Interferon-β1b Treatment in Neuromyelitis Optica

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Introduction

Interferon-β1b (IFN-β1b) treatment significantly reduces the relapse rate [1], areas of lesions, and disease activity as determined by MRI [2] in relapsing-remitting multiple sclerosis (RRMS), and delays the conversion of clinically isolated syndromes to clinically definite MS [3].

The pathogenesis of neuromyelitis optica (NMO) is predominantly antibody mediated because clinical observations show high prevalence of autoantibodies and autoimmune diseases, or high effectivity of plasmapheresis and immunosuppressive medications including azathioprine, corticosteroids, and rituximab [4]. Immunopathologic studies demonstrated the deposition of immunoglobulin and complement in spinal cord lesions. Anti-aquaporin-4 antibody (anti-AQP-4-Ab) found in the sera of patients with NMO is a disease-specific marker [5]. These findings suggest that NMO is distinct from MS, although the effector cells causing demyelinating lesions in the central nervous system and encephalitogenic antigens reacting with effector cells in MS have not yet been identified. Most neurologists in Western countries consider that IFN-β is ineffective for NMO patients [4]. A recent study has shown that the relapse-free period is shorter in 7 NMO patients treated with IFN-β than in 19 NMO patients treated with immunosuppressive drugs [6]; however, the number of patients observed was very...
small. We reviewed the medical records of our Japanese patients with NMO and determined whether IFN-β₁b treatment affects disease exacerbation and disability progression as indicated by an increase in Kurtzke’s Expanded Disability Status Scale (EDSS) score [7] in patients with NMO.

**Methods**

We conducted a retrospective study by examining the medical records of 104 consecutive patients treated with IFN-β₁b at one national center from December 2000 to December 2005, including 69 patients with RRMS (19 men, 50 women), aged 16–69 years, who fulfilled McDonald’s criteria [8], and 35 patients with relapsing NMO (5 men, 32 women), aged 28–78 years, who fulfilled the criteria proposed by Wingerchuk et al. [9]. The NMO patients in this study did not show systemic autoimmune diseases. The durations from onset were 3–46 years in the RRMS patients and 3–35 years in the NMO patients. The patients received 250 μg of IFN-β₁b (Betaferon) subcutaneously every other day for 1 year. Of the 35 patients with NMO, 19 showed anti-AQP-4-Ab in their sera.

Patients with primary or secondary progressive MS and relapsing optic neuritis were excluded from the study. We did not include spinal MS patients because transition to classic MS or NMO from spinal MS is common in patients with short disease duration such as 5 years. We did not include in this study the patients whose IFN-β₁b treatment was stopped because of the development of skin ulcers (3 RRMS patients and 3 NMO patients, 1 of them was positive for anti-AQP-4-Ab), liver dysfunction (2 RRMS patients), relapsing pneumonia (1 NMO patient negative for anti-AQP-4-Ab), fever, and depression (1 RRMS patient each) within 1 year of IFN-β₁b treatment. We excluded 2 patients who were started on IFN-β₁b treatment together with mitoxantrone or steroid pulse therapy every 3 months (1 RRMS patient each). One RRMS patient was excluded from this study because of irregular IFN-β₁b treatment.

Relapse was defined as the appearance of a new symptom or the worsening of an old symptom caused by MS, accompanied by a documented new neurological abnormality lasting for at least 48 h and preceded by a stable condition or improvement for at least 30 days. We compared the decrease in relapse number (expressed as relapse number within 1 year after IFN-β₁b treatment minus that within 1 year before IFN-β₁b treatment) of the RRMS patients with that of the NMO patients.

Kurtzke’s EDSS score [7] was used to evaluate the clinical ratings. We compared the EDSS score of each patient at the start of treatment and 1 year after treatment and compared the change in the EDSS score of each patient expressed as the score after treatment minus the score before treatment.

The statistical significance of the difference in values was determined by Fisher’s exact test for the change in the percentage of patients showing relapse, by Mann-Whitney U test for the decrease in relapse number and for the change in the EDSS score after treatment with IFN-β₁b, by Wilcoxon’s signed-rank test for the change in annualized relapse rates in each patient before and after treatment, and by McNemar’s test for the change in the relapse number or EDSS scores before and after treatment.

**Results**

Of the 69 (75.4%) RRMS patients, 52 showed relapse before treatment but only 24 (34.8%) showed exacerbation after IFN-β₁b treatment. Of the 35 patients with NMO, 26 (74.3%) showed exacerbation before treatment and 25 (71.4%) showed exacerbation after treatment. The change in the percent of patients showing exacerbation before and after treatment was not different between the RRMS and NMO patients as determined by Fisher’s exact test (p = 0.0629); however, the relapse number in the RRMS patients significantly decreased 1 year after treatment (from 97 to 39; p < 0.00001) as determined by McNemar’s test; on the other hand, that in the NMO patients did not show a significant decrease (from 76 to 72; p = 0.5601) as determined by McNemar’s test (table 1).

The decrease in relapse number after treatment with IFN-β₁b was higher in the RRMS patients (from –2 to 5; 0.74 ± 1.31) than in the NMO patients (from –3 to 3; 0 ± 1.60) as determined by Mann-Whitney test (p = 0.0375). The annualized relapse rates in each RRMS patient after treatment (0–4) were significant (p < 0.01), but those in each NMO patient (0–6) were not as determined by Wilcoxon’s signed-rank test (p > 0.05). In the patients with NMO, the decrease in exacerbation number after treatment with IFN-β₁b was not significantly different between the anti-AQP-4-Ab-positive group (from –3 to 2 in 19 patients) and the anti-AQP-4-Ab-negative group (from –3 to 3 in 16 patients) as determined by Mann-Whitney test (p = 0.3696). The decreases in the annualized relapse rates after treatment in each NMO patient with anti-AQP-4-Ab (p > 0.05) and in each NMO patient without anti-AQP-4-Ab were not significant as determined by Wilcoxon’s signed-rank test (p > 0.05).

The EDSS scores of the patients with RRMS and NMO before treatment with IFN-β₁b were 3.85 ± 2.47 (mean ± SD; from 0 to 7.5) and 5.02 ± 2.27 (from 0 to 8.5), and those after the treatment were 4.10 ± 2.63 (from 0 to 7.5) and 5.61 ± 2.76 (from 0 to 9), respectively. The EDSS score of the NMO patients was higher than that of the
RRMS patients before the treatment as determined by Mann-Whitney test (p = 0.0318). Both patient groups showed increased EDSS scores after the treatment; however, the NMO patients showed more pronounced worsening (p ≤ 0.0001) than the RRMS patients (p < 0.0008) as determined by McNemar’s test. We directly compared the change in the EDSS score between the RRMS patients and the NMO patients. The change in the EDSS score, obtained as the EDSS score after treatment minus the EDSS score at the start of treatment, was higher in the NMO patients (0.92 ± 1.08; from 0 to 3.5) than in the RRMS patients (0.31 ± 0.72; from –2 to 2.5) as determined by Mann-Whitney test (p = 0.0225) (table 2). In the patients with NMO, the change in the EDSS score was not significantly different between the anti-AQP-4-Ab-positive group (from 0 to 3.5 in 12 patients) and the anti-AQP-4-Ab-negative group (from 0 to 2.5 in 9 patients) as determined by Mann-Whitney test (p = 0.6511).

Discussion

We examined the effect of IFN-β1b treatment on the exacerbation number during the periods 1 year before and after treatment, and on the change in the EDSS score at the start of treatment and 1 year after treatment in the patients with RRMS and NMO. This study showed that IFN-β1b treatment can suppress relapses in the RRMS patients as reported in European and North American populations [11], but cannot inhibit the increase in the EDSS score. In the patients with NMO, treatment with IFN-β1b did not significantly suppress the relapse numbers or the increase in EDSS score (tables 1 and 2, respectively). To compare the effect of IFN-β1b treatment on the change in the EDSS score of the patients with RRMS and NMO, we reviewed the difference in the EDSS scores at the start of IFN-β1b treatment and 1 year after the treatment in both patient groups. The increase in the EDSS score was high-

### Table 1. Effects of IFN-β1b treatment on exacerbation number in patients with MS and NMO

<table>
<thead>
<tr>
<th></th>
<th>MS (n = 69)</th>
<th>NMO (n = 35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before Tx¹</td>
<td>after Tx</td>
<td>before Tx</td>
</tr>
<tr>
<td>Percentage of patients showing relapses</td>
<td>75.4%</td>
<td>34.8%</td>
<td>74.3%</td>
</tr>
<tr>
<td>Total exacerbation number</td>
<td>97</td>
<td>39</td>
<td>76</td>
</tr>
<tr>
<td>Annualized relapse rate, mean (range)</td>
<td>1.28 (0–4)</td>
<td>0.58 (0–4)</td>
<td>2.05 (0–6)</td>
</tr>
</tbody>
</table>

¹ Tx: treatment with IFN-β1b. ² Determined by Fisher’s exact test. ³ Determined by McNemar’s test. ⁴ Determined by Wilcoxon’s signed-rank test. ⁵ Determined by Mann-Whitney test.

### Table 2. Comparison of disease progression represented by increase in EDSS score after treatment with IFN-β1b between patients with MS and NMO

<table>
<thead>
<tr>
<th></th>
<th>MS (n = 40)</th>
<th>NMO (n = 26)</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>after Tx</td>
<td>baseline</td>
</tr>
<tr>
<td>EDSS score</td>
<td>3.85 ± 2.47</td>
<td>4.10 ± 2.63</td>
<td>5.02 ± 2.27</td>
</tr>
<tr>
<td>Change in EDSS score after Tx</td>
<td>–2 to 2.5</td>
<td>0.31 ± 0.72</td>
<td>0.31 ± 0.72</td>
</tr>
</tbody>
</table>

¹ Determined by McNemar’s test. ² Determined by Wilcoxon’s signed-rank test.
er in the patients with NMO than in the RRMS patients (table 2). These results suggest that treatment with IFN-β<sub>1b</sub> is not effective in reducing the relapse number and the disability progression in NMO patients.

This study also showed that the decrease in relapse number after IFN-β<sub>1b</sub> treatment was not significantly different between the anti-AQP-4-Ab-positive and anti-AQP-4-Ab-negative patients with NMO. We have reported that seropositive patients with a long spinal cord lesion (LCL) had more relapses than seronegative patients with LCL [12]. This study included patients with LCL reported previously, although our previous study included patients who had not been treated with IFN-β<sub>1b</sub>. Many patients in this study had been treated with IFN-β<sub>1b</sub> a few years earlier, and the presence of the anti-AQP-4-Ab was not related to disease activity during the periods 2 years before and after the start of treatment.

A Japanese randomized controlled trial has shown that IFN-β<sub>1b</sub> treatment is effective in decreasing attack frequency even in patients with optic-spinal MS (OSMS) characterized by lesions restricted to the optic nerves and spinal cord [13]. Recent observations including those from our study suggest that OSMS includes a benign phenotype without LCL showing some features commonly seen in classic MS [12, 14, 15], and that these patients may show beneficial effects with IFN-β<sub>1b</sub> treatment. In a Japanese IFN-β<sub>1b</sub> MS study [13], classic MS might include NMO with symptoms related to brain lesions. We have found that 70% of the patients with NMO showed brain symptoms [Komori, unpubl. data]. Therefore, the effect of IFN-β<sub>1b</sub> treatment in patients with Japanese classic MS [13] was underestimated and that in Japanese patients with OSMS [13] was overestimated. To evaluate the therapeutic effects of IFN-β<sub>1b</sub> in NMO patients, it should be considered that OSMS and NMO are different [12].

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**References**


