

Successful treatment with minocycline and Saiko-keishi-to for COVID-19

Masashi Ohe^{1*} , Haruki Shida¹ , Junya Yamamoto¹ , Masahide Seki¹ ,
Ken Furuya¹ 

¹ Department of Internal Medicine,
JCHO Hokkaido Hospital, Japan

Keywords: COVID-19, Tetracycline, Minocycline, Kampo, Saiko-keishi-to

Correspondence:

Masashi Ohe

Address: Department of Internal
Medicine, JCHO Hokkaido Hospital,
Japan

Email: oktsp1218@sweet.ocn.ne.jp

Dear Editor,

Coronavirus disease 2019 (COVID-19) is characterized by early exponential viral replication, cytokine-associated organ damage and dysfunction, endothelial injury with proximal platelet aggregation, and thrombosis [1].

Regarding central nervous system (CNS) damage, neuropsychiatric lesions of COVID-19 bring about delirium, general malaise, headache, and psychiatric symptoms. These lesions are related to the neuroinflammatory response to viral antigens and proinflammatory mediators/immune cells. In the CNS, the macrophage known as microglia cell mediates the excessive production of inflammatory cytokines, free radicals, and damage signals, which has neurotoxic effects [2].

Tetracyclines (TCs), such as minocycline (MINO), have antibacterial and anti-inflammatory properties [3]. Saiko-keishi-to (SKT), a traditional Japanese Kampo medicine, also has anti-inflammatory properties [4].

Given the anti-inflammatory properties of MINO and SKT, we describe two cases of COVID-19 with prolonged headaches and general malaise that were treated with these medications.

CASE 1

A 42-year-old woman was taken to our hospital with symptoms of fever, sore throat, headache, and general malaise. She was identified as having mild COVID-19 based on a positive polymerase chain reaction

(PCR) test for the disease and 98% O₂ saturation by pulse oximetry (SpO₂). A 500-mg dose of acetaminophen was administered to her upon request. The sore throat and fever subsided after 5 days. However, headache and general malaise persisted, which was probably caused by aforementioned neuroinflammatory reaction to viral antigens and proinflammatory mediators/immune cells. Considering the anti-inflammatory properties of these two medications, she received treatment with SKT (2.5 g, t.i.d.) for 7 days and MINO (100 mg, b.i.d.) for 7 days. As a result, headache and overall malaise subsided after 3 days.

CASE 2

Symptoms of a typical cold included headache, sore throat, and fever in a 48-year-old female patient. A PCR test for COVID-19 was conducted as her coworkers were COVID-19 positive. She was identified as having mild COVID-19 based on the positive PCR test result and 97% of SpO₂. Fever and sore throat subsided over the clinical course. The headache persisted, and a general malaise gradually developed. These two symptoms persisted for 7 days; therefore, she was taken to our hospital. Due to MINO's anti-inflammatory properties, she received treatment with MINO (100 mg, b.i.d.) for 7 days. Headache and general malaise improved 4 days following MINO medication.

As previously mentioned, TCs also have anti-inflammatory properties that, in a dose-dependent manner, reduce the production of tumor necrosis factor (TNF)- α ,

Received: 13.12.2022,
Accepted: 22.12.2022
<https://doi.org/10.29333/jcei/12999>

interleukin (IL)-6, and IL-8 [3]. Several recent studies have successfully used MINO to treat rheumatoid arthritis as evidence of its anti-inflammatory effects [5].

TCs provide neuroprotective and anti-inflammatory properties in the CNS. Additionally, TCs can inhibit neuroinflammation and microglial reactivity by blocking nuclear factor kappa B signaling, cyclooxygenase 2, and matrix metalloproteinases [2]. Miwa reported a long COVID-associated CNS lesion of myalgic encephalomyelitis, which was successfully treated with MINO and had symptoms including headache and general malaise [6].

Kampo is a traditional Japanese medicine with original theories and therapeutic methods based on traditional Chinese medicine. Kampo medications are mainly created using organic plant-based components. The components used to make SKT include JP Bupleurum Root, JP Pinellia Tuber, and JP Scutellaria Root [7]. Saikosaponin, one of the components of SKT and a Bupleurum extract, has anti-inflammatory properties that inhibit proinflammatory cytokines, including TNF- α , IL-1 β , IL-6 and IL-8 [4]. In Japan, doctors prescribe SKT to treat persistent colds and flu to promote general health. Recently, two cases of COVID-19 pneumonia with headache and general malaise successfully treated using SKT in combination with other drugs, were reported [7].

Based on these findings, it is suggested that MINO and SKT treatment could effectively treat a CNS lesion linked to COVID-19.

In any case, clinical trials need to be conducted to better assess the optimal doses and durations, and the efficacy and tolerability of this treatment before it can be adopted on a broader basis.

Author contributions: All authors have sufficiently contributed to the study, and agreed with the results and conclusions.

Funding: No funding source is reported.

Ethical statement: Authors stated that ethical approval was not required. Informed consent was obtained from the patients.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. McCullough PA, Alexander PE, Armstrong R, Arvinte C, Bain AF, Bartlett RP, et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). *Rev Cardiovasc Med.* 2020; 21: 517-30. doi: 10.31083/j.rcm.2020.04.264.
2. Chaves Filho AJMC, Gonçalves F, Mottin M, Andrade CH, Fonseca SNS, Macedo DS. Tetracyclines for COVID-19 neurological and neuropsychiatric manifestations: a valid option to control SARS-CoV-2-associated neuroinflammation? *J Neuroimmune Pharmacol.* 2021; 16: 213-8. doi: 10.1007/s11481-021-09986-3
3. Bernardino ALF, Kaushal D, Philipp MT. The antibiotics doxycycline and minocycline inhibit the inflammatory responses to the Lyme disease spirochete *Borrelia burgdorferi*. *J Infect Dis.* 2009; 199: 1379-88. doi: 10.1086/597807
4. Yuan B, Yang R, Ma Y, Zhou S, Zhang X, Liu Y. A systematic review of the active saikosaponins and extracts isolated from Radix Bupleuri and their applications. *Pharm Biol.* 2017; 55: 620-35. doi: 10.1080/13880209.2016.1262433
5. Langevitz P, Livneh A, Bank I, Pras M. Benefits and risks of minocycline in rheumatoid arthritis. *Drug Saf.* 2000; 22: 405-14. doi: 10.2165/00002018-200022050-00007
6. Miwa K. Oral minocycline challenge as a potential first line therapy for myalgic encephalomyelitis and long COVID-19 syndrome. *Ann Clin Med Case Rep.* 2022; V8: 1-4.
7. Takayama S, Namiki T, Odaguchi H, Arita R, Hisanaga A, Mitani K, et al. Prevention and recovery of COVID-19 patients with Kampo medicine: review of case reports and ongoing clinical trials. *Front Pharmacol.* 2021; 12: 656246. doi: 10.3389/fphar.2021.656246