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Efficacy and Safety Doxycycline in treating COVID-19 Positive Patients: A pilot clinical study

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Abstract:

Objective: Given the high morbidity and mortality caused by Coronavirus 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 essential role in initiating cytokine storms and probably causing death in patients with COVID-19, its use is associated with low side effects and can be used orally; 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 who were diagnosed with COVID-19 based on polymerase chain reaction (PCR) test from nasopharyngeal secretions or computerized tomography scan (CT Scan). Patients who met the inclusion criteria received doxycycline at a dose of 100 mg every 12 hours for seven days and then were evaluated on the baseline day. On days 3, 7, and 14 after admission for cough, shortness of breath, temperature, and oxygen saturation.

Finding: Out of 21 patients, 11 patients were male, and ten patients were female. Cough, shortness of breath, temperature, and O2 sat improved in both 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.

Conclusion: The results of this study show that doxycycline with the dose and duration prescribed in our study could play a useful role in treating patients with COVID-19.

Keyword: Doxycycline, COVID-19, Outpatients, Inpatients, Treatment

Introduction

The new coronavirus has emerged since late 2019 and spread rapidly worldwide, 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 Nidovirales, family Coronaviridae (2, 3). January 2nd; September 14; September 28, 2020, 41 patients were diagnosed with Coronavirus 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 primary pathogenesis of COVID-19 is severe pneumonia, RNAaemia, the 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. In some severe cases admitted to the intensive care unit, an increase in mortality with high levels of proinflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, has been observed (4). Tetracyclines are lipophilic compounds that have good tissue penetration; hence, there is 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 and 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 the 30S and possibly 50S ribosomes and 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. It's binding to proteins is more than 90%. One of the advantages of this drug is that no dose adjustment is required in patients with hepatic impairment.

The bioavailability of this drug decline at high pH conditions, such as gastrectomy, gastric bypass surgery, or achlorhydric disorder. The half-life of this drug is 18 to 22 hours. It is contraindicated in children less than eight years of age, during pregnancy, and lactation (8, 9). The anti-inflammatory mechanism of doxycycline is inhibition of bacterial products, including reducing the production of chemotactic neutrophil cytokines, which stimulates inflammatory processes. Doxycycline in vitro and dermal studies inhibit leukocyte migration by intracellular chelating 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 assessed the effect of doxycycline in both outpatients and inpatients with COVID-19. Patients were evaluated on the baseline day and 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 a non-randomized pilot study were conducted on both inpatients and outpatients with COVID-19 who were referred to Baghaeipour Clinic, Shahid Sadoughi Hospital, Yazd, Iran, from January 2nd; September 14; September28. The patients

were diagnosed with COVID-19 based on polymerase chain reaction (PCR) test or computerized tomography scan (CT) manifestations. The patients referred to Baghaei Pour Clinic, Shahid Sadoughi Hospital, Yazd, Iran, who indicated inpatients and outpatient 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.

After the patients were evaluated for inclusion criteria, signing the informed consent form by patients, 21 patients entered the study. This is a pilot study and the presented results are part of the products. 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 research 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 a 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 seven days along with standard treatment.

Data gathering & Measurements

Demographic, clinical, and therapeutic information was obtained by writing down the desired information from the patients' files and designing a questionnaire. This questionnaire contains

information about age, sex, underlying condition, cough, temperature, SOB, temperature, and percentage of O2 sat.

Patients were evaluated on the baseline day and 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 the Ethics Committee of Biomedical Research, School of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran. This study was 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. P values less than 0. 05 were considered to be statistically significant**.**

Results

Out of 21 cases, nine 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 an underlying disease, including diabetes, hypertension, and lymphoma. Only two patients were admitted to the ICU**,** and no deaths 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 a very severe form of SOB was not observed. On the fourteenth day, a severe and very severe SOB form was not observed in inpatients (Table 2). In both inpatients and outpatients, body temperature improved significantly from day three onwards, but this change was greater 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).

Discussion

This study aimed to evaluate the efficacy of doxycycline in treating COVID-19 patients. Patients were assessed 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 a CT scan and PCR test. According to the results, doxycycline was effective in treating both inpatients and outpatients, and no patients was excluded from the study due to side effects. Alam et al., (15) evaluated the impact of the combination of doxycycline and ivermectin on 100 high-risk COVID-19 patients. The symptoms of all patients improved within 72 hours, and no significant side effects were observed. They concluded that the combination of ivermectin and doxycycline was very effective in viral clearance in mild and moderately sick COVID-19 patients. Although in our study doxycycline was given to patients for a shorter period, the patients' symptoms resolved within 72 hours.

Doxycycline is a bacteriostatic antibiotic, and inhibit 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 are shown in Figure1. As shown in this figure, doxycycline inhibits IL-6 and TNF-alpha, which play an

essential role in disease and mortality from COVID-19 (16). Doxycycline in doses of 100 and 200 mg usually has no significant side effects and is well tolerated by patients. The most crucial side effects of this drug are gastrointestinal side effects, such as diarrhea, nausea, vomiting, and esophagitis. The risk of esophagitis can be reduced using 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, only gastrointestinal side effects were observed, and doxycycline was safe and tolerable by patients.

Conclusion

It seems that doxycycline at the dose and duration prescribed in our study can be useful in the treatment of patients with COVID-19 given that improved patients' cough, SOB, temperature, and O2 sat during the research, and safe and tolerable for patients. Also, this drug is covered by insurance, can be used orally, and does not have hepatic metabolism; therefore, this drug can be prescribed without dose adjustment in hepatic impairment.

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.

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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.

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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 the Ethics Committee of Biomedical Research, School of Medicine, Shahid Sadoughi University of Medical Science, Yazd, Iran. This study was approved in the Iranian Registry of Clinical Trials (IRCT20191211045691N2).

Consent for publication

Not Applicable.

Competing interests

None declared.

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

Day			Baseline	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 follows: zero: no, 1: mild, 2: moderate, 3: severe and 4; very severe cough.

** The Friedman test was used for the statistical differences.

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

Day			Baseline	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 follows: zero: no, 1: mild, 2: moderate, 3: severe, and 4; very severe SOB.

** The Wilcoxon test was used for the 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 for the 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.

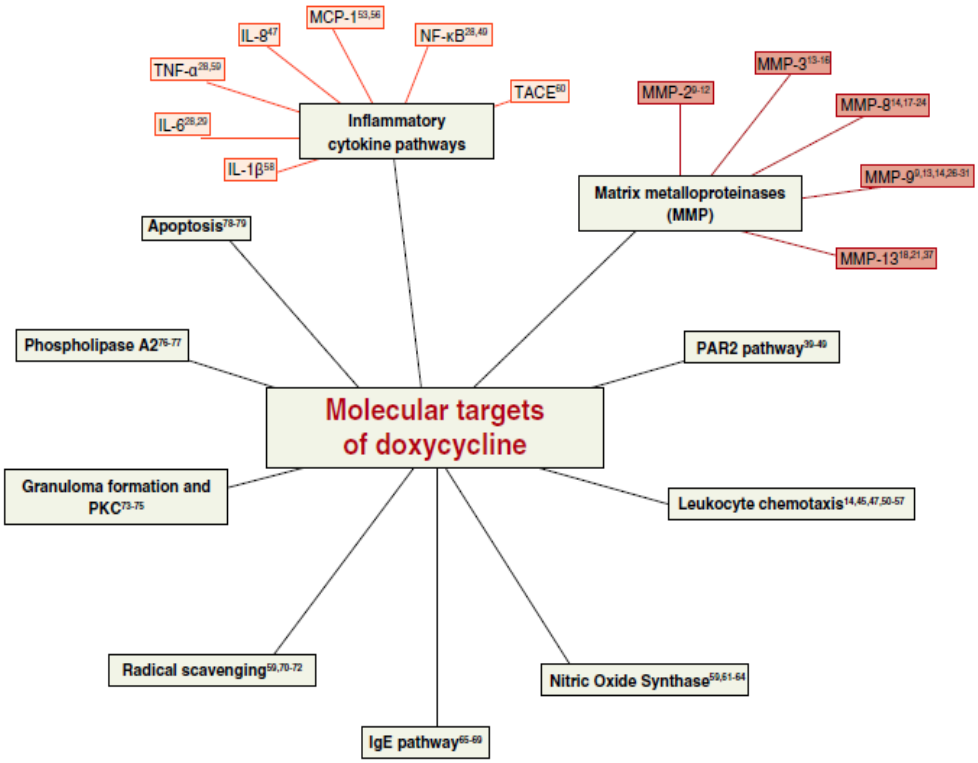

Fig. 1 A summary of the anti-inflammatory activities induced by doxycycline