

Doxycycline in the Coronavirus Disease 2019 Therapy

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Abstract: Acute respiratory syndrome, associated with coronavirus 2 (SARS-CoV-2), is the most important medical and epidemic problem of today. The biggest challenge is to find an effective treatment and to reduce the need for hospitalisation. In the article, the patients with mild to moderate coronavirus disease 2019 (COVID-19) treated with doxycycline with significant improvement have been discussed. Doxycycline is a known antibiotic, but also an anti-inflammatory and immunomodulatory drug, so it seems to be ideal for the treatment of COVID-19. Doxycycline, as an easily available and low-cost medication, should be considered as a COVID-19 therapy in all patients in the first days of the symptoms of a SARS-CoV-2 infection. Due to its immunomodulatory, anti-inflammatory, cardioprotective and antiviral effects, it seems to be an ideal drug for patients with mild, moderate and severe disease. A large multicentre study is needed to evaluate the effects of this medication.

Keywords: COVID-19, COVID-19 therapy, doxycycline, SARS-CoV-2

Introduction

Acute respiratory syndrome is associated with coronavirus 2 (SARS-CoV-2), a virus which caused an unbelievable crisis around the world. As of the 23rd of May, 2021, 167,070,799 cases were diagnosed, 148,011,966 people have recovered, and 3,469,436 have died.¹ The crisis has affected medical services and public health, but also the global economy.² The pathophysiology of the disease is based on an infection of the upper and lower respiratory tract caused by the virus, as well as an excessive response of the immune system, or autoimmunity.³ Patients with a positive test result are recommended to stay isolated, rest and be treated with fluid therapy.¹ Hospitalisation is indicated in moderate and severe cases with risk factors such as chronic lung diseases, cardiovascular diseases, obesity and diabetes.¹ The immaturity of the immune system in children can protect them from the severe course of this disease and any possible complications. The infection can lead to severe lung damage, acute respiratory distress syndrome (ARDS) and, consequently, multiple organ failure.⁴ There are still no validated and effective guidelines for the treatment of SARS-CoV-2.

Doxycycline is a long-acting, broad-spectrum, semi-synthetic tetracycline antibiotic. It is a bacteriostatic antibiotic and blocks protein biosynthesis. A strong anti-inflammatory effect of this drug has been demonstrated before.^{5,6} It is recommended in the guidelines for chronic sinusitis as an immunomodulating and disease-stabilising medication.⁷ It is also an antiviral antibiotic against RNA viruses. It is used, for example, in dengue fever.⁵ It has been well proven to block a cytokine storm. Malek

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et al^{8,10} in their publications highlighted the important role of doxycycline in the treatment of COVID-19.

Materials and Methods

In the paper, four cases of patients with confirmed SARS-CoV-2 infection have been presented.

Case 1

A 34-year-old male, never smoked, body mass index (BMI) of 24.7, regularly practising sports. Suffering from allergic multimorbidity, and asthma controlled from early childhood. On the 21st of October 2020 he noticed a slight sore throat and headache. The next day, his symptoms including weakness, particularly sweating of the face and back, temperature of 37.3 degree Celsius, fatigue, sore throat, and occasional dry cough. A real-time polymerase chain reaction (RT-PCR) test was performed confirming SARS-CoV-2 infection. Oxygen saturation was normal, 96–98%. Chest X-ray confirmed inflammatory lesions of the interstitial type. Blood tests showed leucocytosis and CRP level of 40. Doxycycline therapy was started initially with 200 mg, and then continued with 100 mg for 7 days. Complete remission of symptoms was achieved after 2 doses.

Case 2

A 34-year-old female, never smoked, healthy, BMI of 22.8. Comorbidity included allergy, controlled asthma and IgA deficiency. Due to the infection of the household member, the patient was tested on the 23rd of October 2020 with a positive result. On the 25th of October 2020 the first symptoms, including a severe headache in the area of the forehead and eyes, a slight sore throat, weakness, sweating, temperature of 35.2 degree Celsius, nasal congestion without discharge, loss of smell and taste, and lack of appetite appeared. The next day, she experienced a dry cough, chest pain, feeling of arrhythmia, periodic tachycardia, heart rate of 100–120, feeling of shortness of breath, and oxygen saturation of about 90%. Chest X-ray confirmed lung inflammation. Doxycycline therapy at a dose of 200 mg was started and continued for 5 days; then, 100 mg were administered for 7 days, after 3 doses of the drug, significant improvement was achieved, oxygen saturation returned to normal, periodically productive cough, chest pain subsided, heart rate 80–90.

Case 3

An 83-year-old male patient with arterial hypertension, chronic obstructive pulmonary disease, diabetes and hyperlipidaemia, BMI of 28. On the 13th of October 2020 an infection with symptoms and a fever up to 38 degree Celsius appeared. Tachypnoea. After 2 days, a test that confirmed the SARS-CoV-2 infection was performed. At the beginning of the infection (on the 13th of October 2020), treatment with doxycycline 2×100 mg was started. After three doses of the antibiotic, the patient's condition improved significantly. The patient did not require hospitalisation. Symptoms resolved after 5 days of treatment. Laboratory tests showed slight leucocytosis. Chest X-ray unchanged.

Case 4

A 59-year-old male patient, generally healthy, BMI of 25, a physician. He suffered from symptoms of extreme weakness, pain in muscles and joints, shortness of breath and chest pain. Electrocardiography performed in the patient confirmed arrhythmia, and inflammatory markers were elevated. Chest X-ray confirmed lung lesions of the interstitial type. The patient was tested for SARS-CoV-2. On the 5th of October 2020, the patient had a positive test result. From that day on, the therapy included doxycycline at a dose of 2×100 mg. After the second dose of the antibiotic, shortness of breath and chest pain completely subsided. Pain in muscles and joints disappeared after 4 days. Treatment with antibiotics was completed after 10 days and the patient did not require hospitalisation.

Discussion

COVID-19 is an infection of the upper and lower respiratory tract. The main symptoms include fever, cough, tachypnoea and hypoxia, as well as smell and taste disorders.⁹ The four described cases indicate a significant influence of doxycycline on the course of the coronavirus infection in mild and moderate stages in young patients. It is difficult to unequivocally confirm the effectiveness of the medication in the presented cases, but similar observations were made by other researchers.^{3,9–12} In the study of Mohammad M. Alam et al,⁹ a description of a series of 89 elderly patients with confirmed moderate to severe COVID-19 with concomitant diseases was presented. All patients in this group were treated with doxycycline for 7 days at a dose of 100 mg daily. The mean age of the patients was 78 years. The authors documented recovery

in 85% of patients. Similarly, Paul A. Yates et al³ described a series of 4 cases of patients treated for COVID-19 with concomitant lung diseases, all patients improved after treatment with doxycycline. One patient in this group switched to doxycycline, despite the initial failure of azithromycin, which resulted in improvement. The described patients suffered from lung cancer or sarcoidosis. Malek et al¹⁰ also mention the possible role of doxycycline in COVID-19 therapy in combination with hydroxychloroquine instead of azithromycin. Administration of hydroxychloroquine with azithromycin causes viral remission in 100% of patients on the 5th day of therapy.¹³ Treatment with azithromycin is associated with cardiotoxicity for the elderly; therefore, Malek et al.¹⁰ suggest switching to doxycycline primarily in elderly patients. Yasemin Cag et al,¹¹ also draw attention to the success of the use of doxycycline in the therapy of dengue haemorrhagic fever, while negating the effectiveness of lopinavir in the treatment of COVID-19 patients.

Hayder M. Al-kuraishy et al¹² indicate tetracyclines as a possible therapy for COVID-19 patients. They emphasise the effectiveness of doxycycline and minocycline in treatment, as well as the synergistic effect with chloroquine. Tetracyclines are effective especially in pneumonia and complications such as acute lung injury (ALI) and ARDS.

Bonzano et al¹⁴ confirmed that doxycycline at a dose of 200 mg daily in patients with COVID-19 administered for 8 days improved the sense of smell. This improvement was associated with the modulation of ACE2 and CD147 expression in the olfactory epithelium.

Mostafa¹⁵ confirmed that doxycycline is effective in reducing ARDS induced by COVID-19 and cytokine storms. This is related to the easy penetration of tetracyclines into the pulmonary alveoli due to lipophilicity.

Mosquera-Sulbaran and Hernandez-Fonseca¹⁶ found that doxycycline reduces virus replication by inhibiting its penetration into cultured cells.

COVID-19 induces the proliferation of mast cells in the airway mucosa,¹⁷ activates the NF- κ B pathway,¹⁸ thus increasing the inflammatory response. COVID-19 is also associated with the activation of IL-1 β , TNF and IL-6. Myocardial injury, as well as an increase in troponin levels, have also been documented.¹⁹ Doxycycline reduces DPP4 expression by blocking the NF- κ B pathway, and consequently blocking the penetration of the virus into cells.^{5,20} Doxycycline blocks IL-6, MMPs, and especially MMP-9. MMP-9 is necessary for the penetration of the

virus into the cell.⁵ IL-6 and MMPs are cytokine storm regulators often associated with severe viral pneumonia.^{6,21} In vivo inhibition of CD14 +/EMMPRIN by doxycycline was found, which may inhibit penetration of SARS-CoV-2 into T cells.²²

Doxycycline also has a cardioprotective effect. It regulates the MMP-2 pathway, protecting the systolic function of the heart.²³ As a result, it inhibits arrhythmias caused by myocardial ischemia.

The antiviral activity of tetracyclines may be associated with increased transcription of intracellular zinc-finger antiviral protein (ZAP).²⁴ ZAP may also bind to specific target viral mRNAs and inhibit RNA translation.²⁵ In experimental studies, tetracycline was used to induce overexpression of the host ZAP in HEK293, rat and monkey (Vero cells) cell lines, which contributed to the inhibition of RNA viruses such as dengue virus, Ebola virus, human immunodeficiency virus, Zika virus and influenza A virus.^{24,26,27}

Conclusions

Doxycycline, as an easily available and low-cost medication, should be considered as a COVID-19 therapy in all patients in the first days of symptoms of SARS-CoV-2 infection.

Due to its immunomodulatory, anti-inflammatory, cardioprotective and antiviral effects, it seems to be an ideal drug for patients with mild, moderate and severe type of COVID-19.

A large multicentre study to evaluate the effects of this medication is needed.

Disclosure

The authors report no conflicts of interest in this work.

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