

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

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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 ,

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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.

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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