IDENTIFYING NON-RESPONDERS TO BRAKE THERAPIES IN MULTIPLE SCLEROSIS USING ADVANCED PREDICTIVE MODELS

INTRODUCTION

- Disease modifying drugs such as interferons and glatiramer acetate collectively known as BRAKE therapies can reduce multiple sclerosis (MS) relapse and progression (with Repertory Relaxation Multiple Sclerosis (RRMS) BRAKE therapies include Betaseron® [Interferon Beta-1a, Rebif® (interferon beta-1a), Gilenya® (fingolimod), and Copaxone® (glatiramer acetate)])
- Approximately, 53% of Multiple Sclerosis (MS) patients may not respond to these treatments and a lengthy follow-up may be required to ascertain the response status. This may be a delay in administration of other treatment options
- There is limited evidence on the predictors of non-response to BRAKE treatments for patients with RRMS
- Consequently, little is known about which types of RRMS patients may be the best candidates for switching to second-line treatment
- Logistic regression analysis with Lasso could be used to predict non-responsiveness to BRAKE therapies. Since this determination of non-response is unknown a priori and different types of models are more appropriate for different settings, there is a need to test, compare alternative approaches and select the best method in a systematic and scientific way

Study design

- The objectives of this study were:
  - To explore the applicability of novel analytical methods at identifying treatment effect heterogeneity i.e. differences in response to BRAKE therapy amongst different types of RRMS patients
  - To select the best method in a systematic and scientific way

Materials and methods

- This was a retrospective database analysis using administrative health plan claims data. This included medical and pharmacy data from the IMS PharMetrics Plus Database from the US which was accessed through the MS Value and Evidence in Real World (MSVERW) platform developed by Novartis
- The index window was 1 January 2007 to 31 March 2012 and months two continuous enrolment both pre-index and post-index was required

Study population

- The study population comprised of patients who had at least one diagnosis of MS in the pre-index period (ICD-9-CM: 340) in the pre-index period
- Patients with RRMS who had at least one pre-index relapse and no post-index relapse were considered to be “BRAKE responders”, whereas patients who had at least one pre-index relapse and at least one post-index relapse were considered to be “BRAKE non-responders” (Table 2)
- Approximately, 51.8% of patients were BRACE responders

Data analysis

- Different range of models were applied to predict the outcome of interest as each model has different properties and makes extensive use of random sampling of both observations and predictors
- A diverse range of binary classification models were estimated
  - Standard logistic regression: Standard logistic regression is appropriate where the dependent outcome variable is categorical and it allows us to generate insights on which attributes are more or less likely to predict an event
  - Logistic regression with Least Absolute Shrinkage and Selection Operator (Lasso): Logistic regression with Lasso if appropriate. A regression-based approach is preferred and one feature may be selected
  - Random Forests: Random Forests is an ensemble approach (based on many decision trees) and makes extensive use of random sampling of both observations and predictors
- The study included 3,668 patients that comprised 1,767 responders and 1,902 non-responders, indicating a 51.6% non-response rate. Patients who had at least one pre-index relapse and no post-index relapse were considered to be BRAKE responders, whereas patients who had at least one pre-index relapse and at least one post-index relapse were considered to be BRAKE non-responders (Table 2)

RESULTS

- The study included 3,668 patients that comprised 1,767 responders and 1,902 non-responders, indicating a 51.6% non-response rate. Patients who had at least one pre-index relapse and no post-index relapse were considered to be BRAKE responders, whereas patients who had at least one pre-index relapse and at least one post-index relapse were considered to be BRAKE non-responders (Table 2)
- Approximately, half of the patient population was aged between 34 and 50 and a large proportion (77%) of patients were females (Table 2)
- Approximately, 53% of patients switched from no pre-index MS treatment to an interferon drug, 25% from an interferon drug to glatiramer acetate and 22% from a glatiramer acetate to another interferon (Table 2)

Selection of model and model performance

- Model selection was based on several criteria, including maximizing out-of-sample accuracy, model stability, familiarity with choice of method and minimizing overfitting (Table 4)

CONCLUSIONS

- The study concluded that patients were less likely to respond to BRAKE treatment if they were young and/or had active disease
- No single model has optimal performance according to all criteria and the more advanced models did not yield to markedly improved performance compared to standard logistic regression
- Logistic regression with Lasso penalty was selected as the preferred model and it was able to discriminate between those who are likely to respond and those who do not respond to BRAKE therapy
- The study concluded that logistic regression model and LASSO feature selection are more appropriate for different settings, there is a need to test, compare alternative approaches and select the best method in a systematic and scientific way

REFERENCES

4. Nurmohamed MT, Saad A, O’Sullivan MJ, Vermeulen M, Kassam A, Jones SE, et al. Repertory Relaxation Multiple Sclerosis (RRMS) Brake therapies include Betaseron® (interferon beta-1a, rebif® [interferon beta-1a], Gilenya® (fingolimod), and Copaxone® (glatiramer acetate)).

Figure 2

Logistic Regression with Lasso was selected as the preferred model as it had reasonable out-of-sample accuracy

Approximately, 73.5% of patients in the highest quintile group did not respond to BRACE therapy

This was a retrospective database analysis using administrative health plan claims data. This included medical and pharmacy data from the IMS PharMetrics Plus Database from the US which was accessed through the MS Value and Evidence in Real World (MSVERW) platform developed by Novartis

Models were optimized based on the Area Under the Curve (AUC) computed using internal tenfold cross-validation

Approximately, 42.8% and 33.1% of patients switched from no pre-index MS treatment to an interferon drug, 25% from an interferon drug to glatiramer acetate and 22% from a glatiramer acetate to another interferon

Table 2

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<td>≥ 1 diagnosis of MS (ICD-9-CM: 340) in the pre-index period</td>
<td>Receipt of more than one MS DMT on the index date</td>
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<td>A minimum of 12 months of continuous health plan enrolment prior to the index date</td>
<td>Evidence of greater than or equal to 1 relapse in the one year prior to the index date</td>
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<td>Inclusion criteria: Exclusion criteria</td>
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Table 3

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<th>Model Type</th>
<th>AUC on training</th>
<th>SD of AUC on training</th>
<th>AUC on test</th>
<th>SD of AUC on test</th>
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<tbody>
<tr>
<td>Logistic regression</td>
<td>67.9</td>
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<td>62.3</td>
<td>1.6</td>
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<td>Lasso logistic</td>
<td>66.8</td>
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<td>Random Forests</td>
<td>74.1</td>
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<td>70.6</td>
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Table 5

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<tr>
<th>Model Type</th>
<th>AUC on training</th>
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The model ability to discriminate BRACE responders and Non-responders

- Approximately, 75.0% of patients in the study did not respond to BRAKE therapy compared to 30.6% in the group who were more likely to respond according to baseline characteristics, which is a major improvement from the logistic regression with Lasso (Table 5) and Figure 2 shows the patients’ characteristics associated with being more likely to be BRACE non-responders

CONCLUSIONS

- The study concluded that patients were less likely to respond to BRAKE treatment if they were young and/or had active disease
- No single model has optimal performance according to all criteria and the more advanced models did not yield to markedly improved performance compared to standard logistic regression
- Logistic regression with Lasso penalty was selected as the preferred model and it was able to discriminate between those who are likely to respond and those who do not respond to BRAKE therapy
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REFERENCES