasmic membrane. (5, 6, 7). Oral doxycycline is almost completely absorbed and its plasma concentration is reduced by 20% when consumed with high-fat foods or milk. It is well distributed in most body fluids, including pleural, synovial, and bronchial secretions. Its binding to proteins ismore than 90%. The advantage of this drug is that it does not have hepatic metabolism; therefore, dose adjustment is not needed in patients with hepatic disease.

The bioavailability of this drug is reduced at high pH conditions, such as gastrectomy, gastric bypass surgery, or achlorhydric condition. The half-life of this drug is 18 to 22 hours. It is contraindicated in children less than 8 years of age, during pregnancy, and lactation (8, 9). The mechanism of anti-inflammatory effects of doxycycline is to inhibit bacterial products (reducing the production of chemotactic neutrophil cytokines) that stimulate inflammatory processes. Doxycycline in vitro and dermal studies inhibit leukocyte migration by chelating intracellular calcium at the onset of the inflammatory process. Tetracyclines can also suppress alpha-amylases, phospholipase A2, TNF (α), and interleukin1beta (IL-1β). Doxycycline can reduce the levels of inflammatory cytokines in neonatal rats, such as TNFα, IL-1β, and IL-6 (7, 10- 12). However, doxycycline is more effective than tetracycline in reducing pro-inflammatory cytokines (13). In this study, we evaluated the effect of doxycycline in both outpatients and inpatients with COVID-19. Patients were evaluated on the baseline day and on days 3, 7, and 14 after admission for cough, Shortness of breath (SOB), temperature and O2 sat.

Methods

Setting and population

This prospective, *open-label and* non-randomized pilot study was performed on both inpatients and outpatients with COVID-19 who referred to *Baghaeipour Clinic, Shahid Sadoughi Hospital*, Yazd, Iran, from September 14, 2020, to September 28, 2020. The patients were diagnosed with COVID-19 based on

polymerase chain reaction (PCR*) test* or computerized tomography scan (CT) manifestations. The patients referred to who referred to Baghaei Pour Clinic, Shahid Sadoughi Hospital, Yazd, Iran, who had the indication for inpatients and outpatients treatment, were evaluated for inclusion and exclusion criteria. On initial examination, patients were evaluated for cough, SOB, temperature, and O2 sat. Cough and SOB were scored as follows: zero: no cough or SOB, 1: mild cough or SOB, 2: moderate cough or SOB, 3: severe cough or SOB, and 4: very severe cough or SOB. This is a pilot study.

After the patients were evaluated for inclusion criteria, signing the informed consent form by the patients, 21 patients entered the study. This is a pilot study. The presented results are part of the results and the full results will be published in another article.

Exclusion and inclusion criteria

Patients were included in the study if they met the following criteria: minimum age 18 and maximum age 80 years, willingness to participate in the study and signing the informed consent form, not take doxycycline during the past 14 days, being suspected with COVID-19 based on clinical signs and CT scan manifestations, and being candidate for inpatient and outpatient treatment.

Intervention

Patients who met the inclusion criteria received doxycycline at a dose of 100 mg every 12 hours for 7 days along with standard treatment.

Data gathering & Measurements

Demographic, clinical and therapeutic information of the disease was obtained by writing down the desired information from the patients' files and designing a questionnaire. This questionnaire contains information about age, sex, underlying disease, cough, temperature, SOB, temperature and percentage of O2 sat.

Patients were evaluated on the baseline day and on days 3, 7, and 14 after admission for cough, dyspnea (SOB), temperature and O2 sat.

Ethical approval

This study was initiated after obtaining the Ethics ID (IR.SSU.MEDICINE.REC.1399.140) by Ethics Committee of Biomedical Research, School of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran. This study was also approved in the Iranian Registry of Clinical Trials (IRCT20191211045691N2).

Statistical analysis

The data were coded and entered into SPSS version 20. We used Friedman and Wilcoxon tests to compare qualitative variables. The significance level of 0.05 was considered

Results

Out of 21 cases, 9 patients were inpatients (42.86%) and 12 were outpatients (57.14%). Men made up 52.38% and women 47.62% of the patients. Three patients had underlying disease, including diabetes, hypertension, and lymphoma. Only 2 patients needed to be admitted to ICU and no deaths were occurred in this study. Cough and SOB were scored as follows: zero: no cough or SOB, 1: mild cough or SOB, 2: moderate cough or SOB, 3: severe cough or SOB, and 4: very severe cough or SOB. In both groups, cough improved compared to baseline. This improvement was significant on days 7 and 14 ($p<0.05$), but on the fourteenth day, 75% of outpatients and 33.3 % of inpatients had a zero score (Table 1). SOB in both inpatients and outpatients improved significantly on days 7 and 14 ($p<0.05$). In outpatients, on days 7 and 14, moderate, severe, or very severe form of SOB was not observed; however, in inpatients on the seventh day, only very severe form of SOB was not observed. On the fourteenth day, severe and very severe form of SOB was not observed in inpatients (Table 2). In both inpatients and outpatients, body temperature improved significantly from day 3 onwards, but this change was higher in inpatients (Table 3). Inpatients' O2 sat improved significantly on day 14 compared to baseline ($p<0.012$). However in outpatients, O2 sat improved significantly on days 3, 7, and 14 ($p<0.37$, $P<0.37$, and $P<0.012$ respectively) (Table 4).

The presented results are part of the results and the full results will be published in another article**.**

Discussion

The aim of this study was to evaluate the efficacy of doxycycline in treating COVID-19 patients. Patients included in this study were evaluated for cough, shortness of breath, temperature, and O2 sat on baseline day and 3, 7, and 14 days. They were definitively diagnosed with COVID-19 based on CT scan and PCR test.

According to the findings of this study, administration of doxycycline was effective in treating both inpatients

and outpatients and no patient was excluded due to side effect.

Paul et al., (15) reported a case series of four high-risk, symptomatic, COVID-19 patients who had known pulmonary disease. Their patients were initially treated with doxycycline at the dose of 200 mg followed by 100 mg daily for 5 days. In the aforementioned study, subsequent rapid clinical improvement was reported and no side effects were noted following the use of doxycycline. In this study, we evaluated the efficacy of doxycycline in treating inpatients and outpatients suffering from COVID-19. The dose of doxycycline and the duration of its administration were different from those in Paul et al.'s study. . In addition, none of our cases had underlying lung disease, and three patients had other underlying diseases, including diabetes, hypertension and lymphoma. Nevertheless, the results in both studies were similar in terms of effectiveness and side effects associated with doxycycline. Alam et al., (16), in another study, evaluated the effect of the combination of doxycycline and Ivermectin on 100 high-risk,

symptomatic, COVID-19 patients. The symptoms of all patients improved within 72 hours. No significant side effects were observed. They concluded that combination of Ivermectin and doxycycline was very effective in viral clearance in mild and moderately sick COVID-19 patients. Although the administration of doxycycline was done alone and for a shorter period of time in our study, patients' symptoms resolved within 72 hours.

Doxycycline is a bacteriostatic antibiotic. Doxycycline inhibits bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit and preventing the association of aminoacyl-tRNA with the bacterial ribosome. A summary of the anti-inflammatory activities of doxycycline is shown in Figure 7. As shown in this Figure, what is more important is the effect of doxycycline on IL-6 and TNF-alpha, which play an important role in morbidity and mortality caused by COVD-19 disease (17). Doxycycline is usually given in doses of 100 and

200 mg and is well tolerated by the patients. The most important side effects of this drug are gastrointestinal

side effects, such as diarrhea, nausea, vomiting, and esophagitis.

The risk of esophagitis can be reduced by use of enteric-coated products and monohydrates formulation or consumption of medicine with enough water and be upright for 30 minutes after administration (18). In our study, the drug was well tolerated by the patients.

The only observed complication was related to gastrointestinal side effects, but no patient was excluded due to this complication.

Conclusion

It seems that doxycycline at the dose and duration prescribed in our study can be effective in the treatment of patients with COVID-19 given that improved patients' cough, SOB, temperature, and O2 sat during the study and no serious side effects were reported by the patients. In addition, this drug is covered by insurance, can be used orally, and it does not have hepatic metabolism; therefore, dose adjustment is not needed in patients with hepatic disease.

Abbreviations

COVID-19: Coronavirus Disease 2019; PCR*: polymerase chain reaction test*; CT: Computerized tomography scan;

O2 sat: oxygen saturation; ICU: intensive care unit; IL-1β: interleukin1beta; SOB: Shortness of breath

Declarations

Acknowledgements

We thank all those who helped us in this project.

Authors' contributions

Study design and protocol development: MBO, SO, ZAM and SRM. Patients recruitment and follow up: ZA. Data analysis: SRMN. Manuscript preparation and submission: MBO, ZAM and SRMN. All authors will read and approved the final manuscript before submission.

Funding

This study was not funded by any organization or institution.

Availability of data and materials

We, the authors, apologize for providing patient information to this journal because we did not consent to the publication of their medical records.

Ethics approval and consent to participate

This study was initiated after obtaining the Ethics ID (IR.SSU.MEDICINE.REC.1399.140) by Ethics Committee of Biomedical Research, School of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran. This study was also approved in the Iranian Registry of Clinical Trials (IRCT20191211045691N2). Patients signed an informed consent form to participate in the study.

Consent for publication

Not Applicable.

Competing interests

No conflicts of interest have been declared by the authors

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Tables

Table 1 Comparison of cough on days 3, 7, and 14 of compared to the baseline day in inpatients and outpatients

Day			Base line	Day 3	Day 7	Day 14
Variable			Number (percent)	Number (percent)	Number (percent)	Number (percent)
Cough	Outpatients	Zero*	0 (0)	0 (0)	5 (41.7)	9 (75)
		1	3 (25)	8 (66.7)	6 (50)	2 (16.7)
		2	7 (58.3)	4 (33.3)	1 (8.3)	1 (8.3)
		3	1 (8.3)	0 (0)	0 (0)	0 (0)
		4	1 (8.3)	0 (0)	0 (0)	0 (0)
		p-value**	-	0.114	<0.001	<0.001
	Inpatients	Zero*	0 (0)	0 (0)	0 (0)	3 (33.3)
		1	1 (11.1)	3 (33.3)	7 (77.8)	4 (44.4)
		2	5 (55.6)	4 (44.4)	1 (11.1)	2 (22.2)
		3	3 (33.3)	2 (22.2)	1 (11.1)	0 (0)
		4	0 (0)	0 (0)	0 (0)	0 (0)
		p-value	-	0.52	0.036	0.002

*Cough was scored as: zero: no, 1: mild, 2: moderate, 3: severe and 4; very severe cough.

** The Friedman test was used to detect any statistical differences.

Table 2 Comparison of SOB on days 3, 7, and 14 compared to the baseline day in inpatients and outpatients

Day			Base line	Day 3	Day 7	Day 14
Variable			Number (percent)	Number (percent)	Number (percent)	Number (percent)
SOB	Outpatients	Zero*	4 (33.3)	9 (75)	11 (91.7)	11 (91.7)
		1	6 (50)	1 (8.3)	1 (8.3)	1 (8.3)
		2	0 (0)	2 (16.7)	0 (0)	0 (0)
		3	2 (16.7)	0 (0)	0 (0)	0 (0)
		4	0 (0)	0 (0)	0 (0)	0 (0)
		p-value**	-	0.058	0.007	0.007
	Inpatients	Zero*	0 (0)	2 (22.2)	13 (33.3)	5 (55.6)
		1	3 (33.3)	2 (22.2)	4 (44.4)	2 (22.2)
		2	4 (44.4)	3 (33.3)	1 (11.1)	2 (22.2)
		3	2 (22.2)	2 (22.2)	1 (11.1)	0 (0)
		4	0 (0)	0 (0)	0 (0)	0 (0)
		p-value	-	0.27	0.006	0.001

*SOB was scored as: zero: no, 1: mild, 2: moderate, 3: severe and 4; very severe SOB.

** The Wilcoxon test was used to detect any statistical differences.

Table 3 Comparison of temperature on days 3, 7, and 14 compared to the baseline day in inpatients and outpatients

Variable		Days	Min-Max	Mean±SD	p-value*
Temperature	Outpatients	Baseline	(36 – 38.5)	37.2±0.82	-
		Day 3	(36 -37.6)	36.8±0.46	0.043
		Day 7	(35.5 -37.5)	36.46±0.58	0.012
		Day 14	(35.5 -37.5)	36.46±0.58	0.012
	Inpatients	Baseline	(37 – 38)	37.84±0.34	-
		Day 3	(36 -38.5)	37.25±0.73	0.022
		Day 7	(36 -38)	36.72±0.66	0.010
		Day 14	(36 -38)	36.72±0.66	0.010

* The Wilcoxon test was used to find any statistical differences.

Table 4 Comparison of O2 sat on days 3, 7, and 14 compared to the baseline day in inpatients and outpatients

Variable		Days	Min-Max	Mean±SD	p-value*
O2 sat (%)	Outpatients	Baseline	(89-96)	95.25±2.00	-
		Day 3	(94-98)	96.58±0.99	0.002
		Day 7	(95-98)	96.66±0.88	0.006
		Day 14	(95-98)	96.66±0.88	0.006
	Inpatients	Baseline	(79-94)	88.77±4.08	-
		Day 3	(84-95)	89.77±4.2	0.373
		Day 7	(78-96)	91.33±7.1	0.373
		Day 14	(90-96)	93.88±2.26	0.012

* The Wilcoxon test was used to find any statistical differences.

Figures

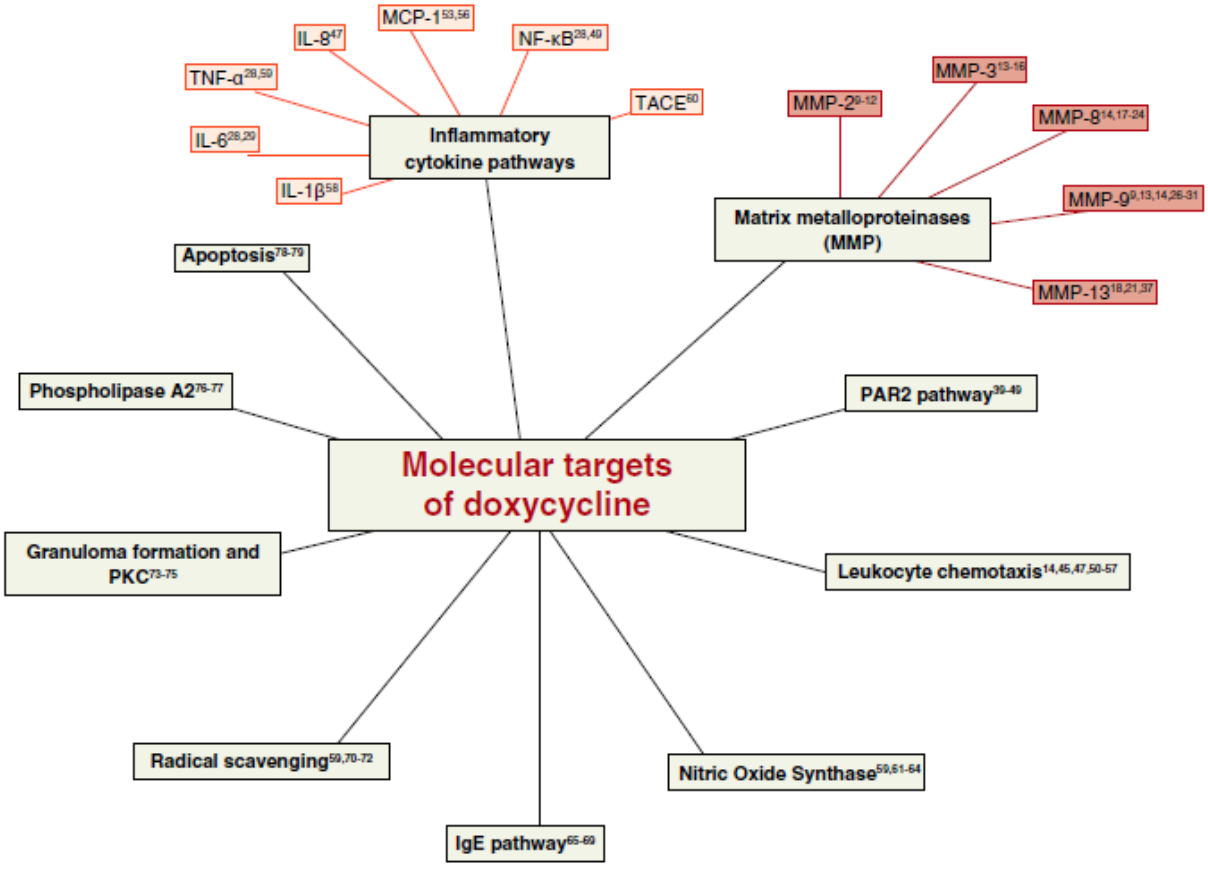

Figure 1

A summary of the anti-inflammatory activities induced by doxycycline