Annals of Clinical and Medical Case Reports

Mini Review ISSN: 2639-8109 | Volume 8

Oral Minocycline Challenge as a Potential First-Line Therapy for Myalgic Encephalomyelitis and Long Covid-19 Syndrome

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Received: 12 Jan 2022
Accepted: 21 Jan 2022
Published: 28 Jan 2022
J Short Name: ACMCR

Keywords:

Minocycline; Myalgic encephalomyelitis; Chronic fatigue syndrome; Long COVID-19; Neuroinflammation

Citation:

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(7): 1-4

1. Abstract

Chronic fatigue syndrome characterized by severe disabling fatigue, prolonged post-exertional malaise, and unrefreshing sleep markedly reduces the activities of daily living and impairs the quality of life. Central nervous system dysfunction associated with myalgic encephalomyelitis (ME) has been postulated as the main cause of chronic fatigue syndrome. Recently, oral minocycline therapy has been reported to exert favorable therapeutic effects in some patients with ME, especially in the initial stage of the disease, although many patients discontinued treatment in the first few days because of acute adverse effects such as nausea and/or dizziness. Minocycline appeared to exert a variety of biologic actions against neural inflammation that are independent of their anti-microbial activity, including anti-inflammatory, immunomodulatory, and neuroprotective effects. In recent years, it has been noted that COVID-19 disease may cause persistent signs and symptoms described as post-COVID syndrome or long COVID, in which the clinical presentation is remarkably similar to those seen in patients with ME. A wide range of infectious agents have been suggested to trigger the development of ME, and one of such pathogens may be the COVID-19 virus. Recently, I had a valuable experience of a 22-year-old female patient with a 14-month duration of long COVID who completely recovered from ME-like symptoms after treatment with minocycline. This case suggests that oral minocycline could be an effective first-line therapy for long COVID-19, although a large scale of trial is obviously needed to justify the therapy.

2. Minocycline Therapy for Myalgic Encephalomyelitis and Long COVID

Chronic fatigue syndrome (CFS) characterized by severe disabling fatigue not resolved by rest, prolonged post-exertional malaise, and unrefreshing sleep markedly reduces the activities of daily living and impairs the quality of life [1]. The disease is an important health problem that affects many young people, mainly women, causing a marked reduction in working activity [1]. Despite the public health burden imposed by this disease, effective diagnostic, treatment and prevention strategies are not available because the specific pathophysiology remains to be unclarified. Central nervous system dysfunction associated with myalgic encephalomyelitis (ME) or neuroinflammation has been postulated as the cause of CFS [2]. Recently, the effects of oral minocycline therapy administered as a 6-week regimen in 100 patients with ME was reported [3]. As shown in (Figure 1), it exerted favorable therapeutic effects in 27 patients, although 38 patients did not tolerate it due to adverse effects such as nausea and dizziness, and the remaining 35 patients did not have favorable effects. It was effective in ameliorating symptoms in a considerable number of patients with ME, particularly in those with a disease duration of <3 years, especially in the initial stage of disease (<6 months). As a general observation, the shorter the disease duration, the better the therapeutic outcome. However, many patients were unable to tolerate oral minocycline because of acute adverse effects. The patients with ME seemed to have an increase in drug sensitivity to various drugs including minocycline as the disease duration increased.

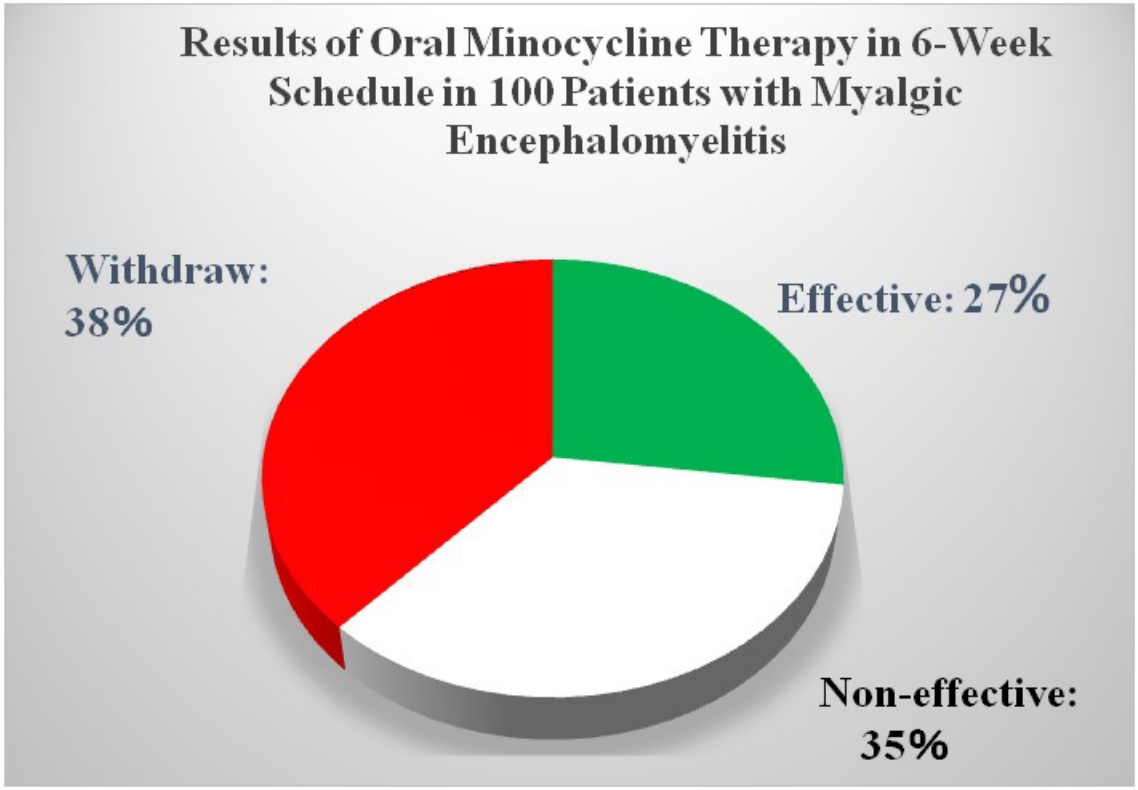

Figure 1: Results of Oral Minocycline Therapy in 6-Week Schedule in 100 Patients with Myalgic Encephalomyelitis

Several infectious pathogens have been suggested as triggers for central nervous system dysfunction in patients with ME [2], including Mycoplasma pneumoniae. Minocycline has persistent and broad central nervous system effects and may act on the Mycoplasma infection to resolve the symptoms. However, the increase in Mycoplasma pneumoniae antibody titer, the evidence of its infection, was comparable between patients with and without favorable therapeutic effects. Another pathogen, Coxiella burnetti is known to cause chronic fatigue following Q fever. Indeed, chronic fatigue following Q fever due to Coxiella burnetti infection, in which various nonspecific symptoms, including general malaise, headache, arthralgia, and myalgia, occur, can be classified as a type of ME according to the recent proposal [2]. A recent report from an open-label study of minocycline in Japan suggested that this drug is useful for improving chronic nonspecific symptoms considered to be CFS following Q fever, caused by Coxiella burnetti infection in patients with the elevated antibody titer [4,5]. However, data from subsequent reports are conflicting. In a randomized study, long-term treatment with doxycycline, another tetracycline, failed to reduce the severity of fatigue symptoms following Q fever [6], suggesting that the favorable effects by minocycline are not mediated by its anti-microbial action.

Minocycline, a second-generation derivative of tetracycline, is a broad-spectrum antibiotic that is active against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria, and against other microorganisms, including Rickettsia, Chlamydia, and Mycoplasma. It has been reported that minocycline can exert a variety of biologic actions that are independent of their anti-microbial activity, including anti-inflammatory, immunomodulatory, and neuroprotective effects [7]. Studies have shown that minocycline can attenuate microglial activation and anti-inflammatory, immunomodulatory, and neuroprotective effects. In fact, minocycline has been shown to exert non-antibiotic biologic effects in vivo and in vitro, such as attenuation of blood–brain barrier breakdown via suppression of matrix metalloproteinase-9 production, neuroprotection from neuronal injury, including ischemia and spinal cord injury, and inhibition of nitrite/nitrate production via inducible nitric oxide synthase overexpression in cultured microglia under hypoxia [8-11]. Minocycline successfully inhibited the development of neuroinflammation in animal models of fatigue [12]. Importantly, minocycline has emerged as the most effective tetracycline derivative in terms of neuroprotection, an effect that has been confirmed in experimental models of ischemia, traumatic brain injury, and neuropathic pain, as well as several neurodegenerative conditions, such as Parkinson and Huntington diseases, amyotrophic lateral sclerosis, Alzheimer disease, multiple sclerosis, and spinal cord injury [13-21]. These preclinical studies have prompted the evaluation of minocycline, which has promising neuroprotective properties, in clinical trials in patients with ME, a neuronal disease.

The drug probably targets neuroinflammation, resulting in the favorable effects in patients with ME. Finally, long-standing persistent microglial inflammation over several years seems to result in irreversible damage in neuronal functions. Since no effective treatment has been established for ME/CFS, the oral minocycline challenge may stand as an effective first-line therapy. Minocycline

may be a "magic bullet" for the treatment of ME/CFS [22]. In recent years, the most important public health problem is SARS-COV-2 infection or the COVID-19 disease. The global COVID-19 pandemic due to SARS-COV-2 has resulted in a large number of hospitalizations with more than 2.5 million deaths. Besides the direct impact of the cardiopulmonary sequelae, and even after resolution of the infection, COVID-19 disease may cause persistent signs and symptoms described as post-COVID syndrome or long COVID [23,24]. The WHO has specifically recognized the occurrence of long-term health effects of an acute SARS-COV-2 infection. Fatigue is the most frequent symptom described, followed by sleep difficulties, muscle weakness, hair loss, olfactory dysfunction, cardiac palpitations, joint pain, loss of appetite, taste dysfunction, dizziness, diarrhea or vomiting, cheat pain, throat discomfort or difficulties swallowing, rash, myalgia, headaches, and fever [25]. Indeed, the clinical presentation and neuroimaging aspects of patients with this condition are remarkably similar to those seen in patients with ME/CFS. Many ME patients have an acute infectious onset with flu-like and/or respiratory symptoms [2]. A wide range of infectious agents have been suggested to be associated with ME, although no agent has been proven to cause the illness. One of such pathogens may be the COVID-19 virus. This virus may trigger the development of neuroinflammation, resulting in long COVID, although it cannot be completely excluded that infection with COVID-19 virus may have a long-term effect on the central nervous system as a form of persistent or latent infection with reactivation. Recently, I had a valuable experience of a patient with long COVID who completely recovered from ME-like symptoms after treatment with minocycline.

3. Case Report

A 22-year-old Japanese woman who was previously healthy, began to present signs of COVID-19 infection. She had fever, chill sensation, light-headedness, cough, and headache, and complained orthostatic intolerance. She was admitted to a hospital in Sendai, Japan for one month. After discharge, she started working as a staff preparing food in a restaurant. Shortly after, she was not able to continue working due to general malaise, easy fatigability, severe post-exertional malaise, muscle weakness, lack of concentration or brain fog, unrefreshing sleep, sore throat, and generalized pain sensation. In addition, she felt speech disturbance from brain fog, dyspnea, finger and foot paresthesia, dizziness, and nausea. She resigned from the work in October, and returned to her parents' home in Niigata in November. She developed severe orthostatic intolerance and was not able to go out by herself. She took antidepressant therapy, but there was no improvement. She gained 10 kg of body weight, and had dyspnea and palpitation on effort. In addition, she had alternative bowel habits between diarrhea and constipation. She visited to my institute (Miwa Naika Clinic) on May 31, 2021. Her vital signs and the doctor's physical examination are shown as below.

Height: 154.0 cm, body weight: 57.7 kg, body temperature: 36.5 °C, pulse rate: 98/min, blood pressure: 137/80 mmHg, pharyngeal redness, bilateral neck lymph nodes swelling with tenderness, tender points by ACR2010: 12/18, and leg muscle grasping tenderness (+). Chest radiography showed clear lung fields and a small heart shadow with a cardiothoracic ratio of 35%. Electrocardiogram showed generalized low T. Blood examination showed no abnormal findings. Conventional 10-min standing test showed postural orthostatic tachycardia (heart rate:78 to 116 /min) with a slight fall in systolic blood pressure of 11 mmHg. She completed the 10-min standing in spite of dyspnea, palpitation and severe fatigue. The neurologic test for disequilibrium including the Romberg test, one-leg standing test and tandem gait test showed no abnormal findings.

Oral minocycline in a 6-week schedule (100 mg x 2 on the first day, followed by 100 mg/day for 41 days) was administered to the patient, according to the therapeutic plan employed in the patients with ME in the recent study [3]. She completed the schedule without any untoward effects. After starting the oral administration of minocycline, she gradually recovered from her symptoms. At the end of the treatment, all the symptoms completely resolved, and the Performance Status score [3] decreased from 6 before the therapy to 1. She was able to begin working at a bakery. This case suggest that oral minocycline seems to be an effective first-line therapy for long COVID-19, although a large scale of trial is needed to justify the therapy.

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