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【 EDITORIAL 】

Could Minocycline Be a "Magic Bullet" for the Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease of unknown etiology that causes severe general malaise and a wide range of systemic symptoms, including pain, sore throat, a mild fever, difficulty standing, sleep disturbance, depressive state, and slowness of thought, in previously healthy individuals. In 2019, a report was published that disappointed both ME/CFS patients and the clinicians and researchers involved in its treatment worldwide. The results of a phase III double-blinded randomized clinical trial of B-lymphocyte depletion therapy with rituximab, which had earlier appeared promising for the treatment of ME/CFS patients, concluded that rituximab did not contribute to symptomatic improvement in the treatment group (1).

However, the results of a clinical trial by Miwa on minocycline, a tetracycline antibiotic for ME/CFS merit attention, despite the fact that it was a prospective open-label study without a comparative control group (2), for it is no easy task to improve the performance status score in 27% of subjects by ≥2 points within 6 weeks with oral medication alone. Studies have shown that minocycline can attenuate microglial activation and exert anti-inflammatory, immunomodulatory, and neuroprotective effects (3). The presence of microglial activation, which is believed to indicate the presence of neuroinflammation, has also been identified in the brains of ME/CFS patients (4). Based on these reports, Miwa hypothesized that minocycline's mechanism of action in inhibiting neuroinflammation may have helped improve the symptoms of ME/CFS patients. Further placebo-controlled, exploratory clinical studies on minocycline are desirable, in addition to more extensive research on the pathogenesis of neuroinflammation.

Apart from the study design, there are two other issues with Miwa's study. The first is the large number of dropouts due to side effects. The fact that 38% of subjects discontinued the study because of side effects, including nausea and vertigo, begs the question of whether or not the dose was appropriate. The dosage used in the study was the same as that used for minocycline as an antibiotic, and a lower dose may be more appropriate for the long-term anti-neuroinflammatory treatment of ME/CFS patients. As an example from another disease, the long-term, low-dose administration of erythromycin, a macrolide antibiotic, is now established as a treatment for diffuse panbronchiolitis due to its anti-inflammatory effects (5). An appropriate dose and the use of additional drugs to prevent side effects may reduce the number of patients discontinuing minocycline because of side effects, thus enabling a larger number of patients to benefit from the treatment. The second issue is that some patients who were able to tolerate oral minocycline without side effects failed to respond: although most patients had suffered from ME/CFS for a relatively long time, some who had developed the condition fairly recently did not respond to minocycline. I previously published a case report on successful personalized treatment with kampo herbal medicine to target neuroinflammation (6). In practice, however, I have also encountered a certain proportion of patients who do not respond even to personalized treatment with kampo medication. Why is this? Unless this issue is fully considered in the study design, further clinical studies of minocycline run the risk of repeating the experience with rituximab. In other words, the heterogeneity of the ME/CFS patient population must be considered. The area of study for ME/CFS is spread across various systems, including inflammation, B-lymphocytes, natural killer cells, and autonomic regulation (7). When this is taken into consideration, we come to realize that the quest for a "magic bullet" with which to treat all patients of ME/CFS may be difficult. In

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my own clinical practice, the same patient may exhibit changes in their symptoms due to lifestyle-related factors and treatment response.

In the future, rather than searching for a single drug to target all ME/CFS patients, we may need to carry out studies that classify patients according to the cause of the onset, disease duration, medical history (including trauma), treatment history, pathological conditions confirmed by symptoms and/or test results, and psychosocial factors, and only then explore methods of treatment that are effective for these different patient groups. These treatment methods must not be limited to pharmacological therapies but should also include exercise therapy, cognitive behavioral therapy, and physiotherapy. Research in this way may help clarify the pathophysiology and characteristics of ME/CFS patients whose symptoms are improved by minocycline.

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

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