Temporal Relationship of Serum Neurofilament Light (Nfl) Levels and Radiological Disease Activity in MS Patients

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Introduction

• Serum neurofilament light (sNfL) is a promising biomarker in multiple sclerosis.
• sNfL levels are increased in patients with high disease activity and predictive of MRI disease activity.

Methods

1 This was a retrospective analysis of patients with MS enrolled in RENEW, a 24-week non-dominated treat-to-target protocol.
2 RENEW was a randomized, placebo-controlled, multinational study of the effect of a 24-week randomized withdrawal treatment interruption (Figure 1A).
3 Excluded patients who had received natalizumab for 12 years had no gadolinium-enhancing (Gd+), lesions on screening MRI and no relapses in the prior year (n=90), were randomized into 4 groups (n=65) and continued on natalizumab, discontinued natalizumab (Figure 1B), or switched to placebo (n=25) or other treatment (n=65) at baseline. MRI was performed every 4 weeks and then switched back to natalizumab for Weeks 28–52.

Results

1 Baseline demographic and clinical characteristics for the 166 patients are presented in Table 1.
2 In patients with n=101, increased sNfL levels were observed by MRI disease activity and sNfL levels increased significantly in patients with developed Gd+ lesions compared with those without lesions.
3 A higher number of Gd+ lesions was associated with higher sNfL levels; however, variability in sNfL increases in patients with similar numbers of MRI lesions was observed, suggesting differing levels of tissue destruction or variable Gd+ lesion volumes.
4 In a majority of patients, an increase in sNfL levels was observed at the initial observation of a Gd+ lesion or within 9 weeks after the first Gd+ lesion, with peak sNfL levels at 16–24 weeks.
5 Levels remained elevated after resolution of Gd+ lesions in some patients, and in a small proportion of patients (14%), did not return to baseline at Weeks 24.
6 These findings add to our understanding of the temporal relationship between Gd+ lesions and sNfL levels in patients with MS and suggest sNfL may serve as a complementary biomarker to MRI in characterizing and monitoring the differential release of tissue injury in individuals with MS.

Conclusion

1 Serum levels remained low and stable in patients continuing on natalizumab.
2 In patients who discontinued natalizumab and had no Gd+ lesions, sNfL levels generally remained low and stable.
3 sNfL levels increased significantly in patients who developed Gd+ lesions compared with those without lesions.
4 A higher number of Gd+ lesions was associated with higher sNfL levels; however, variability in sNfL increases in patients with similar numbers of MRI lesions was observed, suggesting differing levels of tissue destruction or variable Gd+ lesion volumes.
5 In a majority of patients, an increase in sNfL levels was observed at the initial observation of a Gd+ lesion or within 9 weeks after the first Gd+ lesion, with peak sNfL levels at 16–24 weeks.
6 Levels remained elevated after resolution of Gd+ lesions in some patients, and in a small proportion of patients (14%), did not return to baseline at Weeks 24.
7 These findings add to our understanding of the temporal relationship between Gd+ lesions and sNfL levels in patients with MS and suggest sNfL may serve as a complementary biomarker to MRI in characterizing and monitoring the differential release of tissue injury in individuals with MS.

References


Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nalizumab</th>
<th>Placebo</th>
<th>Other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.2 (7.4)</td>
<td>59.9 (10.2)</td>
<td>42.0 (9.7)</td>
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<tr>
<td>EDSS score</td>
<td>2.0 (3.8)</td>
<td>3.5 (8.3)</td>
<td>3.3 (5.7)</td>
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<tr>
<td>Time from first Gd+ lesion</td>
<td>6.0 (3.6)</td>
<td>5.8 (5.7)</td>
<td>13.6 (7.0)</td>
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<tr>
<td>% of prior relapse or infections</td>
<td>42</td>
<td>22</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 2. sNfL increase in patients with different Gd+ lesion groups

<table>
<thead>
<tr>
<th>Gd+ lesions</th>
<th>sNfL increase (pg/mL)</th>
<th>Nalizumab</th>
<th>Placebo</th>
<th>Other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9 lesions</td>
<td>1.5%</td>
<td>22</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>10–19</td>
<td>2.0%</td>
<td>24</td>
<td>32</td>
<td>34</td>
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<tr>
<td>20–29</td>
<td>2.5%</td>
<td>26</td>
<td>33</td>
<td>36</td>
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<tr>
<td>30–49</td>
<td>3.0%</td>
<td>28</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>50+</td>
<td>3.5%</td>
<td>30</td>
<td>36</td>
<td>39</td>
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</table>

Figure 1. sNfL baseline and Week 4 values averaged (if both present) across all patients. (A) Continued natalizumab; (B) Natalizumab interruption period in the RESTORE study.

Figure 2. Relationship between sNfL levels and gadolinium-enhancing (Gd+) lesion activity.

Figure 3. Relationship between sNfL level and percentage change from baseline to minimum sNfL level and number of Gd+ lesions.