Use of Observational Data to Make Causal Inferences About Treatment Decisions in Multiple Sclerosis

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Disclosures

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Outline

- **Background**
  - Treatment options in MS
  - Remaining clinical questions

- **Approaches used for causal inference with examples**
  - Propensity score matching
  - Inverse probability weighting
In the initial stage of the disease, patients experience relapses.

In the second phase of the disease, patients experience progressive worsening of the disease.

Both clinical and MRI measures of each phase are available.
Eleven FDA approved treatments are available.

These treatments have generally been approved because of a reduction in the relapse rate.

Several additional treatments are in phase III trials.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
<th>Treatment</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b (Betaseron)</td>
<td>1993</td>
<td>Interferon beta-1b (Extavia)</td>
<td>2009</td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex)</td>
<td>1996</td>
<td>Fingolimod (Gilenya)</td>
<td>2010</td>
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<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>1996</td>
<td>Teriflunomide (Aubagio)</td>
<td>2012</td>
</tr>
<tr>
<td>Mitoxantrone (Novantone)</td>
<td>2000</td>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>2013</td>
</tr>
<tr>
<td>Interferon beta-1a (Rebif)</td>
<td>2002</td>
<td>Peginterferon beta-1a (Plegridy)</td>
<td>2014</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>2006</td>
<td></td>
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RCT results

- Despite the large number of subjects who have participated in trials, RCTs provide direct information about a relatively small number of the possible treatment comparisons or treatment decision points
  - Most clinical trials have compared a treatment to placebo so active treatment comparisons are limited
  - Many possible treatment decision points are not evaluated in clinical trials
  - Trials also provide only indirect information about long-term treatment effects
What we know

- Treatment with the agents from the previous slide reduce the relapse rate/time to next relapse
  - All treatments also have an impact on GD+ lesions
  - The treatments are reducing the inflammatory component of the disease

- In some case, treatment reduces the time to sustained disability accumulation

- Some head-to-head treatment comparisons have been completed
  - Several studies have shown limited differences between GA and forms of IFN-β
Several important questions remain unanswered

- Treatment comparisons
  - How does the efficacy of the available treatments compare in the absence of direct RCT comparison?
  - What is the impact of the treatment on long-term disability accumulation?

- Treatment decision points
  - Should treatment be changed after a relapse?

None of these questions will be addressed in a RCT so alternative methods are required.
Comparison of treatments: Combination of trial results

- One approach to address the treatment comparisons is to combine the information from the available clinical trials.

- Two recent papers have combined information across multiple trials to assess treatment comparisons not directly available in trials:
  - Indirect meta-analysis: Roskell et al.
    - Comparison of fingolimod and first line treatments
  - Network analysis: Zintzaras et al.
    - Comparison of all potential treatment comparisons
    - Requires many indirect comparisons

- Despite these results, the comparison of treatments outside of a clinical trial setting is desirable.
Comparison of treatments: Observational data

- One key question at present is whether subjects should choose fingolimod or natalizumab
  - Each of these treatments are considered second line treatments
  - No trial has compared these treatments
  - Based on the trial data, natalizumab had a greater difference relative to placebo
  - Natalizumab leads to PML in a small number of subjects who are JC virus positive

- Several recent papers have investigated this question using causal inference approaches
Considerations

- When using observational data to make inferences about treatment comparisons, several considerations are needed
  - Patient selection
    - The choice of the subject selection can impact the validity and generalizability of the findings
    - All available vs. Specific inclusion/exclusion criteria
  - Statistical methods
    - Since the two treatment groups are not balanced, adjustment for group differences are required
    - Propensity scores
    - Inverse probability weighting
Two studies

- Two recent studies have investigated this question
  - Braude et al
    - Subject selection: All available patients
    - Statistical approach: Propensity score stratification
  - Carruthers et al
    - Subject selection: Subjects who used JC virus serology for the choice of the treatment
    - Statistical approach: Multivariate regression and inverse probability weighting

- Each of these studies provides important information about the treatment comparison
Treatment decision point: Changing treatment after a relapse

- In addition to the head-to-head treatment comparisons, causal inference approaches applied to observational datasets provide the opportunity to assess treatment decision points
  - MS physicians are faced with many potential treatment decision points over the course of the disease
  - Example: Should a patient who is being treated change to a new treatment after a single relapse?
Using the causal inference framework, observational data from the CLIMB was selected to mimic the equivalent clinical trial

- Patient selection: Patients who had a relapse after initiation of glatiramer acetate
- Treatment regimen: Subjects who changed to a new treatment within 180 days were compared to subjects who remained on GA
- Statistical approach: Multivariate Cox model and inverse probability weighting to adjust for differences between groups

Results showed no significant benefit of changing to a new treatment after a single relapse (Healy et al, 2010)
Comparison of treatments: Long-term follow-up

Several studies have attempted to address the long-term benefit of disease modifying treatment.

These studies have two potential issues with regards to estimating the causal effect of a treatment:

- Choice of treatment at the beginning of the study can be confounded
  - Similar to previous examples
- Handling of changes in treatment
  - More complex because we have time dependent confounding
Approaches

- Estimate difference in treatment groups without accounting for changes after treatment initiation
  - Long-term follow-up studies of trials use this approach
  - Simplifies the analysis, but only addresses the causal effect of early vs. late initiation of treatment

- Censor subjects at the time of treatment change and inverse probability weight subjects who remain on treatment
  - This approach has been used less frequently, but it is beginning to be used
  - Estimates the parameter of most interest, but can suffer because a very small number of subjects remain on a treatment for many years if worsening
  - May work better if we switch to comparison of treatment regime
Conclusions

- Observational data provide the only source of information regarding important clinical questions in MS
  - The number of clinical questions is too large to have an RCT to address all potential comparisons
  - Many questions cannot be addressed due to challenges in completing the studies
- Research for applying these approaches and for combining indirect treatment comparisons from RCTs and observational data analysis are ongoing
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**THANK YOU to our CLIMB patients!**


