SIGNS domain: Measuring responsiveness & MCID of TIS

Mandy Schram, MD PhD
Aim

To demonstrate the responsiveness and minimal clinically important difference of “Three Item Severity” (TIS) score.
Earlier:

EASI, (objective) SCORAD and POEM

Three Item Severity scale

Sumscore of:
- Erythema (0-3)
- Oedema (0-3)
- Excoriations (0-3)

- At a representative lesion
Data from three trials

- **MAcAD**: methotrexate versus azathioprine in adult patients with atopic eczema (M.E. Schram/Ph.I. Spuls)

- **PROVE**: cyclosporin versus prednisolone in adult patients with atopic eczema (J. Schmitt)

- **SWET**: softened water versus non-softened water on severity of eczema in children (K. Thomas)
Responsiveness

• Synonym: sensitivity to change

• Definition: the ability of an outcome measure to detect change over time

• How was it measured:
  – Global: correlation with reference test
  – Receiver operating characteristics (ROC)/Area Under the Curve (AUC)
Reference test

• How to decide if a patient has changed in disease severity or not?
• Preferably: transitional scale
• MAcAD & PROVE: Investigator global assessment (0-5)
• SWET: Bother score (0-10)
Global responsiveness - PROVE

TIS PROVE

Mean TIS score

Mean IGA score

Time (weeks)

PROVE Pred TIS
PROVE Ciclo TIS
PROVE Pred IGA
PROVE Ciclo IGA
Global responsiveness - MAcAD

![Graph showing the global responsiveness of MAcAD over time. The graph compares different treatments: MAcAD MTX TIS, MAcAD AZA TIS, MAcAD MTX IGA, and MAcAD AZA IGA. The y-axis represents the mean TIS score, while the x-axis represents time in weeks.]
Global responsiveness - SWET

![Graph showing TIS SWET over time](image)
Responsiveness ROC – MAcAD/PROVE & SWET
## Responsiveness ROC – MAcAD/PROVE & SWET

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
<th>Cut-off</th>
<th>Sensitivity%*</th>
<th>Specificity%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORAD</td>
<td>0.70</td>
<td>0.61 - 0.78</td>
<td>4.05</td>
<td>64.7</td>
<td>64.2</td>
</tr>
<tr>
<td>Objective SCORAD</td>
<td>0.73</td>
<td>0.70 - 0.77</td>
<td>6.45</td>
<td>54.8</td>
<td>78.8</td>
</tr>
<tr>
<td>EASI</td>
<td>0.67</td>
<td>0.60 - 0.76</td>
<td>2.75</td>
<td>73.8</td>
<td>57.4</td>
</tr>
<tr>
<td>POEM</td>
<td>0.67</td>
<td>0.59 - 0.75</td>
<td>1.50</td>
<td>62.1</td>
<td>66.1</td>
</tr>
<tr>
<td><strong>TIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MAcAD/PROVE</strong></td>
<td><strong>0.71</strong></td>
<td><strong>0.64 - 0.76</strong></td>
<td><strong>0.5</strong></td>
<td><strong>67.5</strong></td>
<td><strong>67.0</strong></td>
</tr>
<tr>
<td><strong>SWET</strong></td>
<td><strong>0.57</strong></td>
<td><strong>0.51 - 0.63</strong></td>
<td><strong>0.5</strong></td>
<td><strong>52.3</strong></td>
<td><strong>61.7</strong></td>
</tr>
</tbody>
</table>

AUC; area under the curve, CI; confidence interval.

*Sensitivity and specificity reflect the highest correct classification for the cut-off value.*
Minimal clinically important difference

• Definition: the smallest change in an outcome measure that represents a clinically relevant difference in disease status

• How was it calculated:
  – Longitudinal: absolute changes within individuals
  – Sensitivity analyses: Cut-off point ROC
  – Brent & Altman (B&A) analyses/ Limits of agreement
### Longitudinal - MCID

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>RCT</th>
<th>Anchor (IGA)</th>
<th>N of obs.</th>
<th>Mean difference</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>MacAD &amp; PROVE</strong></td>
<td>5 -&gt; 4</td>
<td>8</td>
<td>1.25</td>
<td>0</td>
<td>2</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 -&gt; 3</td>
<td>48</td>
<td>1.06</td>
<td>-1</td>
<td>4</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 -&gt; 2</td>
<td>43</td>
<td>0.91</td>
<td>-2</td>
<td>3</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 -&gt; 1</td>
<td>17</td>
<td>1.00</td>
<td>-1</td>
<td>4</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 -&gt; 0</td>
<td>1</td>
<td>2.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>117</td>
<td>1.02</td>
<td>-2</td>
<td>4</td>
<td>1.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>RCT</th>
<th>Anchor (Bother score)</th>
<th>N of obs.</th>
<th>Mean difference</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Swet</strong></td>
<td>9 -&gt; 8</td>
<td>9</td>
<td>0.78</td>
<td>0</td>
<td>1</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 -&gt; 7</td>
<td>4</td>
<td>0.75</td>
<td>0</td>
<td>2</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 -&gt; 6</td>
<td>16</td>
<td>0.87</td>
<td>-2</td>
<td>4</td>
<td>1.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 -&gt; 5</td>
<td>24</td>
<td>0.63</td>
<td>-3</td>
<td>3</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 -&gt; 4</td>
<td>24</td>
<td>0.58</td>
<td>-3</td>
<td>3</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 -&gt; 3</td>
<td>25</td>
<td>0.52</td>
<td>-2</td>
<td>5</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 -&gt; 2</td>
<td>27</td>
<td>0.33</td>
<td>-2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 -&gt; 1</td>
<td>14</td>
<td>1.07</td>
<td>-1</td>
<td>3</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 -&gt; 0</td>
<td>6</td>
<td>0.33</td>
<td>-3</td>
<td>5</td>
<td>1.35</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>149</td>
<td>0.62</td>
<td>-3</td>
<td>5</td>
<td>1.354</td>
</tr>
</tbody>
</table>
B&A – MAcAD & Prove
Overview of results

• Responsibility:
  – AUC 0.71 (95% CI 0.64-0.76) in MAcAD and PROVE data,
  – AUC 0.57 (85% CI 0.51-0.63) in SWET data

• MCID:
  – MAcAD/ PROVE: 1.02 (SD 1.21)
  – SWET: 0.62 (SD 1.36)
Discussion

- We did not use a transitional scale
- The IGA was not performed in the SWET
- TIS was calculated from SCORAD scores used in the MAcAD & PROVE

- Nevertheless, the TIS does seems fairly responsive

- Does anybody have usable trialdata?
Aknowledgement

HOME

Phyllis Spuls
Kim Thomas
Jochen Schmitt