INTRODUCTION

Relapsing Repeated Multiple Sclerosis (RRMS) is a chronic demyelinating, immune-mediated disease of the central nervous system characterized by remission and exacerbation of the myelin sheath covering of nerve fibres in the brain and spinal cord. RRMS is the most common type of MS and is characterized by unpredictable acute attacks (relapses) accompanied by worsening of symptoms. There is no cure for MS, however there exists a number of disease modifying therapies (DMTs) aimed at preventing and treating relapses, preventing new attacks, managing symptoms, slowing disease progression and preventing or prolonging long-term disability. Interferons (Betaseron®, Avonex®, Rebif®, Extavia®) and glatiramer acetate (Copaxone®) have been available since mid-1990s and are widely used DMTs for the treatment of MS and are known simply as the BRACE therapies. Since 2005 a number of new DMTs with different mechanisms of action, efficacy and safety profiles have been approved. These therapies are grouped into three broad categories according to common clinical practice: first-line BRACE therapies, second-line therapies (Glatiramer and TevaToc) and secondline therapies (Keprela® and Tysabri®).

The increased availability of disease modifying therapies for RRMS is placing a greater focus on clinicians to better understand likely disease activity in order to optimize treatment choice. It is important to understand whether routinely collected EMR data can be used to predict disease activity for RRMS patients since these predictions could potentially be used by clinicians to help improve treatment allocation and patient outcomes.

An assessment of available MS clinical decision-support tools and focus groups with clinicians were carried out as an initial part of this study to provide context, motivation and direction to the analysis. Amongst other things, this research confirmed unmet need for tools to support treatment optimization based on predictions of disease activity using real-world data and helped identify candidate covariates for modeling.

OBJECTIVE

To predict patient disease activity for a cohort of RRMS patients in Germany, both for a composite cohort and separate subcohorts grouped by treatment switch from initial BRACE therapy.

The long-term aspiration is to use results of the algorithm to develop a clinical decision-support tool to aid physicians in treatment choice and patient engagement.

DESIGN/ METHODS

Study Design:

This was a retrospective cohort study using Electronic Medical Records (EMR) data from the Neuro Trans Data (NTD) group of neurology practices in Germany for RRMS patients receiving BRACE therapy. Analysis was carried out for all RRMS patients (a composite cohort) as well as separately for four subgroups grouped by treatment pattern, creating a total of five cohorts for analysis: 1. BRACE continuation – patients continuing on the same initial BRACE treatment; 2. BRACE switch - patients switching from the initial BRACE therapy to a new BRACE therapy.

STUDY ASSESSMENTS

Disease activity, the outcome measure, was proxied by a binary outcome indicating whether a patient experienced a relapse over the twelve-month follow-up period. A relapse is defined as "Patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS (peripheral nervous system), current or historical, with duration of at least 24 hours, in the absence of fever or infection"3

Covariates included demographics, diagnostic history, treatment, disability status, disability history and cranial and spinal lesion counts

STATISTICAL ANALYSIS

Continuous and count covariates were dichotomized following clinical guidelines and/or inspection of the data, to capture non-linear associations whilst facilitating transparency on model parameters.

1. Logistic regression with elastic-net penalty was used to model relapse for each of the five cohorts
2. The Area Under the Curve (AUC) was used as the key performance metric, computed from left-out folds using cross-validation
3. Patients were assigned to risk bands based on quantiles of predicted probability of relapse, with the gradient of actual relapse by risk group used as a secondary performance metric.
4. Variables retained by the elastic-net regression were entered into a standard (unconstrained) logistic regression to compute odds ratios with associated p-values

RESULTS

The table below shows the number of patients in each cohort, along with the proportion experiencing a relapse. Relapse rates varied from 12.4% to 25.0%, the highest for the Composite cohort was 18.2%. These are unconditional means and take no account of differences in attributes by treatment group (confounding by indication)

For instance, patients switching to second-line treatment would be expected to be further advanced on average in their disease course than other patients and hence may experience higher relapse rates, even if second line treatment is more effective

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Area Under the Curve (AUC)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Cohort</td>
<td>0.69</td>
<td>[0.67, 0.71]</td>
</tr>
<tr>
<td>BRACE Continuation</td>
<td>0.70</td>
<td>[0.68, 0.72]</td>
</tr>
<tr>
<td>BRACE to BRACE</td>
<td>0.54</td>
<td>[0.47, 0.60]</td>
</tr>
<tr>
<td>BRACE to monotherapy</td>
<td>0.65</td>
<td>[0.57, 0.72]</td>
</tr>
<tr>
<td>BRACE to second line</td>
<td>0.55</td>
<td>[0.50, 0.60]</td>
</tr>
</tbody>
</table>

The graph below depicts the gradient of actual relapse by quintile of predicted relapse. The actual relapse rate for the highest risk group was 5.6 times higher than the lowest risk group (53.1% vs. 6.3%)