rhIGF-I may slow progression of functional impairment and the decline in health-related quality of life in ALS patients while rhCNTF and TRH do not alter clinical progression of ALS.

**Clinical Problem:** A 57 year old male has typical ALS with diagnostic EMG and nerve biopsy.

**Clinical Question:** Do trophic factors (rhIGF-I, rhCNTF, TRH) alter the clinical progression of ALS?

**Clinical Bottom Lines:**

1. Only one of two valid RCTs of rhIGF-I reveal results favouring improvement in mortality, rate of clinical decline, and QOL in ALS.
2. NNT (95% CI) = 6 (3-25) to deteriorate less than 20 pts on Appel-ALS scale over 9 mo using rhIGF-I 0.1mg/day SC
3. NNT 95% CI = 8 (4-¥) to survive 30 mo using 0.05 or 0.1mg/day SC for 9 mo.
4. rhIGF-I is very well tolerated.
5. rhCNTF is not effective in altering ALS progression and its use is associated with cough, asthenia, nausea, weight loss, aphthous stomatitis, injection site reactions, and fever.
6. TRH is not effective in altering ALS progression and its use is associated with shivering, dysthermia, nausea and vomiting, hypertension, sweating, sensation of full bladder, SOB, headache.
7. Side effects were more pronounced with IV than with SC administration.

**The Evidence:**

**Paper 1**
A multi-centre 183-patient 9-month double-blind placebo-controlled trial of rhIGF-I (0.1 mg/kg/day). Outcome: rate of change of Appel ALS and SIP (QOL) scales.

**Paper 2**
A multi-centre 266-patient 9-month double-blind placebo-controlled triple arm trial of rhIGF-I (0.05mg/kg/day, 0.1mg/kg/day, placebo). Outcomes: rate of change of Appel ALS & SIP (QOL).

**Paper 3**
A 730-patient 9-month double-blind placebo-controlled triple arm trial of rhCNTF (15ug/kg, 30ug/kg, placebo three times per week) using slope of decline of isometric muscle strength, mortality, PFT, subjective score, GCIC, and functional tests for assessment.

**Paper 4**
A 12-patient 72-hour double-blind placebo-controlled cross-over trial of 2 doses and delivery routes of TRH (SC TRH 150mg, IV TRH 150 mg). Outcomes: motor and functional assessment.

**Paper 5**
A 30-patient placebo-controlled trial of TRH (150mg IM). Outcome: strength, PFTs, function.

**Paper 6**
A 16-patient 3-month placebo-controlled cross-over trial with acute TRH (IV 500mg) and chronic TRH (SC 25mg). Outcome: quantitative functional assessment.

**Paper 7**
A 7-patient 12-week placebo-controlled cross-over trial of TRH 4mg/day IM. Outcome: bulbar function, limb function, subjective scoring.

**Data and interpretation:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcome</th>
<th>high dose rhIGF-I</th>
<th>P</th>
<th>low dose rhIGF-I</th>
<th>P</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borasio</td>
<td>rate of change in A-ALS score</td>
<td>2.4 +/- 0.2pts/mo</td>
<td>P=0.22</td>
<td>NA</td>
<td>NA</td>
<td>2.8 +/- 0.3pts/mo</td>
</tr>
<tr>
<td>Author</td>
<td>Result of rHCNTF Trials</td>
<td></td>
<td></td>
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<tr>
<td>--------------------------------</td>
<td>----------------------------------------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>ALS CNTF Study Group</td>
<td>Neither high (30ug/kg) nor low (0.15ug/kg) doses showed any significant differences from placebo</td>
<td></td>
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<table>
<thead>
<tr>
<th>Author</th>
<th>Result of TRH Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imoto</td>
<td>No significant differences from placebo</td>
</tr>
<tr>
<td>Mitsumoto</td>
<td>Both acute (IV) and chronic (SC) TRH: no significant differences from placebo</td>
</tr>
<tr>
<td>Brooke</td>
<td>No significant differences from placebo</td>
</tr>
<tr>
<td>Caroscio</td>
<td>Both IV 500mg and SC 150mg TRH: no significant differences from placebo</td>
</tr>
</tbody>
</table>

### Outcome (Ref 2)

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>rhIGF-I</th>
<th>ARR</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>% not progressing to protocol termination criteria (0.1mg (high) VS placebo)</td>
<td>68%</td>
<td>83%</td>
<td>15%</td>
<td>7</td>
<td>4 - 33</td>
</tr>
<tr>
<td>% not deteriorating 20 points in the A-ALS scale (0.1mg (high) VS placebo)</td>
<td>48%</td>
<td>30%</td>
<td>18%</td>
<td>6</td>
<td>3 - 25</td>
</tr>
<tr>
<td>% surviving 30 months (high+low dose VS placebo)</td>
<td>26%</td>
<td>38%</td>
<td>12%</td>
<td>8</td>
<td>4 - ¥</td>
</tr>
</tbody>
</table>

### Comments:

*Paper 1 (Class 1b):* Methodologically valid therapeutic study.
*Paper 2 (Class 1b):* Methodologically valid therapeutic study. Only 53% patients completed trial.
*Paper 3 (Class 1b):* Methodologically valid therapeutic study, but 2.6 times as many patients in the high dose group dropped out as in the low dose or placebo groups.
*Paper 4 (Class 2b):* Not all patients were adequately accounted for at conclusion. Blinding was lost secondary to obvious side effects with TRH. Inappropriate use of cross-over design.
*Paper 5 (Class 1b):* Blinding lost secondary to obvious side effects with TRH.
*Paper 6 (Class 2b):* Not all patients were adequately accounted for at conclusion. Blinding was lost secondary to obvious side effects with TRH. Inappropriate use of cross-over design.
*Paper 7 (Class 2b):* Not all patients were adequately accounted for at conclusion. Insufficient detail of patient groups at baseline to judge similarity. Inappropriate use of cross-over design.

### References:

5. Brooke MH et al Controlled trial of thyrotropin releasing hormone in amyotrophic lateral sclerosis Neurology 1986;36:146-151

Key Words: ALS/rhIGF-I/rhCNTF/TRH/therapy

Appraiser: Bart Demaerschalk and the UWO Evidence Based Neurology Group

Date appraised: April 1999