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Doxycycline treatment of high-risk COVID-19-positive patients with comorbid pulmonary disease

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***Abstract*:** 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. Tetracycline and its derivatives (e.g. doxycycline and minocycline) are nontraditional 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-19 infection, 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.

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Introduction

SARS-CoV-2 is a newly emerged coronavirus for which there are limited therapeutic options and no available vaccine.[1] Patients who test positive are advised to self-quarantine, with supportive care including rest and fluid intake.[1] Hospitalization is indicated for severe disease and may be considered for patients with moderate disease with high-risk features, including immunocompromised states (e.g. cancer treatment, chronic lung disease, diabetes, severe obesity).[1] Mortality in patients with lung cancer and COVID-19 infection is high; 33% in a recently reported international series.[2]

There is significant interest in repurposing existing, approved medications for treatment of COVID-19. Tetracycline and its derivatives (e.g. doxycycline) may offer a rational and safe treatment for COVID-19$^+$ patients. Doxycycline is commonly dosed at 100 mg twice daily to treat bacterial infections and dermatologic conditions (e.g. acne vulgaris and rosacea).[3] Tetracyclines have both antiviral and anti-inflammatory properties that may ameliorate the response to viral infection.[3–6] Clinical studies indicate efficacy of doxycycline against dengue and chikungunya viral infections.[4,5] In addition, doxycycline may affect several pathways regulating viral replication.[7–9] These pleiotropic features of tetracyclines likely result from actions on nontraditional, antibiotic molecular pathways.[3]

Doxycycline has several potential mechanisms of action through which it may prevent or ameliorate

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the effects of COVID-19 infection. Doxycycline is well known to inhibit metalloproteinases (MMPs), in particular MMP-9, which is likely required for initial viral entry into the cell.[3] Doxycycline inhibits interleukin (IL)-6, with both IL-6 and MMPs key regulators of the 'cytokine storm' often associated with severe viral pneumonitis.[10–12] Doxycycline is an established ionophore, helping transport zinc intracellularly, with increased cellular concentrations of zinc shown *in vitro* to inhibit coronavirus replication.[3,13] Doxycycline inhibits nuclear factor (NF)-κB[3,14], which may lower risk of viral entry due to direct inhibition of DPP4 cell surface receptor[15] and diminish a hyperactive immune response following infection. Nonantimicrobial, low-dose doxycycline has been found *in vivo* to inhibit expression of CD147/EMMPRIN,[16] which may be necessary for SARS-CoV-2 entry into T lymphocytes.[16,17] Structural analysis demonstrates that doxycycline has the potential to inhibit papain-like proteinase (PLpro) and 3C-like main protease (3CLpro), viral proteins both essential to viral replication and lifecycle.[9]

In view of the above considerations, we report a series of four patients with COVID-19 infection and known high-risk pulmonary disease who were placed on standard doses of doxycycline for a course between 5 and 14 days. Patients were initiated on therapy with doxycycline after discussion of potential risks and benefits and after informed consent was obtained. There was no concomitant use of any other antibiotics, antiviral agents, antimalarial drugs, zinc, or any supplements postulated to be beneficial in therapy for SARS-CoV-2 in these four patients.

Case 1

A 48-year-old black woman, never smoker, with stage IV epidermal growth factor receptor (EGFR) mutated adenocarcinoma of lung, diagnosed in August 2018, was treated with osimertinib since November 2018 with response in all sites of disease. Other medications included loperamide and doxycycline, as needed for EGFR inhibitor-related diarrhea and rash, respectively. She worked as a nursing assistant. On 6 April 2020 she reported fever of 101° F, headache, anorexia and anosmia. On examination: temperature 101° F, pulse 102, blood pressure 115/71, O_2 sat 98% on room air. She was noted to have mild cough with normal respiratory effort. Laboratory tests revealed white blood cell count of 2.7, with lymphopenia, similar to prior recent determinations; C-reactive protein (CRP) 10.6 (0–5 mg/l), creatine kinase (CK) 2996 (46–179 U/l), troponin <0.006 (negative), aspartate aminotransferase 105 (13–39 U/l), creatinine 1.3 (05–1.1) mg/dl. Chest X-ray showed chronic stable right retrocardiac midlung opacities with no new focal consolidation or effusion. The following day her swab returned positive for SARS-CoV-2. As she had declined hospitalization, she was instructed to discontinue osimertinib but to start doxycycline initially 200 mg followed by 100 mg daily for 5 days. She noted improvement in all symptoms within 5 days.

Case 2

A 71-year-old white male physician with a 9 year history of pulmonary sarcoidosis, treated with intermittent steroids, noted new intermittent cough and one episode of diarrhea in early April 2020. Nasopharyngeal swab was positive for SARS-CoV-2. No additional evaluation was performed. The patient was started on doxycycline 100 mg orally twice a day and self-monitored pulse oximetry at home. Revisit to the emergency department was prompted by transient drop in oxygen saturation to 88% on day six. His temperature was 100.4° F, chest X-ray showed evidence of his chronic lower lung changes attributed to sarcoidosis, O_2 sat was 96%. The patient returned home without supplemental oxygen and remained on doxycycline for 10 days. Fever resolved and he remained asymptomatic. After 3 weeks retesting was negative for SARS-CoV-2 and he returned to work.

Case 3

A 40-year-old Asian woman, never smoker, with stage IV EGFR mutated lung adenocarcinoma, on osimertinib since 13 June 2018, also treated with stereotactic radiation to right lower lobe primary lesion in July 2019, presented to an urgent care clinic with 4 days of anosmia, mild cough, and mild dyspnea. She worked as a personal care assistant for elderly patients at home. Nasopharyngeal swab testing was positive for SARS-CoV-2 RNA. The patient continued to take osimertinib and doxycycline 100 mg twice daily (previously prescribed for EGFR-I related

rash). Symptoms improved within 1 week. Repeat nasopharyngeal swab testing on 9 May 2020 was negative for SARS-CoV-2 RNA.

Case 4

An 88-year-old white man, with several comorbidities including sick sinus syndrome, cardiovascular disease, lacunar strokes, mild obstructive lung disease, and chronic indwelling bladder catheter, was admitted from a Veterans Nursing Home with fever to 102°F, severe dry cough, weakness, and dyspnea. Chest X-ray showed bilateral diffuse infiltrates. Laboratory tests were notable for nasopharyngeal swab positive for SARS-CoV-2 RNA, CRP 11, mild hypoxia with O_2 sat 89–92%. Ceftriaxone, azithromycin and 2 liters of nasal prong O_2 were begun. His initial hospital course showed progression of his pulmonary symptomatology with decreasing O_2 saturation requiring 4 liters of nasal prong O_2 by day 3, with CRP increase to 13. On day 4 ceftriaxone was discontinued and azithromycin was replaced with doxycycline 100 mg twice daily. His pulmonary course quickly improved alongside decreasing CRP. By day 8, he no longer required oxygen and his CRP was 1.0. He never received any antiviral, IL-6 antibody, nor convalescent plasma. He was discharged on day 28 after his lung infiltrates resolved on chest X-ray after 14 days of doxycycline therapy.

Discussion

These reported cases are the first to provide a correlative relationship between doxycycline and potential reduction of severity of symptoms in COVID-19$^+$ patients. It is difficult to establish a definitive causal link between use of doxycycline and accelerated recovery or decreased morbidity from SARS-CoV-2 infection in a small case series. We believe this study provides a rationale for initiating larger controlled trials evaluating the use of doxycycline in COVID-19$^+$ patients.

The patients we report had a number of high-risk features, predictive of severe disease and increased risk of mortality. Patients one and four had advanced lung cancer on treatment, a group for whom mortality rates with COVID-19 infection is in excess of 33%.[2] Elevated inflammatory markers, including CRP, transaminases, and CK (as in cases 1 and 4) are also associated with worse outcomes.[18] Advanced age and diffuse bilateral infiltrates (case 4), are also predictors of high morbidity and mortality.[19] Case 4 demonstrated a temporal relationship between administration of doxycycline and clinical improvement, after several days of worsening on azithromycin. Patients with active pulmonary sarcoidosis, as in case 2, are also at greater risk of complications from COVID-19 due to immunologic dysfunction and dysregulation.[20] The described patients were at a significant increased risk from COVID-19 morbidity and mortality. All improved, with one showing resolution of bilateral pulmonary infiltrates. None progressed to severe disease.

A standard antimicrobial dose of doxycycline (100 mg twice daily or daily) was administered to the four patients in this case series. Doxycycline is unique among the many tetracycline derivatives, in that it has a clear dosing split between its cellular cytotoxic/antimicrobial effects (>100 mg) and its potential anti-inflammatory/antiviral/pro-ionophoric effects (40 mg).[3,4,7,8,12] This may be an important consideration for low-dose doxycycline (20 mg twice daily) as a potential prophylactic treatment against COVID-19 infection.

Potential efficacy of doxycycline against COVID-19 may be due to pleiotropic effects against the general pathways involved in viral infection, replication, and associated over-exuberant inflammatory response, with associated angiogenic effects.[3] Doxycycline has no known direct specificity for inhibition of SARS-CoV-2. Doxycycline likely has activity against known coreceptors DPP4/CD26, through demonstrated inhibition of NF-κB,[14,15] and coreceptor CD147/EMMPRIN, necessary for entry of SARS-CoV into T lymphocytes, even at submicrobial doses.[16,17] DPP4 appears to have a binding site for NF-κB and inhibition of NF-κB decreases DPP4 expression.[15] DPP4 demonstrates increased expression in older patients and those with diabetes or pulmonary disease, and may account in part for increased morbidity and mortality to COVID-19.[8] Finally, MMP-9 also appears to be required for the virus to traverse the cell wall for infection.[10,11]

Once COVID-19 has infected the cell, structural analysis indicates doxycycline may be able to bind to PLpro, which is responsible for proteolytic cleavage of the replicase polyprotein that releases nonstructural proteins 1, 2 and 3 (Nsp1, Nsp2 and Nsp3), essential for viral replication.[9] It is similarly predicted to bind to 3CLpro or

Nsp5, which is cleaved from the polyproteins, causing further cleavage of Nsp4-16, mediating maturation of Nsps essential in the virus lifecycle.[9] Doxycycline is an ionophore that binds divalent cations (including zinc) to facilitate cell membrane transport, and thereby increase zinc concentration in the cell.[3,13] Elevated zinc has an inhibitory effect on the replication of SARS-CoV-2.[13] The presumed mechanisms are through inhibition of proper processing of replicase proteins and RNA-dependent RNA polymerase (RdRp) activity.[13]

Lastly, doxycycline may help prevent the 'cytokine storm' following COVID-19 infection presumed to be due to hyperactivity of the immune response to SARS-CoV-2. A primary driver of the anti-inflammatory activity of doxycycline is secondary to its direct inhibition of NF-κB.[14] NF-κB directly regulates IL-6 expression, which is a key driver of the cytokine storm.[21] Doxycycline may also precipitate apoptosis of senescent epithelial cells,[8] which have known increased expression of DPP4/CD26, likely exhibiting increased viral replication in these cells which leads to induction of the cytokine storm.

Conclusion

In summary, we present reports of four patients at high risk for morbidity and mortality from SARS-CoV-2 infection who experienced improvement and/or mild clinical course in association with doxycycline. Despite the safety of doxycycline, we would not recommend general use of this medication for treatment of COVID-19^{+} patients, except under direct physician guidance and monitoring. A larger randomized controlled trial should be considered.

Author contribution(s)

Paul A. Yates: Conceptualization; Investigation; Methodology; Project administration; Writing-original draft; Writing-review & editing.

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Ashton M. Leone: Data curation; Investigation; Project administration; Writing-original draft.

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Conflict of interest statement

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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