Natalizumab Extended Interval Dosing Is Associated with a Reduction in Progressive Multifocal Leukoencephalopathy Risk in the TOUCH® Registry

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Conclusions

This study demonstrates that extended interval dosing (EID), as defined here, is associated with a clinically and statistically significant lower risk of progressive multiforme leukoencephalopathy (PML) than standard interval dosing (SID) in anti-JCV (JCVI) antibody positive patients.

Methods

Teva; NC, IC, ER, ZR, BY, CH, P-RH: employees of and own stock and/or stock options in Biogen; IK: has served on advisory boards with Biogen; TS: Shaw Health Research Institute, University of Toronto, is supported by a Shaw Foundation Career Investigator Award; ALL, VV: Biogen employees; DL, BC: Shaw Health Research Institute, University of Toronto, NINDS, NHLBI (Protocol LB250).

Results

Patients – TOUCH Prescribing Program data as of June 1, 2017, were used for this analysis. – This analysis included only patients who were anti-JCV antibody positive. – Patients with any dosing interval ≥12 weeks or <3 weeks were not included.

Dosing definitions – SID and EID were defined and the statistical analysis plan was finalized before the start of the TOUCH Program (January 1, 2014). – SID was defined as >10 infusions/year based on the total number of infusions in the prior 365 days. – EID was defined as ≤10 infusions/year based on the total number of infusions in the prior 365 days. – Baseline demographics were well balanced across dosing groups (Table 1).

Natural history exposure – The number of natalizumab infusions and total duration of natalizumab treatment were higher in the EID groups than in the SID groups with all 3 definitions (Table 1).

Primary definition

In the first 4 years of treatment, only a PML case was observed for EID (with the secondary definition), in years 5 and 6, PML risk was substantially lower for EID than for SID across all 3 definitions (Table 2; data for the tertiary definition are not shown, as no EID cases were observed).

Secondary definition

Cox regression analysis revealed a 94% reduction in PML risk with EID versus SID in the primary analysis and an 88% reduction in the risk in the secondary analysis (both P<0.001; Figure 3A–B). – Cox regression analysis could not be performed for the tertiary definition, as there were no EID cases observed.

The finding is supported by LRF analyses, which demonstrate significantly lower cumulative risk of PML for EID patients than for SID patients with each definition (Figure 3C–F). – Data on anti-JCV antibody index are not captured in TOUCH and therefore could not be included as a covariate in the Cox regression analysis.

Limitations

– The definitions of EID may have potential biases: – Bias that could lead to more PML cases in the EID cohort: EID patients had a greater reason for dose delay than SID patients. – Bias that could lead to fewer PML cases in the EID cohort: there may have been a selection bias, as those patients treated longer without developing PML before subsequently being placed on EID. – TOUCHe do not include effectiveness data; therefore, the relative effectiveness of EID and SID were not compared.

Table 1. Baseline characteristics, natural history exposure, and AIDs across the 3 definitions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary definition mean ± SD (n=13,122)</th>
<th>Secondary definition mean ± SD (n=13,122)</th>
<th>Tertiary definition mean ± SD (n=13,122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45.6 ± 15.8 (13,122)</td>
<td>45.6 ± 15.8 (13,122)</td>
<td>45.6 ± 15.8 (13,122)</td>
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<tr>
<td>Prior immunosuppression, %</td>
<td>689 (9)</td>
<td>689 (9)</td>
<td>689 (9)</td>
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<tr>
<td>Median number of natalizumab infusions, min (max)</td>
<td>50.0 (13,122)</td>
<td>40.0 (13,122)</td>
<td>40.0 (13,122)</td>
</tr>
<tr>
<td>Median duration of natalizumab treatment (min, max), months</td>
<td>50.0 (13,122)</td>
<td>40.0 (13,122)</td>
<td>40.0 (13,122)</td>
</tr>
<tr>
<td>AED, days</td>
<td>3.3 ± 3.9</td>
<td>3.3 ± 3.9</td>
<td>3.3 ± 3.9</td>
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<tr>
<td>Mean (SD)</td>
<td>30.7 (9.4)</td>
<td>30.1 (1.6)</td>
<td>30.0 (1.6)</td>
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