A Model-Based Meta-Analysis for Treatment-Modeled Disease Progression in Multiple Sclerosis.

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In this work, Biogen Inc. is contributing to the work.

Introduction

- Multiple sclerosis (MS) is an autoimmune disease characterized by distinct episodes of acute neurological worsening and formation of brain lesions on MRI (BRMs) followed by a secondary progressive state (SPMS).
- Biogen has over 15 years of clinical trial data for 5 drugs: natalizumab, dimethyl fumarate, peginterferon beta-1a, interferon beta-1a, and glatiramer acetate.
- In the short term, clinical and radiological outcomes often do not align in clinical practice, e.g.,
  - The Expanded Disability Status Scale (EDSS) is a common outcome for clinical trial data.
  - Annualized Relapse Rate (ARR) is the gold standard for relapsing-remitting MS trials.
  - MRI data (Gd+ T1 lesions, T2 lesions) is easily measured.
- The objective of this work was to extend a previous placebo-only disease progression model [1] to include treatment effects predicting long-term clinical outcomes from short-term MRI endpoints.

Methods

- Patient level data was used from 11 clinical trials (Table 1).
- A Bayesian latent variable model [2] was developed with (Figure 1):
  - Two latent variables: one latent variable corresponded to total disease burden and the other corresponded to short-term disease activity.
  - The disease burden latent variable was estimated as a linear function of time, with patient specific parameters (random effects).
  - The disease activity latent variable was a Gaussian process.
  - There was an (additive) treatment effect on the latent variables.
- Model evaluation focused on out-of-sample predictive performance, using a test set of held-out year-two data.
- The model was implemented in Stan using the default NIs-U-Turn Sampler with Hamiltonian Monte Carlo method [4].

Results

Table 1: Description of the 11 studies used in the modeling. Duration is summarized as mean (sd). There were 9 BRMs and 2 SPMS studies included. The studies included both phase 2 and phase 3 studies of a maximum of 2 years and phase 3 studies of approximately 2 years in duration. Some of the studies were placebo controlled and others used only active controls.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Duration in Years (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFTIM (C-1801)</td>
<td>2001</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>SENTINEL (C-1802)</td>
<td>2002</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>C-1803</td>
<td>2003</td>
<td>4.2 ± 0.1</td>
</tr>
<tr>
<td>C-1800</td>
<td>2004</td>
<td>6.8 ± 0.1</td>
</tr>
<tr>
<td>DEFINE (105MS301)</td>
<td>2007</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td>CONFORM (109MS302)</td>
<td>2007</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td>ADVANCE (105MS301)</td>
<td>2009</td>
<td>4.4 ± 0.1</td>
</tr>
<tr>
<td>ASCEND (101MS326)</td>
<td>2010</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>SENTINEL (101MS326)</td>
<td>2013</td>
<td>7.0 ± 0.1</td>
</tr>
<tr>
<td>EMD3005</td>
<td>2013</td>
<td>7.0 ± 0.1</td>
</tr>
<tr>
<td>EMD3008</td>
<td>2015</td>
<td>7.0 ± 0.1</td>
</tr>
</tbody>
</table>

Figure 3: Simulated year-two ARR for different observations at day 0. Default values were placebo arm, mean values of the covariates, female, T2 volume of 13 ml, 3/9 NE T2 lesion, and no lesions. The observed data was used to estimate subject level random effects, and the random effects were used to simulate year-two ARR. This simulation was not limited to day 0 and any plot of placeable observed values could have been used, e.g., certain outcomes at day 4, day 30, and 60.

Figure 4: Ensemble predictions of phase 3 ARR treatment effects were made from phase 2 published results, which showed good agreement with observed data. Phase 2-ARR, Gd+ T1 lesion count, and T2/NE/T2 lesion count were aggregated to make the phase 3 predictions. Interquartile are 80% prediction intervals.

Conclusions

- A Bayesian latent-variable model was developed that characterized placebo data and drug effects across studies, populations, outcomes, and drugs at an individual level.
- The model showed predictive validity of 2-year clinical endpoints (ARR) from 6 month MRI data and was able to predict phase 3 results using phase 2 summary data, leveraging multiple reported phase 2 endpoints in the literature.
- The model as a conceptual framework is extensible to include additional study data including clinical outcomes, MRI measures, and pharmacodynamic biomarkers.
- The model serves as the foundation for a platform to guide decision making for future phase II trials of novel compounds in MS.

References


Acknowledgements

This work was funded by Biogen Inc.