Rituximab in secondary-progressive MS: A two-year retrospective analysis

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Background

- Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation-driven demyelination of the CNS. Secondary-progressive MS (SPMS) develops from the relapse-remitting form with progressive worsening of baseline or without the presence of relapses.¹
- While many immunomodulatory and immunosuppressive drugs have been used to treat SPMS, management has been difficult and mitoxantrone remains the only FDA-approved treatment.² This drug, however, has severe adverse effects of bone marrow suppression, cardiotoxicity, and leukemia which complicate its use.³
- With oligoclonal IgG implicating a role of B cells in MS, studies have identified leptomeningeal B cells adjacent to cortical lesions in SPMS as well as elements of a microenvironment supporting their development, such as the B-cell attracting chemokine CXCL13.⁴ Cells comprising these follicles have demonstrated CD5+ T cells, CD20+ B cells, CD138+ plasma cells, CD68+ macrophages and large perivascular B-cell aggregates, all contributing to more severe inflammation and demyelination.⁵,⁶,⁷
- Thus, depletion of B cells has therapeutic potential to reduce the severity of MS and other autoimmune diseases. Rituximab is a chimeric anti-CD20 antibody, capable of selectively depleting developing, naïve, and memory B cells.⁸ To date, rituximab use in case reports of primary- and secondary-progressive MS have been encouraging.⁹,¹⁰ Phase I and Phase II trials in relapse-remitting MS have also shown improvement.¹¹,¹²

In this study, we examine the therapeutic effect of rituximab in SPMS patients following poor responses to traditional therapies.

Methods

- This retrospective analysis was conducted by chart review of SPMS patients receiving treatment of rituximab at the University of Massachusetts Memorial MS Center.
- Inclusion criteria for this study: 1) Diagnosis of SPMS, 2) At least two cycles (1g rituximab IV, two weeks apart) of rituximab therapy, 3) Records of all primary outcomes for each patient time point analyzed in a patient's clinical course to facilitate a within-subjects design.
- 26 patients, 11 men and 15 women with a mean age of 57 years and an average disease duration of 12 years, met the inclusion criteria.
- All patients were evaluated on clinical measures of EDSS, 25-foot walk, and modified 9-hole peg test. Approach to analysis of these values was two-fold. First, relative to rituximab, measures at two years and one year prior to therapy, at treatment initiation, and at two subsequent treatments formulated a temporal analysis to observe the degree of progression before and following rituximab therapy. Second, rituximab was compared to prior therapies in a treatment-based analysis to determine relative effectiveness in controlling progression.
- MRI data was used to monitor safety of the treatments. Any adverse reactions were also noted such as infections and changes in therapies.
- Statistical analysis: The difference in EDSS score, nine-hole-peg test time, and 25-ft walk time between each interval or treatment period was computed for each patient. The mean score differences across all patients for specified time periods or treatments were compared using a two-tailed t-test. Significant results exhibited a p < .05 and were marked by an asterisk.

Results

- Figure 1: Progression of SPMS before and after rituximab treatment. SPMS patients demonstrated significant worsening for the EDSS outcome through a full year prior to the treatment induction. Once treatment was initiated, reduction in the rate of progression was observed with each subsequent treatment of rituximab, suggesting an intervention capable of stabilizing SPMS. Rituximab, comparing with other therapies, is shown to be effective in SPMS patients following poor responses to traditional therapies.

Table 1: Different therapies in SPMS. Most patients with SPMS had already been placed on a disease-modifying therapy (Avonex, Copaxone, or Rebi), for which they experienced breakthrough in transitioning from RRMS to SPMS. Other second-line agents such as chemotherapeutics and immunosuppressants were also prescribed to many patients. The table indicates the spectrum of medications that SPMS patients failed before considering rituximab.

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Number of Patients who failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex</td>
<td>20</td>
</tr>
<tr>
<td>Copaxone</td>
<td>10</td>
</tr>
<tr>
<td>Rebi</td>
<td>2</td>
</tr>
<tr>
<td>Cellept</td>
<td>12</td>
</tr>
<tr>
<td>Cytophosphamide</td>
<td>8</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2</td>
</tr>
</tbody>
</table>

Conclusions

- While statistically significant increases in EDSS were present for a variety of drug regimens before rituximab therapy, treatment with rituximab in patients with SPMS decreased the rate of progression. Moreover, the increase in EDSS that occurred during progression was reduced to a greater extent with each subsequent treatment.
- Comparison of the different drug regimens across EDSS, 25-ft walk, and nine-hole peg test demonstrated that rituximab was capable of maintaining baseline measurements.
- Extrapolations from baseline changes prior to therapy revealed improvements across all three clinical outcomes, most notably EDSS. While no nine-hole peg test, when comparing projected to observed values for subsequent rituximab treatments.
- There were no changes in MRI activity for patients through their course of treatment, except for one non-enhancing lesion in one patient. No significant adverse reactions were reported.
- Therefore, rituximab could have an important therapeutic benefit for SPMS patients. However, in developing this potential therapy, more support for these results must be achieved through larger studies.

Acknowledgments

This project was funded through a grant from the Foundation of the Consortium of Multiple Sclerosis Centers’ MS Workforce of the Future program.

References