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Original Article

Doxycycline for the Treatment of Patients in Hospital with COVID-19 in Taiwan: A Retrospective Study

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SUMMARY

Objectives: The aim of this study was to investigate the association between doxycycline treatment and severity, as well as mortality, for patients with COVID-19. In addition, to investigate whether this association was changed in cases of concomitant treatment with corticosteroids, remdesivir, clarithromycin, low molecular weight heparin, or statin.
Material and methods: This is a retrospective cohort study conducted by analyzing electronic medical records of 104 hospitalized patients into the Infectious Disease Ward of a 2068-bed tertiary care medical center, with laboratory-confirmed COVID-19 between May 01, 2021 and August 31, 2021. Patients were classified as receiving doxycycline if they were treated with either oral or intravenous drug, at any dose, within ± 7 days of COVID-19 screening and/or hospital admission. Doxycyline use was extracted directly from the electronic medical record.
Results: Current study failed to identify doxycycline as a protective factor associated with a significant reduction in the risk of in-hospital mortality (odds ratio 1.385, 95% confidence interval (CI) 0.269–7.140, $p = 0.697$) or a significant reduction in the risk of intensive care unit (ICU) admission (odds ratio 0.476, 95% CI 0.125– 1.813, $p = 0.277$). However, a non-significant trend towards a lower rate of ICU admission in association with doxycycline prescription was observed.
Conclusions: The results of this study reflect the real-world use of doxycycline does not reduce the risk of in-hospital-mortality or ICU admission of hospitalized COVID-19 patients.

1. Background

The coronavirus disease 2019 (COVID-19) was first recognized in Wuhan, China, in December 2019. Since its recognition, COVID-19 has rapidly spread across mainland China and became a pandemic in less than 3 months.[1] The typical symptoms of a patient who has been infected with COVID-19 are fever, dry cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia. Covid-19 patients may also present with radiological ground-glass lung changes, lymphopenia, and thrombocytopenia.[2,3] Doxycycline, a tetracycline antibiotic has both antiviral and anti-inflammatory properties that may ameliorate the response to viral infection.[4–7] Doxycline exhibits several potential mechanisms of action which may modulate the effects of COVID-19 infection. Among the postulated mechanisms of action, doxycycline's inhibition of metalloproteinases (MMPs) may be vital in preventing SARS-CoV-2's entry into host cells.[4] Doxycycline also inhibits interleukin (IL)-6, which, a key regulator in the presence of the viral cytokine storm,[8,9] and nuclear factor (NF)-κB, which results in direct inhibition of DPP4 cell surface receptor and subsequently lower the risk of viral entry.[4,10] Moreover, structural analysis have shown that doxycycline holds potential in inhibiting papain-like proteinase (PLpro) and 3C-like main protease (3CLpro) viral proteins, both of which are essential to viral replication and lifecycle.[11] Furthermore, doxycycline showed efficacy in COPD by inhibiting the neutrophilic inflammation and proteolytic activity that can be present in late COVID-19.[12] In light of the facts that cytokine storm and lung fibrosis sequalae are the devastating outcomes in COVID-19, we seek to investigate the efficacy of doxycycline as an adjuvant therapy in improving pulmonary affection and the mortality outcome in COVID-19.

2. Methods

2.1. Study population and data collection

This retrospective, observational study was conducted at MacKay Memorial Hospital, a 2068-bed tertiary care medical center in Taipei and New Taipei City, Taiwan. The MacKay Memorial Institutional Review Board (21MMHIS226e) approved the study and certified that it met the criteria for a waiver of the requirement to obtain informed consents.

The study population for this study was derived from an electronic database collected at MacKay Hospital encompassing consecutive patients screened for COVID-19 between May 01, 2021,

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and August 31, 2021. All patients who tested positive for severe acute respiratory syndrome (SARS-CoV-2) by nasopharyngeal polymerase chain reaction and who required inpatient admission into Infectious Diseases Ward were included in this study.

Patients were classified as receiving Doxycycline if they were treated with oral drug, appropriate dose, within +/- 3 days of COVID-19 screening and/or hospital admission. Doxycycline use was extracted directly from the electronic medical record.

2.2. Primary and secondary outcomes

The primary outcomes of the study included in-hospital death as recorded in the medical chart, requirement for mechanical ventilation, and composite of death or requirement for ventilation. Secondary outcomes include serum markers of disease severity included white blood cell count, lymphocyte count, neutrophil count, band cell count, platelet count, serum ferritin, C-reactive protein (CRP), high sensitivity D-dimer, erythrocyte sedimentation rate (ESR), and procalcitonin. All data were extracted from the electronic medical record.

2.3. Additional variables

Potential predictive variables were chosen based on prior reports of risk factors for acute outcomes in patients positive for COVID-19. Covariates included pre-existing comorbidities, and treatment with antiviral, and corticosteroid medications. Comorbidities included history of pre-existing hypertension, diabetes mellitus, obesity (BMI > 30 kg/m^2), coronary artery disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease (CKD), or prior history of malignancy. In-hospital treatment medications included use of azithromycin, remdesivir, corticosteroids, and low-molecular heparin.

2.4. Statistical approach

Continuous variables that were normally distributed were compared with a Student t test. If not normally distributed, the Mann-Whitney U test was used. Categorical variables were analyzed using the X^2 test or Fisher exact test, as appropriate. Univariate analyses were performed using mortality or combined mortality/ventilation as the dependent variables, and multivariate logistic regression was performed by entering all predictors using a p value of less than 0.05 cut-off. All effects were considered significant at a p value of less than 0.05. The statistical analyses were performed with IBM SPSS release 26.0 (IBM, Armonk, New York).

3. Results

Of 104 patients in the analysis, 15 (14.4%) received Doxycycline. The mean age of the study population was 62.95 (±15.379) years. The study population is comprised of 48 (46.2%) male patients and 56 (53.8%) female patients. A total of 11 (10.5%) patients died during hospitalization, 34 (32.7%) required mechanical ventilation and 9 (8.6%) met the criteria for combined death and intubation. Table 1 summarizes the baseline demographics, characteristics, clinical fea-

Table 1
Demographics and comorbidities: all patients and subpopulations with and without doxycycline.

Variable: n (%), median (IQR), mean (±SD)	All patients (n = 104)		
	Doxycycline (n = 15)	No doxycycline (n = 89)	*p* value
Age			0.187
< 50	1 (5.9%)	16 (94.1%)	
50–65	9 (22.0%)	32 (78%)	
> 65	5 (10.9%)	41 (89.1%)	
Sex			0.601
Male	6 (11.3%)	42 (88.7%)	
Female	9 (17.6%)	47 (82.4%)	
BMI			0.379, Excluding unknow data
< 25.0	3 (17.6%)	14 (82.4%)	
25.0–29.9 (Overweight)	0 (0.0%)	10 (100.0%)	
≥ 30.0 (Obese)	1 (14.3%)	6 (85.7%)	
Unknow	11 (15.7%)	59 (84.3%)	
Charlson Comorbidity Index			0.263
0	1 (8.3%)	11 (91.7%)	
1–2	9 (23.7%)	29 (76.3%)	
3–4	4 (13.3%)	26 (86.7%)	
5–6	1 (6.3%)	15 (93.8%)	
7+	0 (0.0%)	8 (100.0%)	
Quick COVID-19 Severity Index (qCSI)			0.321
0–2 (0)	13 (17.6%)	61 (82.4%)	
3–5 (1)	0 (0.0%)	16 (100.0%)	
6–7 (2)	1 (20.0%)	4 (80.0%)	
≥ 8 (3)	1 (11.1%)	8 (88.9%)	
The Ventilation In COVID-19 Estimation (VICE) Score	0.2282 (±0.2220)	0.1931 (±0.2418)	0.603
WHO Ordinal Clinical Severity Scale at admission			0.023
3	2 (6.3%)	30 (93.8%)	
4	4 (9.8%)	37 (90.2%)	
5	7 (29.2%)	17 (70.8%)	
6	2 (50.0%)	2 (50.0%)	
7	0 (0.0%)	3 (100.0%)	
Comorbidities			
Diabetes	3 (11.1%)	24 (88.9%)	0.754
Hypertension	2 (5.4%)	35 (94.6%)	0.078
Kidney disease	1 (9.1%)	10 (90.9%)	> 0.999
Liver cirrhosis	0 (0.0%)	0 (0.0%)	NA
Heart failure	0 (0.0%)	2 (100.0%)	> 0.999
COPD	3 (37.5%)	5 (62.5%)	0.088
Cancer	0 (0.0%)	4 (100.0%)	> 0.999
Autoimmune disease	0 (0.0%)	3 (100.0%)	> 0.999
Human immunodeficiency virus (HIV)	0 (0.0%)	4 (100.0%)	> 0.999

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NA, non available.

tures, and severity of illness upon admission of the doxycycline and non-doxycycline study populations. Baseline characteristics were similar between the two groups, however, the non-doxycycline group showed a statistically significant higher ordinal scale at admission.

Of the 15 patients who received doxycycline, all patients received oral doxycycline within 24 hours of hospital admission. Doxycycline users received prescription from admission till discharge. For the matched study groups of 104 patients with COVID-19, a total of 33 (31.7%) received remdesivir, 80 (76.9%) received corticosteroids, 20 (19.2%) received clarithromycin, 40 (38.5%) received low molecular weight heparin, and 12 (11.5%) received statin. As shown in Table 2, significant differences were found for corticosteroid use and clarithromycin prescription between the doxycycline and non-doxycycline cohorts with respect to treatment of these agents.

In-hospital death, requirement of ICU admission, and combined ICU admission/death occurred in 2 (13.3%), 12 (80%), and 2 (22.2%) patients in the doxycycline groups, respectively, compared with 13 (86.7%), 3 (20%), and 7 (77.8%) in the non-doxycycline group, respectively. The results of the logistic regression to assess the independent predictors of death in the matched cohort are shown in Table 3. The analysis failed to identify doxycycline as a protective factor associated with a significant reduction in the risk of in-hospital mortality (odds ratio 1.385, 95% confidence interval (CI) 0.269–7.140, p = 0.697). Furthermore, current study also failed to identify doxycycline as a protective factor associated with a significant reduction in the risk of ICU admission (odds ratio 0.476, 95% confidence interval (CI) 0.125–1.813, p = 0.277) in Table 4. However, a non-significant trend towards a lower rate of ICU admission in association with doxycycline administration can be observed.

Table 5 shows laboratory test results for the doxycycline and non-doxycycline groups at follow-up after one week of oral doxycycline administration. Patient receiving doxycycline failed to express lower levels of serum markers for severe disease including mean CRP levels (3.93 vs. 3.76 mg/dL, p = 0.209), mean procalcitonin levels (0.51 vs. 0.11 ng/mL, p = 0.717), and mean serum ferritin levels (768.75 vs. 666.00 ng/mL, p = 0.826).

4. Discussion

Doxycycline is a broad-spectrum antibiotic of the tetracycline family. Prior studies have demonstrated successful treatments of various bacterial and viral infections with doxycycline. Rothan et al. suggested doxycycline's capability of inhibiting viral serine protease, disrupt viral replication, and viral entry into cells via in-vitro assays of cultured cells inoculated with the dengue virus.[13] In the case of COVID-19, Fredeking et al. reported in 2015 that doxycycline lowers significantly pro-inflammatory cytokines (including IL-6 and tumor necrosis factor α), which may be associated with the lower mortality rates observed in dengue hemorrhagic fever patients treated with doxycycline.[5] Moreover, previous research has revealed that elevated levels of intracellular zinc may inhibit SARS-CoV-2 viral replication,[14] coincidentally, doxycycline may act as a zinc ionophore, increasing intracellular concentrations of zinc, thus inhibiting viral replication of COVID-19. Furthermore, a study in 2020 showed doxy-

Table 2
Treatment with remdesivir, corticosteroids, clarithromycin, low molecular weight heparin, and statin.

Agent	Doxycycline	No doxycycline	p value
Remdesivir	6 (18.2%)	27 (81.8%)	0.372
Corticosteroids[a]	15 (18.8%)	65 (81.3%)	0.021
Clarithromycin	0 (0.0%)	20 (100.0%)	0.069
Low molecular weight heparin (Enoxaparin)	8 (20.0%)	32 (80.0%)	0.257
Statin[b]	2 (16.7%)	10 (83.3%)	0.683

[a] Corticosteroid medications include prednisolone, methylprednisolone, hydrocortisone, and dexamethasone.
[b] Statin medications indlude atorvastatin, rosuvastatin, pitavastatin.

Table 3
Patient risk of death after treatment with doxycycline, remdesivir, corticosteroids, clarithromycin, low molecular weight heparin, and statin.

Agent	Mortality	Survive	OR (95% CI)	p value
Doxycycline	2 (13.3%)	13 (86.7%)	1.385 (0.269–7.140)	0.697
Remdesivir	4 (12.1%)	29 (87.9%)	1.222 (0.331–4.506)	0.764
Corticosteroids[a]	10 (12.5%)	70 (87.5%)	3.143 (0.381–25.941)	0.288
Clarithromycin	3 (15.0%)	17 (85.0%)	1.699 (0.408–7.077)	0.467
Low molecular weight heparin (Enoxaparin)	4 (10.0%)	36 (90.0%)	0.889 (0.243–3.255)	0.859
Statin[b]	2 (16.7%)	10 (83.3%)	1.844 (0.348–9.766)	0.472

[a] Corticosteroid medications include prednisolone, methylprednisolone, hydrocortisone, and dexamethasone.
[b] Statin medications include atorvastatin, rosuvastatin, pitavastatin.
CI, confidence interval; OR, odds ratio.

Table 4
Patient risk of ICU admission after treatment with doxycycline, remdesivir, corticosteroids, clarithromycin, low molecular weight heparin, and statin.

Agent	Admission into ICU	No admission into ICU	OR (95% CI)	p value
Doxycycline	12 (80%)	3 (20%)	0.476 (0.125–1.813)	0.277
Remdesivir	12 (36.4%)	21 (63.6%)	1.429 (0.593–3.439)	0.426
Corticosteroids[a]	27 (33.8%)	53 (66.3%)	1.936 (0.652–5.750)	0.234
Clarithromycin	6 (30.0%)	14 (70.0%)	0.872 (0.303–2.513)	0.800
Low molecular weight heparin (Enoxaparin)	15 (37.5%)	25 (62.5%)	1.659 (0.711–3.870)	0.242
Statin[b]	4 (33.3%)	8 (66.7%)	1.103 (0.307–3.960)	0.880

[a] Corticosteroid medications include prednisolone, methylprednisolone, hydrocortisone, and dexamethasone.
[b] Statin medications include atorvastatin, rosuvastatin, pitavastatin.
CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

Table 5
Laboratory findings: all patients and in subpopulations with and without one week of doxycycline treatment.

	Reference range	All patients (n = 104)	Doxycycline[a] (n = 15)	No doxycycline[a] (n = 89)	*p* value[a]
Hematologic					
WBC, $\times 10^9$/L	4.0–10.0	7.83 (±3.889)	8.10 (8)	8.75 (9)	0.786
Lymphocytes, $\times 10^9$/L	20–40	16.45 (±10.326)	14.20 (18)	17.60 (22)	0.618
Percent neutrophils count (%)	55–75	73.63 (±12.739)	80.35 (39)	74.15 (33)	0.698
Percent band cells count (%)	0–6	0.45 (±1.392)	0.0 (0)	0.0 (0)	0.555
Platelets, $\times 10^9$/L	140–450	228.67 (±109.641)	239.00 (94)	131.00 (62)	0.130
Biochemical					
AST, U/L	15–41	40.95 (±56.715)	26.00 (4)	25.00 (16)	0.902
ALT, U/L	14–40	49.86 (±67.311)	38.00 (30)	26.00 (16)	0.726
BUN, mg/dL	8–20	22.00 (±20.188)	11.90 (10)	12.30 (11)	0.584
Creatinine, mg/dL	0.4–1.2	1.13 (±0.909)	0.80 (0)	0.80 (0)	0.608
PT	8.0–12.0	11.15 (±1.141)	10.80 (1)	11.00 (1)	0.325
aPTT	23.9–35.5	27.64 (±3.401)	26.80 (3)	28.20 (4)	0.461
D-dimer, ng/mL	< 0.55	926.96 (±990.791)	NA	402.00 (447)	0.750
Infection-related indexes					
CRP, mg/dL	0–0.79	3.00 (±3.986)	3.93 (8)	3.76 (11)	0.209
Serum ferritin, ng/mL	11–336	600.86 (±484.191)	768.75 (725)	666.00 (659)	0.826
Procalcitonin, ng/mL	< 0.09	0.24 (±0.288)	0.51 (0.30)	0.11 (0)	0.717
ESR, mm/hr	0–15	42.06 (±31.981)	54.00 (50)	36.00 (76)	0.673

Laboratory values mean (±SE) or median (IQR).
ALT, alanin aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.
[a] Mann-Whitney *U* test.

cycline exerting in-vitro antiviral activity against SARS-CoV-2.[15]

In the light of doxycycline's anti-inflammatory, immunomodulatory, and antiviral properties, this lipophilic tetracycline analog may prove to be an invaluable adjuvant therapy in the treatment regimen of COVID-19 patients. No real world, retrospective observational study has yet been done using an early regimen of doxycycline to treat COVID-19 inpatients in Taiwan. This retrospective study demonstrated that doxycycline treatment of hospitalized COVID-19 patients does not improve clinical mortality or ICU admission rates. However, a non-significant trend towards a lower rate of ICU admission in association with doxycycline administration was observed. Moreover, doxycycline patients failed to show lower levels of biomarkers for serious disease after one week of treatment, including CRP, serum procalcitonin, and serum ferritin levels. The findings of our study echo the results of the recent randomized, controlled, open-label adaptive platform UK PRINCIPLE trial, which enrolled 2689 participants randomized into usual care plus doxycycline, usual care only, and usual care plus other interventions groups. UK PRINCIPLE trial concluded that treatment of doxycycline of suspected COVID-19 patients at high risk of adverse outcomes, was not associated with clinically meaningful outcomes (including reduction in time to recovery or hospital admissions or deaths related to COVID-19).[16]

The results of this real-world study are from a single tertiary medical center in northern Taiwan. This study is retrospective and observational in nature, thus, the findings should be interpreted with caution. A limitation of the current study is the lack of consideration for the strength, dose, or duration of exposure for any of the treatments involved in this study and may not be able to generalize to the higher-dose exposures. Additional studies are required to further elucidate the potential impact and efficacy of doxycycline in treating COVID-19 patients, including various dosing regimen, routes of administration, and timing of treatment initiation. Moreover, confounding due to higher prescription of dexamethasone and clarithromycin in the non-doxycycline group, and unobserved factors, such as pre-admission drug use or concurrent bacterial infection, may exist. Our study findings reflect the real-world use of doxycycline for COVID-19 patients during admission into a tertiary medical center in northern Taiwan. Given the inherent bias of existing observational studies, further evidence is needed to demonstrate the potential benefits associated with doxycycline treatment of COVID-19 patients.

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