Measurement Issues in Short Term Clinical Trials

Brian Healy, PhD
Overview

- In order to identify treatment effects or predictors of disease course, measurement of disease course is required.

- Although this sounds straightforward, measurement of disease worsening is challenging in several neurological diseases.
  - For clinical trials, we require measures that change in the short term.
  - For phase II trials, surrogate markers are desirable.
Common themes

- Multiple outcome measures
  - MS: relapses, EDSS
  - ALS: ALSFRS, death
  - Parkinson’s: Multiple scales

- Multiple mechanisms of action for treatment
  - MS: Reduce relapse rate (anti-inflammatory) or reduce disease worsening (neuroprotective)
  - Parkinson’s: Symptomatic or neuroprotective

- Surrogate markers
  - MS: Neuroimaging, biomarkers
Multiple sclerosis

In the first talk, the challenges associated with measuring neurodegeneration over the short term will be discussed:

- Measurement of disease worsening over the long-term in MS has defined endpoints, but short-term surrogate measures have performed poorly:
  - Typical trials not long enough to measure outcome of interest
- Treatment effects on inflammation have been shown, but measures for neurodegeneration are uncertain
In the second talk, the challenges associated with measuring neurodegeneration in a clinical trial will be discussed.

- Symptomatic vs. neuroprotective effects
  - Modern trial design can distinguish between these two types of effects

- Rescue therapy
  - Subjects who experience specific events are given rescue therapy
  - Simple treatment vs. placebo comparisons may be inappropriate
Questions

- How can we improve measurement of all aspects of the disease?
- Can changes in trial design, outcome, or analysis allow us to measure the parts of the disease we are most interested in?
- Can we identify surrogate markers that allow measurement of treatment effect in short duration studies?
Measurement Issues in Short Term Clinical Trials of Multiple Sclerosis

Brian Healy, PhD
I receive research support from Merck Serono and Novartis
Outline

- Background
  - Outcome measures for MS

- Measurement of neurodegeneration
  - Long-term vs. short-term
  - Confirmed (sustained) disease progression
  - Sample size considerations
  - MRI outcomes
Background

- MS is the most common neurologic disease among young people
- The typical disease course for over 80% of subjects is to start with a relapsing-remitting course (inflammatory phase)
- After inflammatory phase, patients have more steady disease worsening (neurodegenerative phase)
Outcome measures

- **Inflammatory**
  - Clinical: Relapse
  - MRI: Gadolinium enhancing lesions, new T2 lesions
    - Relationship between these is strong

- **Neurodegeneration**
  - Clinical: Expanded disability status scale (EDSS) landmarks (EDSS=6), Confirmed worsening on EDSS
  - MRI: Brain atrophy
    - Relationship between these is weaker

- **Disability**
  - EDSS
Neurodegeneration

Despite the availability of and proven effectiveness of treatments, uncertainty remains about the impact of the treatments on neurodegeneration

- How do we measure neurodegeneration in a short duration trial?
  - How do our present definitions perform?
- Does the analysis approach/outcome measure change the power to detect a treatment effect?
- Are alternative outcome measures better?
Expanded disability status scale (EDSS) is a 0-10 ordinal scale with 0.5 unit steps

- At the low end of the scale, the EDSS combines information from 7 functional system scales to calculate the EDSS score
- At the higher end of the scale, the EDSS is largely determined by the walking score for the patient
- Changes in EDSS are small over the short term

EDSS score is most commonly used measure of disability by neurologists
Measuring neurodegeneration-
long term

- Long-term natural history studies have identified important disease landmarks
- EDSS=6
  - Requires assistance to walk
  - When a patient reaches this level, it is generally assumed that they have reached the progressive phase of the disease
- Even though this is a well defined landmark, the median time to EDSS=6 in our sample is over 25 years
  - Not a practical endpoint for clinical trials
  - Even in long term follow-up studies, this is not observed sufficiently often
Although the EDSS provides a measure of disability, change in EDSS does not directly provide a measure of neurodegeneration.

– EDSS is elevated during a relapse because disability has increased even though patient may recover.

– To address this limitation, the most common measure in clinical trials is to require the increase on the EDSS to be confirmed for a specific amount of time.

– Idea is that if the EDSS is elevated for more than one time point, the increase on the EDSS is a true measure of disease worsening.
Confirmed (sustained) disease progression

- Most common definition
  - Increase on the EDSS of at least 1 point confirmed for 3 or 6 months for subjects with baseline EDSS<5.5
  - Increase of at least 0.5 point confirmed for 3 or 6 months for subjects with baseline EDSS>=5.5

- Sometimes, an additional caveat is added that the increase on the EDSS must be at least 1.5 points for subjects with baseline EDSS=0

- No single definition is used in all trials/studies
Is sustained progression truly sustained?

- Even though a reasonable number of subjects experience sustained progression, more than half fail to maintain the sustained progression (Healy et al, 2013)

- Interpretation: Not truly irreversible disability

<table>
<thead>
<tr>
<th>EDSS</th>
<th>Patients with sustained progression</th>
<th>Patient with sustained progression and subsequent visits</th>
<th>Patients who always progressed among those with subsequent visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D1) Increase of 0.5</td>
<td>392</td>
<td>15</td>
<td>137</td>
</tr>
<tr>
<td>(D2) Increase of 1</td>
<td>278</td>
<td>25</td>
<td>98</td>
</tr>
<tr>
<td>(D3) Increase of 1.5</td>
<td>147</td>
<td>20</td>
<td>61</td>
</tr>
<tr>
<td>(D4) Increase of 1/ increase 1.5 for baseline EDSS=0</td>
<td>212</td>
<td>169</td>
<td>73</td>
</tr>
</tbody>
</table>
Functional scales

- As described previously, the EDSS in the low end of the scale is determined based on the functional system scales

- One potential explanation for the poor performance of sustained progression on the EDSS is that by combining across the functional scales, we are losing information

- To assess whether we could just switch to the functional scales, we performed a similar set of analyses

- Using FS scales failed to identify irreversible disease progression
  - Much less than 50% of subjects maintained progression
Recommenda\ons

Lublin et al (2014) proposed changing the definitions of MS disease categories and states to clarify some of the terms

- Change from sustained disease progression to confirmed disease worsening will lead to better understanding of changes in patients

Although these changes in terms reduce confusion regarding what is measured, these do not necessarily improve measurement of neurodegeneration

- Alternative analysis approaches using available outcomes
- Alternative outcome measures
Although confirmed disease worsening solved one problem (transient increases on the EDSS), it introduces a couple of new problems:

- Confirmed disease worsening is a dichotomous variable so the amount of change is ignored.
- Fails to incorporate any improvement on the EDSS.
- Unequal likelihood of changing disease state is not incorporated into the model.
Comparison of approaches

Given the potential problems associated with confirmed progression, six analysis approaches were compared in terms of power for a 2 year clinical trial (Healy et al 2011)

- Logistic regression for confirmed progression
- Cox model for time to confirmed progression
- Stratified Wilcoxon test (van Elteren’s test)
- Repeated measures proportional odds model (GEE)
- Markov transition model

Results showed that analyses based on confirmed progression had least power

- Alternative analysis approaches could improve power even if no change to the measurement was made
Could we develop an alternative measure of disability to better measure changes in disability/neurodegeneration?

Challenge: Must develop a measure that is highly correlated with the EDSS

Clinical
- MSFC
- Other scales in development

MRI
- Whole brain atrophy
- Gray matter atrophy
- Spinal cord atrophy
Multiple sclerosis functional composite (MSFC)

- MSFC was developed as an alternative measure of disability that combined three components:
  - Timed 25 foot walk (Walking function)
  - 9 hole peg test (Hand function)
  - Paced Auditory Serial Addition Test (cognitive function)
- Scores from each component are normalized and summed using equal weights.

\[ MSFC = z_{T25FW} + z_{9HPT} + z_{PASAT} \]
MSFC

Pro

- Easy to deal with statistically
- More powerful than sustained progression

Con

- Uncertain clinical meaning
  - Cautionary tale regarding making new outcome measure
- Lengthy to administer (limited the use of the scale in the clinic)
Atrophy measures

- Phase II studies in MS use MRI measures of inflammation to reduce sample size required to detect treatment effect

- Several studies have investigated the sample size considerations for clinical trials using atrophy as a measure
  - Healy et al (2009) investigated whether gray matter atrophy might provide power advantages over whole brain atrophy
  - Although trials have been designed with atrophy as a secondary outcome measure, atrophy is not the gold standard for neurodegeneration in early trials
Conclusions

Measurement of neurodegeneration is one of the major challenges in MS clinical trials.

Traditional short-term measure performs poorly.

Alternative analysis approaches and measures are available, but these have not become the standard in clinical trials.

Better approaches may lead to more success in identification of treatments for neurodegeneration.
<table>
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<tr>
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**THANK YOU**

to our

**CLIMB patients!**
References


