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ORIGINAL ARTICLE

Minocycline Does Not Decrease Intensity of Neuropathic Pain, but Improves Its Affective Dimension

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ABSTRACT

Purpose: Recent understanding of the neuron–glia communication shed light on an important role of microglia to develop neuropathic pain The analgesic effect of minocycline on neuropathic pain is promising but it remains unclear in clinical settings. *Methods:* The study included 20 patients with neuropathic pain of varied etiologies. We administered 100 mg/day of minocycline for 1 week and then 200 mg/day for 3 weeks, as an open-label adjunct to conventional analgesics. An 11-point numerical rating scale (NRS) and the short-form McGill Pain Questionnaire (SF-MPQ) were used to evaluate pain severity. The data were collected at baseline and after 4 weeks of therapy and analyzed using the Wilcoxon signed-rank test. *Results:* All except two patients tolerated the full dose of minocycline. There was no significant improvement in the scoring of NRS (5.6 ± 1.2 at baseline vs. 5.3 ± 1.9 at 4 weeks; $p = .60$). The total score of the SF-MPQ decreased significantly (17.2 ± 7.4 vs. 13.9 ± 9.6; $p = .02$), particularly in the affective subscale (4.4 ± 2.7 vs. 3.3 ± 3.6; $p = .007$) but not so in the sensory subscale (12.8 ± 5.2 vs. 10.6 ± 6.2; $p = .06$). *Conclusion:* Minocycline failed to decrease pain intensity but succeeded in reducing the affective dimension associated with neuropathic pain.

KEYWORDS neuropathic pain, minocycline, microglia, SF-MPQ

INTRODUCTION

Chronic pain is characterized by enhanced sensory neurotransmission that underlies increased sensitivity to noxious stimuli (i.e., hyperalgesia) and the perception of non-noxious stimuli as painful (i.e., allodynia), and its related affective disorders. Neuropathic pain is one of the most debilitating chronic pain conditions that considerably affects the activities of daily living (ADL) and the quality of life (QoL) of patients.[1] Several strategies are used in the clinical treatment of neuropathic pain; however, it is often resistant to therapy and pain intensity remains severe. Therefore, the search for novel treatments continues.

Pharmacological treatments of neuropathic pain have primarily targeted neurons, including the axons and dendrites. And thereby, some adverse effects (e.g., somnolence), related to restraint of neuronal activity, cannot be avoided, although they have limited analgesic efficacy. Recent advances in the understanding of the neuron–glia communication shed light on an important role of microglia in the spinal dorsal horn for the development and persistence of neuropathic pain.[2] Microglia are primary immune sentinels of the central nervous system (CNS). Pain arising from neuronal injury enhances the release of pro-nociceptive mediators (e.g., ATP, glutamate, cytokines, and neurotrophic factors) and activates both neurons and microglia in the spinal dorsal horn. Following the nerve injury, activated microglia further produce pro-nociceptive neurotransmitters (e.g., NO, cytokines, and chemokines), all of which promote synaptic transmission. This process

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of neuron–glia communication ultimately leads to increased excitability of the spinal dorsal horn neurons and causes the sensation of persistent pain in the absence of continuous noxious stimuli to the tissue.[3] Once microglia are activated, the neuron–microglia communication maintains this vicious process and prolongs neuropathic pain.[4]

Numerous physiological and pharmacological studies have succeeded in attenuation of neuropathic pain by using a variety of molecules that target inhibition of microglial activation through suppression of divergent purinergic receptors (e.g., P2 X 4, P2Y12) on the microglial surface.[5] Among these, minocycline is a lipophilic molecule absorbed rapidly and readily across the blood–brain barrier. In addition to its actions as an antibiotic, minocycline has neuroprotective and anti-inflammatory effects in the CNS, probably due to its potent and preferential inhibitory action on the microglia rather than neurons. The mechanism of action of minocycline on the microglia is multifaceted;[6] but for example, previous studies have shown that its inhibitory effect on microglia activation attenuates the development of hypersensitivity in rat models of neuropathic pain.[4,7] Moreover, because of neuroprotective properties, minocycline can restore locomotor property in the model of spinal cord injury and reduce the lesion size after injury, indicating the ability to prevent neuronal apoptosis in the injury site.[8,9] Apoptosis of spinal dorsal horn neurons was reported in patients with post-herpetic neuralgia, even though it is a peripheral neuropathic pain condition.[10]

Considering the above data, the analgesic effect of minocycline is promising but it remains still unclear whether it will be clinically useful in the treatment of neuropathic pain. To elucidate this question, the present study was designed to investigate the analgesic effect of minocycline in patients with neuropathic pain.

MATERIALS AND METHODS

The study was approved by an institutional ethical review board and registered in the University Medical Information Network (UMIN), which is one of data center as public institution in Japan (trial ID: UMIN000008594).

Subjects

The study included 20 patients with the diagnosis of neuropathic pain recruited from our outpatient clinic. Diagnosis of neuropathic pain was established for each patient by their pain specialist based on the available diagnostic grading system.[11] The inclusion criteria were as follows: (1) diagnosis of neuropathic pain (irrespective of its origin); (2) mean pain intensity in the past week of >4 on an 11-point numerical rating scale (NRS) (where 0 stands for no pain, and 10 for worst possible pain); (3) pain duration >3 months; and (4) age between 20 and 80 years. Patients with slight or more clinically relevant cognitive dysfunction and those with a history of allergy to tetracycline antibiotics were excluded. All patients gave written informed consent to participate in the study.

Minocycline Treatment

All patients took a stable dose of analgesics, including gabapentinoids, tricyclic antidepressants, opioids and others, for at least 1 month before baseline screening. Next, they started an open-label treatment with minocycline. Participants were required to continue the same dose of analgesics throughout the study. After baseline assessment, minocycline treatment was initiated according to the following titration schedule: 50 mg orally twice a day (daily dose, 100 mg) for the first week, and 100 mg orally twice a day (daily dose, 200 mg) for 3 weeks. At the end of the first week, patients were screened for any side effects of minocycline.

Treatment was continued providing that the patients gave their consent and accepted potential complications.

Evaluation of Neuropathic Pain

We evaluated pain intensity using an 11-point NRS and the Japanese version of the short-form McGill Pain Questionnaire (SF-MPQ). The total score and both sensory and affective subscales of the SF-MPQ were used. ADL were assessed by the Japanese version of the Brief Pain Inventory (BPI). Because different characteristics of pain description can indicate different underlying mechanisms,[12] we evaluated seven pain characteristics (burning sensation, tingling or prickling sensation, tactile allodynia, electric shock-like pain attacks, thermal allodynia, numbness, and hyperpathia) on a 6-point scale (0 = never, 1 = hardly noticed, 2 = slightly, 3 = moderately, 4 = strongly, and 5 = very strongly) for speculating the analgesic mechanism(s) by minocycline. To evaluate pain characteristics, we took an example from the rating system of PainDETECT.[13] PainDETECT is a screening questionnaire that describes all the seven characteristics as specific for neuropathic pain and has been confirmed to screen for a neuropathic pain component from a variety of pain complaints.

All of the above measures were conducted twice: at baseline and after 4 weeks of minocycline therapy. The primary outcome measure of the present study was a decrease in the NRS score of more than 30%, because it is known that a decrease in pain intensity of at least 30% can lead to the improvement of general health status of patients with chronic pain.[14] All data were expressed as means ± standard deviation. We used the Wilcoxon signed-rank test to compare between parameters at baseline and those at 4 weeks. The level of statistical significance was set at a p-value of less than 0.05.

Since minocycline has been reported to reverse opioid-induced antinociceptive tolerance,[15] we divided patients into two groups (those who used opioid analgesics vs. those who did not). Using the Mann–Whitney test, we compared the two groups in terms of a percent decrease in the NRS score caused by minocycline.

RESULTS

Of 20 patients, 2 dropped out of the study. One patient was a 77-year-old woman with postherpetic neuralgia who suffered from severe allergic skin rash 3 days after starting minocycline. She was treated with oral steroids for 2 weeks and the rash disappeared completely. The other patient was a 76-year-old man with chronic inflammatory demyelinating polyneuropathy who complained of nonspecific hoarseness and showed poor medication compliance at the end of the first week. The remaining 18 patients tolerated the full dose of minocycline (100 mg/d for 1 week and 200 mg/d for 3 weeks) (6 patients had post-brachial plexus avulsion injury pain, 2 post herpetic neuralgia, 1 thalamic pain, 1 median nerve injury, 1 phantom limb pain after amputation, 1 spinal cord injury, 1 lumbar radicular nerve injury, 1 chemotherapy-induced polyneuropathy, 3 failed back surgery syndrome, and 1 caudal neurinoma). No adverse events were observed in these patients; thus, our final analysis included these 18 patients with neuropathic pain. Their demographical data as well as the results of the outcome measures are presented in Table 1.

There was no significant change in pain intensity after minocycline therapy (5.6 ± 1.2 at baseline vs. 5.3 ± 1.9 at 4 weeks; $p = 0.60$). The total scores of BPI were also comparable before and after treatment (31.3 ± 13.9 vs. 27.9 ± 18.0; $p = 0.23$). The total score of the SF-MPQ decreased significantly (17.2 ± 7.4 vs. 13.9 ± 9.6; $p = 0.02$), particularly in the affective subscale (4.4 ± 2.7 vs. 3.3 ± 3.6; $p = 0.007$) but not so in the sensory subscale (12.8 ± 5.2 vs. 10.6 ± 6.2; $p = 0.06$). Of 7 pain characteristics, only thermal allodynia improved significantly (1.6 ± 1.4 vs. 1.0 ± 1.1; $p = 0.02$). The remaining six characteristics did not improve after minocycline therapy (Table 1).

Simultaneous use of opioids and minocycline did not significantly relieve pain. In the group with opioid use ($n = 9$), we observed a decrease in the NRS of 5.5% ± 37.8%, and in that without opioid use ($n = 9$), it was 14.9% ± 22.2% ($p = 0.23$).

TABLE 1. Demographic and clinical data of participants with neuropathic pain

		Pre	Post	p-value**
No. of patients*		18	18	
Male: Female		14:4		
Age (y)		58.5 ± 13.9		
Duration of pain (wk)		109.6 ± 94.8		
Pain intensity (NRS)		5.6 ± 1.2	5.3 ± 1.9	0.60
BPI		31.3 ± 13.9	27.9 ± 18.0	0.23
SF-MPQ	Total	17.2 ± 7.4	13.9 ± 9.6	0.02
	Sensory	12.8 ± 5.2	10.6 ± 6.2	0.06
	Affective	4.4 ± 2.7	3.3 ± 3.6	0.007
Pain characteristics	Burning	2.2 ± 1.6	1.9 ± 1.1	0.22
	Tingling/prickling	2.7 ± 1.3	2.5 ± 1.2	0.53
	Tactile allodynia	1.8 ± 1.0	1.9 ± 1.1	0.85
	Electric shock-like	2.5 ± 1.4	2.3 ± 1.4	0.45
	Thermal allodynia	1.6 ± 11.4	1.0 ± 1.1	0.02
	Numbness	2.9 ± 1.9	2.8 ± 1.6	0.61
	Hyperpathia	1.9 ± 1.4	1.8 ± 1.4	0.93

*Initially, 20 patients were enrolled into the study; 2 patients dropped out during the study and their data were not included in the table.
**Statistical analyses were conducted by the Wilcoxon signed-rank test.
NRS = Numerical Rating Scale; BPI = Brief Pain Inventory; SF-MPQ = short-form McGill Pain Questionnaire

DISCUSSION

In the present study, minocycline did not reduce the intensity of neuropathic pain, as measured by the NRS. Likewise, a recent study found that minocycline improves neuropathic pain, which is naïve to analgesics other than nonsteroidal anti-inflammatory drugs and acetaminophen, compared to placebo but its effect size is very small, and concluded that minocycline is not likely to be clinically meaningful.[16] Several studies involving animal pain models indicated that minocycline could exert an analgesic effect on neuropathic pain when given preemptively or immediately after neural injury, but the same effect was not observed at longer times after injury.[4,7,8] This suggests that there may be a therapeutic time window for postinjury administration of minocycline. Prescribing minocycline at the initiation of neuropathic pain can prevent prolonged pain. In clinical practice, most patients with neuropathic pain, including those in our study, seek treatment only after the signs and symptoms of pain have developed. The time point when minocycline was administered to our patients was probably not within the therapeutic time window.

The majority of studies involving animal pain models focused on the measures of hypersensitivity and allodynia subsequent to tissue or nerve injury. Among these, both tactile and thermal allodynia have been reported to be attenuated by minocycline.[4,7,17] In our study, minocycline did not reduce tactile allodynia but improved thermal allodynia. Thus, our data from humans are not in line with the previous findings in animals. At the level of nerve conduction and neurotransmission, the underlying mechanisms of tactile and thermal allodynia are different, which may explain the differences in analgesic action of minocycline on neuropathic pain in human subjects. Another explanation might be that thermal allodynia was the least impaired of all seven characteristics evaluated in this study, and hence it might be most responsive to minocycline.

Minocycline has also been reported to reverse opioid-induced antinociceptive tolerance,[15] which is considered to share some common pathological mechanisms with neuropathic pain. These mechanisms possibly explain why opioid analgesics show the ceiling effect on neuropathic pain.[18] In our study, minocycline was less effective in patients who used opioid analgesics compared with those who did not. Our study did not show any clinical evidence that minocycline can reverse opioid-induced antinociceptive tolerance. The development of opioid-induced antinociceptive tolerance can be prevented if minocycline is administered at the adequate stage.[19] The time point when minocycline was administered to our patients was probably not within the therapeutic time window.

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (by The International Association for the Study of Pain). Thus, pain always has two aspects: sensory and affective. In the present study, minocycline did not decrease pain intensity but improved neuropathic pain-associated affective disorders. In several studies on animal pain models, affective disorders, such as depression and anxiety, were improved by a pharmacological treatment, and the results were directly related to particular brain regions (e.g., anterior cingulate cortex and amygdala).[20] Our findings indicate that minocycline works mainly at the supraspinal level. Supporting evidence comes from several reports that minocycline has a potential to protect cerebral damage in multiple sclerosis and Parkinson's disease,[6] and that it can normalize neuronal dysfunction in schizophrenia. In particular, minocycline improved not only positive symptoms (i.e., hallucination, delusion, and catatonia) but also negative affective symptoms (i.e., depression and flattening of emotion) of schizophrenia.[21] Previous basic studies reported that neuropathic pain occurred after microglial activation in the spinal cord, and, what follows, minocycline attenuated neuropathic pain by inactivating spinal microglia. However, those studies did not investigate the microglia in the supra-spinal CNS, and our clinical findings require basic research to reveal the close associations between neuropathic pain, affective disorders, and microglia.

To adequately control chronic pain in the clinical setting, it is vital for healthcare professionals to educate patients on how to cope with chronic pain.[22] For example, cognitive behavioral therapy sometimes fails to decrease pain intensity but usually succeeds in reducing distress associated with chronic pain and improving ADL and QoL in the long term.[23] Thus, minocycline might become a novel treatment for neuropathic pain, in that it could be used as a pharmacological pain-coping strategy. Of note, some of our patients expressed a wish to continue minocycline at the end of the study, although they recognized that it did not satisfactorily decrease pain intensity.

Our findings have to be interpreted with caution owing to a number of limitations of the study, including an open-label design, lack of a control group, and a small sample size, in addition to no significant improvement in the ADL. However, our results may possibly lead to novel basic-science insight into the mechanisms of neuropathic pain and associated

affective disorders because pain is both sensory and affective experience. What follows, our findings may indicate the necessity to consider the sensory and affective aspects of pain separately in clinical settings.

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Conflict of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Implication statement

Microglia in the spinal dorsal horn play an important role for the development of neuropathic pain. Minocycline modulates microglial activation and its inhibitory effect on microglia attenuates neuropathic pain. In neuropathic pain patients, minocycline failed to decrease pain intensity but succeeded in removing the distress associated with neuropathic pain.

Author contribution

M Sumitani directed the whole study, conducted experimental procedures, and drafted the manuscript. H. Ueda and T. Ogata provided advices to M. Sumitani about the potential analgesic and neuroprotective effect of minocycline on the basis of their basic investigations, and discussed the present findings. J. Hozumi, R. Inoue, and T. Kogure recruited the participants and they assisted data acquisition by M. Sumitani. Y. Yamada discussed the present findings and critically commented on the manuscript.

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