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【 ORIGINAL ARTICLE 】

Oral Minocycline Therapy Improves Symptoms of Myalgic Encephalomyelitis, Especially in the Initial Disease Stage

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Abstract:

Objective Central nervous system dysfunction associated with myalgic encephalomyelitis (ME) has been suggested to be the main cause of chronic fatigue syndrome. In animal models of chronic fatigue, minocycline was reported to act as a suppressor of neural inflammation. Minocycline may thus exert favorable therapeutic effects in patients with ME.

Methods Oral minocycline (100 mg×2 on the first day, followed by 100 mg/day for 41 days) was administered to 100 patients with ME. The performance status score (0-9), orthostatic intolerance during the 10-min standing test, neurologic disequilibrium, and neuropathic pain were compared before and after treatment.

Results After therapy completion, favorable effects were observed with a decrease in the performance status score of ≥2 points in 27 patients (27%). Before treatment, 6 of the 27 patients had orthostatic intolerance with an inability to complete the 10-min standing test; after treatment, this symptom resolved in 4 and improved in 2 patients. In addition, after treatment, postural orthostatic tachycardia resolved in five of eight patients, disequilibrium resolved in five of eight patients, and fibromyalgia or neuropathic pain was attenuated in four of five patients. The favorable effects appeared dependent on a shorter disease duration, primarily for a duration of less than three years and most frequently within six months of the disease onset. However, acute adverse effects with nausea and/or dizziness caused 38 patients (38%) to discontinue treatment in the first few days.

Conclusion Oral minocycline therapy may be an effective treatment option for patients with ME, especially in the initial stage of the disease.

Key words: minocycline, myalgic encephalomyelitis, chronic fatigue syndrome, orthostatic intolerance, disequilibrium

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Introduction

Dysfunction of the central nervous system associated with myalgic encephalomyelitis (ME) has been postulated as the main cause of chronic fatigue syndrome (CFS), which is characterized by severe disabling fatigue, prolonged post-exertional malaise and unrefreshing sleep, causing a marked reduction in activities of daily living and an impaired quality of life (1, 2). The disease occurs in many relatively young people, mostly women, who lose their working ability and income. Despite the public health burden, an effective treatment for ME remains to be established.

Nakatomi et al. (3) demonstrated that a neuroinflammatory process was widely evident in the brain in patients with ME/CFS based on positron emission tomography findings of translocator protein ligand accumulated in the inflammatory region with activated microglia. In addition, recent studies in animal models have demonstrated that the fatigue-like behavior is caused by neuroinflammation of the brain tissue (4, 5).

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 (6). One such pathogen is *Mycoplasma*, which is

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known to cause respiratory tract infection and pneumonia and is sensitive to tetracycline-derivative antibiotics (7). Infection with *Mycoplasma* may have a long-term effect on the central nervous system as a form of persistent or latent infection with reactivation. Another pathogen, *Coxiella burnetti (C. burnetti)*, is known to cause chronic fatigue following Q fever (8), for which minocycline therapy has been reported to be effective in patients who have the antibody to this pathogen (8, 9).

Minocycline, a semisynthetic 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 as well as against other microorganisms, including *Rickettsia*, *Chlamydia*, and *Mycoplasma* (10). Interestingly it has been reported that tetracyclines can exert a variety of biologic actions that are independent of their anti-microbial activity, including anti-inflammatory, immunomodulatory, and neuroprotective effects (11, 12). In fact, minocycline has been shown to exert non-antibiotic biologic effects *in vivo* and *in vitro*, such as attenuation of the blood-brain barrier breakdown via suppression of matrix metalloproteinase-9 production (13), neuroprotection from neuronal injury, including ischemia and spinal cord injury (14, 15), and inhibition of nitrite/nitrate production via inducible nitric oxide synthase overexpression in cultured microglia under hypoxia (16). Minocycline successfully inhibited the development of neuroinflammation in animal models of fatigue (4, 5). 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 (17), traumatic brain injury (18), and neuropathic pain (19, 20), as well as in several neurodegenerative conditions (21), such as Parkinson (22) and Huntington diseases (23), amyotrophic lateral sclerosis (24), Alzheimer disease (25), multiple sclerosis (26), and spinal cord injury (27). These preclinical studies have prompted the evaluation of minocycline for its promising neuroprotective properties in clinical trials in patients with ME, a neuronal disease.

In the present study, the possible therapeutic effects of the oral administration of minocycline were examined in patients with ME by comparing the performance status (PS) scores, orthostatic intolerance during an active standing test, neurologic disequilibrium, and neuropathic pain before and after the therapy.

Materials and Methods

Study participants

The study population was 100 consecutive patients treated at the author's clinic between April 2016 and April 2020. The inclusion criteria were as follows: an ME diagnosis based on the 2011 International Consensus Criteria (2) with over a two-month disease duration before the study; the ability to stand and walk; and the provision of informed consent to participate. Alternative diagnoses for fatigue and other symptoms were ruled out. Pregnant or lactating women were excluded from the present study. One woman was excluded because she declined oral minocycline treatment based on a fear of exacerbating a genital candida infection. Of the 100 study patients, 36 were men, and 64 were women, with a mean age of 36±12 (16-73) years. Infectious onset was reported by 41 (41%) of the patients.

The study was approved by the Miwa Naika Clinic Ethics Committee (Approval#: 2016-001) and the Toyama Prefectural Medical Association Ethics Committee (Approval#: 2016-010) and was performed in accordance with the Declaration of Helsinki.

Procedures

Oral minocycline in a 6-week schedule (100 mg×2 on the first day, followed by 100 mg/day for 41 days) was administered to 100 study patients with ME. To evaluate the possible therapeutic effects, all patients underwent PS grading, a neurologic examination, a conventional active 10-min standing test, and digital palpation for 18 specified tender points proposed by the American College of Rheumatology (ACR) in 1990 (28). All tests were conducted before initiating minocycline therapy and within one month after therapy. Ongoing medications, including nutritional supplements and multi-enzyme tablets were not discontinued, throughout the study, although adrenergic β-receptor-blocking agents were not administered.

PS grading

Subjective symptom severity was reported by patients as described previously (29). Based on patients' reports, the PS was graded on a 10-point scale as follows: PS 0, The patient can perform the usual activities of daily living and social activities without malaise; PS 1, The patient often feels fatigue; PS 2, The patient often needs to rest because of general malaise or fatigue; PS 3: The patient cannot work or perform usual activities for a few days a month; PS 4, The patient cannot work or perform usual activities for a few days a week; PS 5, The patient cannot work or perform usual activities but can perform light work; PS 6, The patient needs daily rest but can perform light work on a "good day"; PS 7, The patient can take care of himself or herself but cannot perform their usual duties; PS 8, The patient needs help taking care of himself or herself; PS 9, The patient needs to rest the whole day and cannot take care of himself or herself without help.

A neurologic examination for disequilibrium

All patients underwent the Romberg test (standing with feet together and eyes closed), which is used to diagnose disequilibrium; a positive diagnosis was scored when postural stability was lost by closing the eyes while standing, thereby producing wide oscillations and possibly a fall (a positive Romberg test) or instability present on standing with the feet together and eyes open, worsened further upon

Table 1. The Comparison of the Clinical Data between the Study Patients with ME Who Were Tolerant and Intolerant of Oral Treatment with Minocycline for Six Weeks.

	Patients tolerant to minocycline	Patients intolerant to minocycline	p value
Number of patients	62 (62%)	38 (38%)	
Men/Women	25/37	11/27	0.29
Age (years)	36±12	36±13	0.98
<30	18 (29%)	14 (37%)	0.51
≥40	26 (42%)	18 (47%)	0.68
Disease duration (years)	4.0±5.1	5.1±5.3	0.31
Infectious onset	28 (45%)	13 (34%)	0.30
Contact with pet animal	6 (10%)	4 (11%)	1.00
Multiple drug allergy	1 (2%)	10 (26%)	<0.01
Mycoplasma Ab titer ≥40	18 (29%)	14 (37%)	0.51
Performance status score	3-9	3-8	
Median score	5.5	6	0.54
Failed to stand for 10 min	13 (21%)	8 (21%)	1.00
Disequilibrium	18 (29%)	12 (32%)	0.82
Tender points ≥8	12 (19%)	10 (26%)	0.46

Disequilibrium: instability upon standing with feet together and eyes closed. Values are presented as mean±standard deviation. ME: myalgic encephalomyelitis, Ab: antibody

closing the eyes (30-32).

Active 10-min standing test

The conventional active 10-min standing test was performed as reported previously (29). The patients were asked to stand and remain standing without changing their foot positioning. Postural orthostatic tachycardia was diagnosed as an increase in the heart rate of ≥30 beats/min during the test. Instantaneous or delayed orthostatic hypotension was diagnosed as a decrease in the systolic blood pressure of ≥20 and/or ≤90 mm Hg or a decrease in the diastolic blood pressure of ≥10 mm Hg. Neurally mediated hypotension was diagnosed as orthostatic hypotension with a decrease in the heart rate of ≥20 beats/min during the test.

Tender points examination

The number of the tender points on digital palpation for 18 specified tender points proposed by the ACR in 1990 (28) was determined in all study patients, including those who had chronic neuropathic pain or fibromyalgia.

Statistical analyses

Continuous variables are presented as the mean±standard deviation and were compared using Student's *t*-test. Proportional data were analyzed using Fisher's exact test. The Mann-Whitney U test was used to compare the median PS scores between the groups. Statistical significance was set at $p<0.05$.

Results

Among the 100 study patients who began oral minocycline, 38 (38%) experienced adverse effects during the first 3 days and stopped taking the drug, primarily because of severe nausea and/or dizziness. The other 62 (62%) patients completed the 6-week treatment plan. Comparative data between patients with and without treatment completion are shown in Table 1. A significantly higher prevalence of a history of allergy to multiple (≥3) drugs was noted in patients who experienced adverse effects and stopped treatment.

PS scoring

Among the 62 patients who completed treatment, the PS score decreased by at least 2 in 27 patients (44%) but was essentially unchanged in the remaining 35 (56%). A decrease in the PS score by at least 2 was associated with an objective evaluation of "getting better" in most cases and therefore counted as favorable therapeutic effects induced by oral minocycline. Comparative data between patients with and without favorable therapeutic effects for ME symptoms are presented in Table 2. Infectious onset for ME was less likely in patients with favorable therapeutic effects. The rate of an elevated serum antibody titer (≥40) against *Mycoplasma pneumoniae (M. pneumoniae)* did not differ significantly between groups with and without favorable therapeutic effects. The mean disease duration was significantly shorter in the patients with favorable therapeutic effects than in those without such effects. As shown in Figure, favorable therapeutic effects were significantly more prevalent in patients with a short (0.5-3 years) disease duration (54%) than in those with a disease duration of ≥3 years (22%). Notably, the prevalence of favorable therapeutic effects in the patients with a disease duration <0.5 years was as high as 78%, which was also significantly higher than that in patients with

Table 2. A Comparison of the Clinical Data between the Study Patients with ME with and without Favorable Therapeutic Effects after Oral Treatment with Minocycline for Six Weeks.

	Patients with favorable effects	Patients without favorable effects	p value
Number of patients	27 (44%)	35 (56%)	
Men/Women	10/17	15/20	0.79
Age (years)	37±13	36±11	0.81
<30	9 (33%)	9 (26%)	0.58
≥40	10 (37%)	16 (46%)	0.61
Disease duration (years)	2.2±3.3	5.4±5.8	0.01
Infection onset	10 (37%)	18 (51%)	0.31
Contact with pet animal	2 (7%)	4 (11%)	0.69
Mycoplasma Ab titer ≥40	7 (26%)	11 (31%)	0.78
Performance status score	3-8	3-9	
Median score	5	6	0.30
≥7	6 (22%)	13 (37%)	0.27
≤5	15 (56%)	16 (46%)	0.61
Failed to stand for 10 min	6 (22%)	7 (20%)	1.00
Disequilibrium	8 (30%)	10 (29%)	1.00
Tender points ≥8	5 (19%)	10 (29%)	0.39

Disequilibrium: instability upon standing with feet together and eyes closed. Values are presented as mean±standard deviation. ME: myalgic encephalomyelitis, Ab: antibody

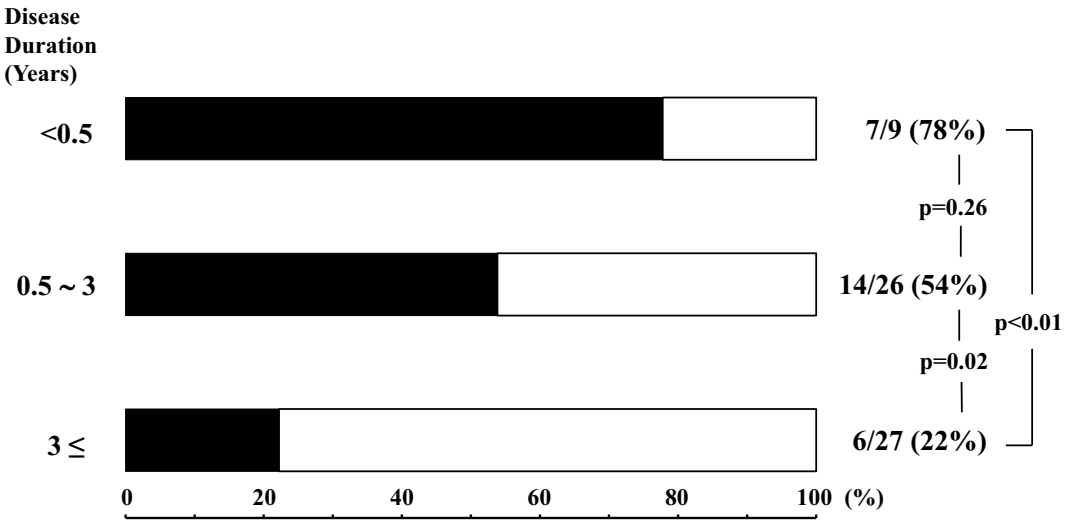

Figure. Comparison of the Ratio of Favorable Therapeutic Effects by Oral Minocycline Among ME Patients with Different Disease Duration. The black portion in each bar graph shows the patients who achieved favorable therapeutic effects with oral minocycline among those with different disease durations. ME: myalgic encephalomyelitis

a disease duration of ≥3 years. The data of each patient who experienced favorable therapeutic effects are shown in Table 3.

Active 10-min standing test

Among the 27 patients with favorable therapeutic effects, 6 were unable to complete the 10-min standing test before therapy; after therapy, 4 of 6 completed the test, and the remaining 2 prolonged the standing time to >2 min. The test showed postural orthostatic tachycardia in 8 patients before therapy versus 3 after therapy (63% decrease). Orthostatic hypotension was observed in one patient before therapy and resolved after treatment.

Among the 35 patients without favorable therapeutic effects, 7 were unable to complete the 10-min standing test before therapy; after therapy, 1 of the 7 completed the test. The test showed postural orthostatic tachycardia in six patients before therapy versus five after therapy. The or-

Table 3. Clinical Characteristics and Favorable Therapeutic Effects in ME Patients Treated with 6-Week Oral Minocycline.

Patient #	Age/sex	Disease duration (years)	Infectious onset	Mycoplasma Antibody	PS score		10 min standing test		Disequilibrium		Tender points	
					Before	After	Before	After	Before	After	Before	After
1	46/F	0.2	(-)	<40	3 → 1		C → C		(-) → (-)		6 → 2	
2	22/M	0.2	(+)	<40	3 → 1		C, POT → C		(-) → (-)		0 → 0	
3	39/F	0.2	(-)	×80	3 → 0		C, POT → C		(-) → (-)		0 → 0	
4	31/F	0.2	(+)	×40	4 → 2		C → C		(-) → (-)		3 → 2	
5	55/M	0.3	(+)	<40	6 → 1		3 min → C		(+) → (-)		8 → 0	
6	45/F	0.4	(-)	<40	6 → 4		7 min → C		(+) → (-)		12 → 8	
7	41/F	0.4	(-)	<40	4 → 2		C → C		(-) → (-)		4 → 4	
8	36/F	0.5	(-)	<40	4 → 2		C → C		(+) → (-)		4 → 1	
9	21/F	0.6	(+)	<40	3 → 1		C → C		(-) → (-)		4 → 0	
10	25/F	0.7	(-)	<40	6 → 1		C → C		(-) → (-)		0 → 0	
11	22/M	0.9	(-)	<40	3 → 0		C, POT → C, POT		(-) → (-)		4 → 2	
12	45/F	1	(-)	<40	7 → 5		5'30" → C		(+) → (-)		4 → 0	
13	73/M	1	(-)	<40	4 → 1		C, OH → C		(-) → (-)		0 → 0	
14	35/M	1	(-)	×40	7 → 4		C → C		(-) → (-)		0 → 0	
15	54/F	1.5	(+)	<40	5 → 3		C → C		(-) → (-)		4 → 1	
16	49/M	1.9	(+)	<40	7 → 0		C → C		(-) → (-)		0 → 0	
17	36/F	1.9	(+)	×40	6 → 4		C, POT → C		(-) → (-)		0 → 1	
18	32/F	2	(-)	<40	4 → 2		C → C		(-) → (-)		2 → 4	
19	22/M	2.2	(+)	×40	3 → 1		C → C		(-) → (-)		0 → 0	
20	48/M	2.3	(-)	<40	5 → 1		C → C		(-) → (-)		0 → 0	
21	39/F	2.5	(-)	×40	7 → 5		5'15" → 8'32"		(++)* → (+)		10 → 4	
22	32/F	3	(-)	<40	5 → 3		C, POT → C, POT		(-) → (-)		4 → 1	
23	22/M	3.3	(+)	<40	8 → 6		4 min, POT → 6'11"		(+) → (+)		10 → 10	
24	22/M	4	(-)	<40	6 → 4		C, POT → C		(-) → (-)		0 → 0	
25	28/F	5	(-)	×40	6 → 4		C → C		(-) → (-)		0 → 0	
26	21/F	5	(-)	<40	5 → 3		C, POT → C, POT		(+) → (-)		10 → 4	
27	53/F	17	(+)	<40	8 → 6		7 min → C		(+) → (+)		6 → 8	

(++)*: Instability on standing with eyes closed and eyes open. See text for details. ME: myalgic encephalomyelitis, PS: performance status, C: completed, POT: postural orthostatic tachycardia, OH: orthostatic hypotension

thostatic hypotension observed in three patients before therapy did not resolve after therapy. Neurally mediated hypotension appeared in one patient after therapy.

Disequilibrium

Among the 30 patients with disequilibrium 18 completed the treatment plan, with resolution of disequilibrium seen in 6 (33%). Among the 27 patients with favorable therapeutic effects, 8 had disequilibrium before the therapy. Of these eight patients, seven had a positive Romberg test (standing with stability with eyes open and instability with eyes closed), and one had instability standing with feet together and eyes open that worsened after closing their eyes. After treatment, favorable effects were observed for 6 (75%) of the 8 patients with disequilibrium, with resolution noted in 5 patients and remarkable amelioration in 1 patient (Table 3). Among the 35 patients without favorable therapeutic effects, the disequilibrium observed in 10 patients before therapy remained for all patients after therapy.

Neuropathic pain or fibromyalgia

According to ACR 1990 diagnostic criteria (28), 9 patients were diagnosed with fibromyalgia (≥11 tender points), and 22 had neuropathic pain (8 to 10 tender points). Among 31 patients, 15 completed treatment. On digital palpation, the number of tender points decreased remarkably (≥3) in 5 (33%) patients with fibromyalgia or neuropathic pain. Among the 27 patients with favorable therapeutic effects, the number of tender points decreased remarkably in 4 of the 5 patients with fibromyalgia or neuropathic pain. Notably neuropathic pain completely resolved in one patient (Patient #5 in Table 3).

Discussion

The present study is the first systematic report of oral minocycline therapy in patients with ME. Results show that it is definitely effective in ameliorating various symptoms in the patient group just described. Minocycline therapy improved the daily functional capacity or activities of daily living; lessened the symptoms of orthostatic intolerance, which is the primary determinant for activities of daily living (33) and disequilibrium, recently suggested to be an important cause of orthostatic intolerance (30-32); and ameliorated myalgic symptoms. The mechanism through which minocycline exerted such therapeutic effects on the symptoms in

these patients is suggested below.

Possible effects on M. pneumoniae with putative persistent infection in the central nervous system

Several infectious pathogens have been suggested as triggers for central nervous system dysfunction in patients with ME (2), including *M. pneumoniae* (7). A hematologic examination of four *Mycoplasma* species, including *M. pneumoniae*, using forensic polymerase chain reaction revealed a high prevalence of *Mycoplasma* infections among European CFS patients (34). Minocycline may act on *Mycoplasma* infection, which has persistent and broad central nervous system effects, and thus resolve these symptoms. However, the prevalence of an elevated *M. pneumoniae* antibody titer, the evidence of its infection, was comparable between patients with and without favorable therapeutic effects.

Possible effects on C. burnetti with putative persistent infection in the central nervous system

The proposed causes of ME include infectious agents and the suggested involvement of the rickettsia *C. burnetti* (2). Indeed, chronic fatigue following Q fever, in which various nonspecific symptoms, including general malaise, headache, arthralgia, and myalgia, result from prolonged *C. burnetti* infection, have been suggested as a type of ME according to a recent proposal (2). Recent reports of open-label studies of minocycline in Japan suggested that this drug is useful for improving chronic nonspecific symptoms considered to be CFS following Q fever caused by *C. burnetti* infection in patients with the antibody (8, 9). However, data from subsequent reports are conflicting. In a randomized study, long-term treatment with doxycycline, another tetracycline, failed to reduce fatigue severity among fatigue symptoms following Q fever (35), suggesting that the favorable effects by minocycline are not exerted through its anti-microbial action. In the present study, the antibody titer for *C. burnetti* was not determined.

Possible suppressive effects of minocycline on neuroinflammation

Besides its anti-microbial action, minocycline has unique biologic effects, such as attenuation of microglial activation and neuroprotection from neuronal injury (4, 12). The mechanisms involved in the non-antibiotic properties of minocycline include antioxidant activity, inhibition of several enzyme activities, inhibition of apoptosis, and regulation of immune cell activation and proliferation (11, 12). Persistent microbial infection was not shown to be essential to achieve the therapeutic effects of minocycline seen in the study of patients with ME. Instead, it has been suggested that neuroinflammation plays an essential role in the development of central nervous dysfunction in patients with ME/CFS (6, 36, 37). In animal models of fatigue and neuroinflammation, Kataoka et al. (4) demonstrated that pretreatment with minocycline attenuated polyriboinosinic:polyribocytidylic acid-induced interleukin-1β expression in the brain, a transient fever, and a decrease in locomotor activity. Activation of inflammatory and cell-mediated immunity pathways, including increased levels of cytokines, is known to induce fatigue and somatic symptoms (38). Minocycline inhibits microglial activation under various pathologic conditions without affecting astroglia or neurons (39). Furthermore, Yasui et al. (40) reported a rat model for CFS in which the intrathecal administration of minocycline alleviated muscular hyperalgesia and mechanical allodynia by suppressing microglial activation in the spinal cord. These observations from preclinical studies indicate that activated microglia play a key role in the onset of fatigue. Tissue damage in the central nervous system likely arises when inflammation is prolonged and pro-inflammatory cytokines and other inflammatory mediators remain elevated.

Of note, minocycline has emerged as the most effective tetracycline derivative for providing neuroprotection (41). Minocycline shows a better pharmacokinetic profile than other tetracyclines when used orally, being rapidly and completely absorbed, with a longer half-life and excellent tissue penetration and almost complete bioavailability (11, 12). Because of its high lipid solubility, minocycline easily crosses the blood-brain barrier (41). A reduction in the expression of inflammatory mediators within the brain after minocycline treatment has been repeatedly shown in preclinical studies, accounting for its inhibitory effects on infarct size in ischemia models (17, 42) and positive effects on behavioral complications associated with neuroinflammatory processes (43). Many of these studies were initially based on the ability of minocycline to inhibit microglial activation, a process that has deleterious effects on neurogenesis and the neuronal survival and explains this agent's potential efficacy in treating neuroinflammatory and/or neurodegenerative disorders (12, 17, 21, 44). Some reports have shown that the anti-inflammatory action of minocycline is exerted through an inhibitory effect on the p38 mitogen-activated protein kinase pathway (45, 46). A further understanding of the molecular mechanisms involved in the action of minocycline on neuroinflammation is required in order to capitalize on its full therapeutic potential. Microglial activation and neuroinflammation may be promising targets for treating patients with ME (43).

Patient population for favorable therapeutic effects

The study population included patients with a disease duration of less than six months according to the ME criteria (2). Of note, the effects of oral minocycline therapy may depend on the disease duration. The beneficial effects are clearly enhanced when the drug is administered as early as possible, especially if initiated within six months of the disease onset. The antinociceptive effects of minocycline have recently been confirmed in different models of neuropathic pain, particularly with treatment at the initial disease stage (18), and have been attributed to the inhibition of microglial activation. As a general rule, the shorter the disease duration, the better the therapeutic outcome. The six-month

waiting period that has been essential in some major diagnostic criteria (1, 47) seems to be no longer required. An early diagnosis may elicit new insights into the early stages of pathogenesis, and prompt treatment may lessen the disease severity and impact. Indeed, in the present study, favorable effects were much less prevalently observed in the patients with a disease duration of three or more years.

Importantly, the immediate adverse effects of oral minocycline therapy, such as nausea and dizziness, were frequently observed, with a prevalence as high as 38%. These known and most common adverse effects primarily occur early after the drug is initiated and disappear shortly following therapy discontinuation. Most of the study patients with a history of drug allergy to multiple drugs did not tolerate oral minocycline. The mechanism underlying this intolerance remains unknown.

Limitations

Several limitations associated with the present study warrant mention. First, the design was not a double-blind randomized controlled trial; therefore, possible placebo effects could not be excluded. Second, the present study included patients with a short disease duration (less than six months), and no reports on the natural course of disease within the first six months are available. These patients may not have had stable disease activity; therefore, we cannot rule out that some symptoms improved as part of the natural course of the disease during the early stage.

Conclusion

Oral minocycline therapy administered as a six-week regimen was effective in ameliorating symptoms in a considerable number of the study patients with ME, particularly those with a disease duration of less than three years, especially in the initial stage of disease (first six 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, including nausea and dizziness. The drug may target neuroinflammation, resulting in favorable effects, although further investigations will be required to clarify the precise mechanism by which minocycline ameliorates the symptoms in this patient population.

The author states that he has no Conflict of Interest (COI).

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