Efficacy of Ultramicronized Palmitoylethanolamide on the Clinical Symptoms of Charcot-Marie-Tooth Neuropathy

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Introduction

Charcot-Marie-Tooth disease (CMT) is one of the most commonly inherited neuromuscular diseases, with a prevalence of approximately 1 in 2,500 persons. It represents a genetically heterogeneous group of inherited neuropathies, clinically characterised by prevalent distal muscle atrophy, sensory impairment, muscle pain, sensation of fatigue and painful muscle cramps [1]. Although treatment with high doses of vitamin C was effective in an animal model of CMT, studies in humans failed to confirm a benefit of this treatment [2,3]. Progesterone antagonists and subcutaneous neurotrophin-3 injections were also ineffective in humans [4,5]. Recent advances suggest that neuroinflammation may play a role in the pathophysiology of peripheral nerve damage in CMT [6,7]. P2X7 inhibition has recently shown tolerability and efficacy in an animal model of CMT, of peripheral nerve damage in CMT [6,7]. P2X7 inhibition was performed both at baseline (T0) and at end of study treatment (T2). None of the patients received an add-on treatment for these symptoms. A significant improvement of pain, fatigue and cramps was observed in VAS scores after 20 days of treatment with PEA-um microgranules (T1). Mean values of VAS score for pain decreased from 5.9 ± 2.1 to 3.9 ± 1.7, VAS score for fatigue decreased from 6.3 ± 2.4 to 3.4 ± 1.6 whereas VAS score for cramps diminished from 5.4 ± 1.2 to 3.8 ± 1.3. Further clinical improvement was observed also after 80 days (T2) of treatment with the same dosage of PEA-um tablets. Muscle strength, vibratory sensation and motor / sensory nerve conduction velocities did not display any significant modification. Although obviously limited as an open study, the data strongly suggest an efficacy of PEA-um in improving the clinical symptoms of CMT neuropathy.

Results and Discussion

The clinical status, along with gender, age range and genotype characteristics of CMT patients are summarised in Table 1. One patient dropped out of the study because of a previous history of alcoholism that emerged after T0. Complete clinical data were available for 22 patients (7 males and 15 females), mean age 53.5 ± 13.49 years. Mean disease progression was 31.6 ± 12.44 years. Fourteen patients were affected by CMT IA, the most common genotype, which...
is characterised by duplication of chromosome 17p11.2. Eight patients were classified as CMT IB due to a point mutation of P0 located on chromosome 1. Results of VAS scores for pain, fatigue and cramps at T0, T1 and T2 are summarised in Figures 1-3.

A significant improvement of pain, fatigue and painful cramps was observed in VAS scores after 20 days of treatment (T1). Mean values of VAS for pain decreased from 5.9 ± 2.1 to 3.9 ± 1.7 (p<0.0001); VAS for fatigue decreased from 6.3 ± 2.4 to 3.4 ± 1.6 (p<0.0001) whereas VAS for painful cramps diminished from 5.4 ± 1.2 to 3.8 ± 1.3 (p<0.0001). Further clinical improvement was observed also at T2, after another 60 days of treatment with PEA-um tablets maintaining the same dosage. Means values of VAS for pain decreased from 3.9 ± 1.7 to 3.0 ± 1.4 (p<0.0059); VAS score for fatigue diminished from 3.4 ± 1.6 to 3.0 ± 1.3 (ns) and VAS score for cramps decreased from 3.8 ± 1.3 to 2.9 ± 1.3 (p<0.0395). Statistical analysis of MRC score, vibratory sensation measurements and sensory and motor nerve conduction velocities did not display any significant modification. DN4 score was under the cut-off value of 4 in all patients. There were no adverse events related to treatment at any time during the course of the study.

CMT neuropathy is one of the most commonly inherited neuromuscular disorders, characterised by prevalent myelin loss in the demyelinating forms and prevalent axonal damage in axonal ones [12]. Both demyelinating and axonal forms progressively reduce motor performance and the patient quality-of-life [13]. Pain and muscle cramps are frequent, even in pediatric patients affected by CMT [14-16]. CMT patients are also more prone to develop psychiatric disturbances than non-affected individuals [13]. No treatment has proven to be clinically efficacious until now, although high doses of vitamin C, anti-progesterone and neurotrophin-3, and recently P2X7 inhibition, have demonstrated some effects in animal models [2, 3, 8]. Anti-progesterone therapy has potential side effects in women and children, whereas subcutaneous neurotrophin-3 has a very short half-life. The P2X7 inhibition, although tolerable and experimentally effective, must be tested on humans yet.

Conclusions

The present open-label study was performed in patients affected by the most common demyelinating forms of CMT (CMT 1). Fifteen patients suffered from CMT 1A (duplication of 17p 11.2) and 7 patients from CMT 1B (point mutation of P0 gene on chromosome 1). Clinical symptoms such as pain, fatigue and painful muscle cramps dramatically improved after 20 days (T1) of treatment with 1200 mg/day of PEA-um microgranules. Further improvement was observed also after a further 60 days (T2) with the same dosage of PEA-um tablets. All patients included in the study were in an advanced phase of the neuropathy, in fact, mean disease progression was 31.6 ± 12.44 years. Nonetheless, a statistically significant clinical improvement was observed in a relatively short period of observation. Modification of other parameters such as muscle strength, vibratory sensation and electromyographic data is obviously limited by the years of disease progression. In fact, the longer the disease history the greater is peripheral nerve damage, especially axonal loss [12]. It might be of utility as well to obtain data in the future from chronic treatment with PEA-um at the time of diagnosis or in the early phase of the disease, i.e childhood. Based on these encouraging, albeit preliminary data, a double-blind multicenter study seems warranted to confirm

<table>
<thead>
<tr>
<th>CMT form</th>
<th>Gene anomalie</th>
<th>Number of patients</th>
<th>Gender</th>
<th>Age range</th>
<th>Clinical status range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT IA</td>
<td>Duplication 17.11.2</td>
<td>14</td>
<td>9 females and 5 males</td>
<td>26-61 years</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>CMT IB</td>
<td>Point mutation Myelin Protein Zero gene chromosome 1</td>
<td>8</td>
<td>7 females and 1 male</td>
<td>46-79 years</td>
<td>Moderate to severe</td>
</tr>
</tbody>
</table>
the efficacy of PEA-um in treating the clinical symptoms of CMT neuropathy.

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Conflict of Interest

The author declares no conflict of interests.

References