INTRODUCTION

• Fatigue is reported by 75-95% of patients with MS, but the pathogenesis of MS fatigue is poorly understood.1,2
• There are no medications approved for MS fatigue.3
• Oxidative stress may play a role in MS fatigue.
• N-acetyl cysteine (NAC) is an anti-oxidant and is an oral precursor of cysteine approved for the treatment of acetaminophen-induced hepatotoxicity.4
• NAC restores hepatic cysteine which is a precursor to glutathione (GSH), a major intracellular antioxidant.4
• NAC decreases glumatamergic transmission, potentially decreasing excitotoxicity, which may protect from neurodegeneration.

OBJECTIVES

• To test the feasibility, tolerability and safety of NAC for fatigue in progressive MS.
• To evaluate changes in fatigue and oxidative pathway biomarkers on NAC versus placebo.

METHODS

• Randomized double-blind single center trial of individuals 18-75 years with progressive MS and fatigue (Modified Fatigue Impact Scale (MFIS) >38).
• 2:1 NAC 1250 mg TID or placebo for 4 weeks.
• Primary endpoint: Adverse events (AE).
• Primary efficacy endpoint: Change in MFIS from baseline to week 4.
• Secondary endpoints:
  • Change in MFIS from week 4 to 6 (2 weeks off treatment).
  • Change in blood GSH:GSSG ratio (reduced to oxidized glutathione).
  • Change in GSH concentration in grey matter on 7T MR spectroscopy (MRS).

Analyses

• Fisher exact test for categorical outcomes.
• Wilcoxon rank sum for continuous outcomes including change scores between groups.

RESULTS

Figure 1. CONSORT flow diagram.

Table 1. Characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NAC (n=10)</th>
<th>Placebo (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>51.3 (9.2)</td>
<td>65.7 (6.8)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>8 (80%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Disease duration, median years (IQR)</td>
<td>14.9 (8.0-20.8)</td>
<td>22.7 (8.3-29.9)</td>
</tr>
<tr>
<td>MS subtype, n (%)</td>
<td>6 (60%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>EDSS, median (IQR)</td>
<td>6.0 (4.0-6.0)</td>
<td>6.0 (3.5-6.0)</td>
</tr>
</tbody>
</table>

Table 2. Adverse events.

<table>
<thead>
<tr>
<th>Placebo (n=5), (i)</th>
<th>NAC (n=10), (ii)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection (1)</td>
<td>Increased fatigue (1)</td>
</tr>
<tr>
<td>Gait disturbance (1)</td>
<td>Abdominal pain (1)</td>
</tr>
<tr>
<td>Arthralgia (1)</td>
<td>Constipation (1)</td>
</tr>
<tr>
<td>Depression (1)</td>
<td>Common cold (1)</td>
</tr>
<tr>
<td>Back pain (1)</td>
<td>Sialadenitis (1)</td>
</tr>
<tr>
<td></td>
<td>Muscle weakness (1)</td>
</tr>
<tr>
<td></td>
<td>Gait disturbance (1)</td>
</tr>
<tr>
<td></td>
<td>Headache (1)</td>
</tr>
<tr>
<td></td>
<td>Anxiety (1)</td>
</tr>
<tr>
<td></td>
<td>Agitation (1)</td>
</tr>
<tr>
<td></td>
<td>Insomnia (1)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• NAC was well tolerated in patients with progressive MS who had fatigue.
• Fatigue improved during the study period on both NAC and placebo, with a strong placebo effect.
• Fatigue improvement may be more sustained after discontinuing NAC than placebo.
• Effects of NAC compared to placebo on antioxidant biomarkers suggested an antioxidant effect of NAC.

Limitations

• Small sample size
• Short duration of treatment

Strengths

• Pilot study of a novel agent for patients with progressive MS and fatigue
• Randomized, blinded trial
• Use of 7T MR spectroscopy and serum biomarkers to evaluate anti-oxidant effect

Future directions

• Ongoing analysis of MRS data.
• Larger trial with longer term treatment is warranted to evaluate the efficacy and safety of NAC for fatigue in MS.

References


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