Therapeutic Efficacy of Interferon β-1b in Japanese Patients with Optic-Spinal Multiple Sclerosis

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Optic neuritis and myelitis are manifestations in both multiple sclerosis (MS) and neuromyelitis optica (NMO). But unlike MS, NMO is characterized by severe optic neuritis, longitudinally extensive and transverse myelitis, and the presence of aquaporin-4 antibody. Since patients with optic neuritis and myelitis have often been diagnosed with “optic-spinal MS (OSMS)” in Asia, it was obscure whether “OSMS” is synonymous with NMO or includes both NMO and MS. Interferon β (IFNβ)-1a and -1b are used as the first-line disease-modifying therapy for MS. However, some neurologists have been reluctant to use IFNβ to treat patients with optic-spinal symptoms, because IFNβ therapy is not efficacious in NMO. To evaluate the therapeutic effect of IFNβ in patients with “genuine” OSMS, we retrospectively evaluated Japanese MS patients who fulfilled the following six criteria: 1) Relapsing-remitting MS with optic-spinal presentation alone (no brain symptoms), 2) With or without asymptomatic brain MRI lesions, 3) Oligoclonal IgG band-positive, 4) aquaporin-4 antibody seronegativity, 5) No myelitis extending longitudinally over ≥ 3 vertebral segments, and 6) Duration of IFNβ-1b therapy ≥ 2 years. Among 157 patients with MS, six (four women and two men, age 43.8 ± 8.5 years old) met all the criteria. Their Expanded Disability Status Scale scores were lowered (4.1 ± 2.4 → 3.1 ± 2.8) (P = 0.033) and annualized relapse rate was decreased (0.59 ± 0.34 → 0.13 ± 0.15) (P = 0.027) after IFNβ-1b therapy. These results suggest that IFNβ is therapeutically effective in inhibiting functional worsening and reducing relapse rate in “genuine” OSMS.

Keywords: optic-spinal multiple sclerosis; interferon-beta therapy; neuromyelitis optica; aquaporin-4 antibody; oligoclonal IgG band


Neuromyelitis optica (NMO) is clinically characterized by severe optic neuritis and longitudinally extended (often > three vertebral segments [VS]) transverse myelitis, and is often positive for serum aquaporin-4 (AQP4) antibody, but mostly negative for oligoclonal IgG bands (Wingerchuk et al. 2006). These features are different from those in typical multiple sclerosis (MS). Meanwhile, since all patients with selective involvement of the optic nerves and spinal cord have often been diagnosed with “optic-spinal MS (OSMS)” in Japan (Kira 2003) and in some other Asian countries, the relationship between NMO and “OSMS” has been controversial. More specifically, it was obscure whether “OSMS” is synonymous with NMO or includes both NMO and MS.

Interferon β (IFNβ)-1a (once a week intramuscular injection or alternate day subcutaneous injection) and IFNβ-1b (alternate day subcutaneous injection) are a first-line disease-modifying drug that is used to treat MS. However IFNβ therapy is not efficacious in NMO (Shimizu et al. 2008; Tanaka et al. 2009; Uzawa et al. 2010; Shimizu et al. 2010). Thus, some Asian neurologists have been reluctant to use IFNβ to treat patients with optic-spinal symptoms. On the other hand, a recent study (Nakashima et al. 2007) has shown that so-called OSMS can be separated into “NMO” and “MS with optic-spinal presentation”. MS with optic-spinal presentation is considered to be genuine OSMS, and unlike NMO, it might be treatable with IFNβ. Therefore, the present study evaluated the therapeutic effect of IFNβ in patients with genuine OSMS.
Patients and Methods

Patients and Diagnostic Criteria of OSMS

We retrospectively reviewed a total of 157 Japanese patients of MS diagnosed with the revised McDonald (2001) criteria (Polman et al. 2005), who were seen at Tokyo Women’s University Hospital or Tohoku University Hospital, and evaluated those who fulfilled all of the following six inclusion criteria for OSMS:

1. Relapsing-remitting MS with optic-spinal presentation alone (no brain symptoms)
2. With or without asymptomatic brain lesions on MRI
3. Oligoclonal IgG band-positive
4. Negative serum AQP 4 antibody
5. No myelitis extending longitudinally over ≥ 3 VS.
6. Duration of IFNβ-1b (BETAFERON® SC inj., Bayer Yakuhin, Japan) therapy ≥ 2 years

Informed consent was obtained from the patients.

Laboratory tests and Statistical analysis

Oligoclonal IgG band was examined with an isoelectric focusing. AQP-4 antibody was tested with a cell-based assay using human AQP4-transfected HEK293 cells at the laboratory of Tohoku University (Takahashi et al. 2006). We compared the Expanded Disability Status Scale (EDSS) and the annualized relapse rates (ARR) before and after IFNβ-1b therapy, and the differences were statistically analyzed using a Wilcoxon signed rank test.

Results

Among the 157 patients, six patients (3.8%) fulfilled all the six inclusion criteria (four women and two men; age 43.8 ± 8.5 years old) (One patient was seen at Tohoku University Hospital, and the rest were seen at Tokyo Women’s Medical University Hospital.). The clinical profiles of the patients are shown in Table 1. Brain lesions in patients 1, 2 and 3 fulfilled the MRI findings of the McDonald’s criteria, but patients 4, 5 and 6 did not meet them. Their EDSS scores were lowered after IFNβ-1b therapy (4.1 ± 2.4 → 3.1 ± 2.8) (P = 0.033), and their ARR was decreased (0.59 ± 0.34 → 0.13 ± 0.15) (P = 0.027). The clinical course of a representative patient (patient 6, 34y, woman) is shown in Fig. 1.

For comparison, clinical data of 3 NMO patients treated with IFNβ-1b in our institution is shown in Table 2. Unlike OSMS, all of them discontinued the therapy due to increased relapses.

Discussion

IFNβ is a disease-modifying drug for relapsing-remitting MS and the favorable effects on clinical, MRI and immunological parameters in MS have been established. Meanwhile, its therapeutic efficacy in NMO is unclear, and there are some patients of NMO who have experienced severe relapses within a year after IFNβ treatment was started (Shimizu et al. 2008; Tanaka et al. 2009; Uzawa et al. 2010; Shimizu et al. 2010). We cannot completely exclude the possibility that some of our patients diagnosed with OSMS actually had AQP4 antibody-seronegative NMO, but the six criteria of OSMS in the present study were used to exclude NMO as much as possible. Moreover, Tanaka (2009) reported that IFNβ failed to reduce relapse in both AQP4 antibody-seropositive and -seronegative NMO patients, indirectly supporting that our patients did not contain seronegative NMO. We speculated that the extensive brain lesions developed in those NMO patients receiving IFNβ were probably related to immunological alterations caused by IFNβ (Yong et al. 1998). Those findings could make neurologists reluctant to treat patients with optic-spinal symptoms by IFNβ.

The present study first demonstrated that IFNβ-1b is therapeutically effective to inhibit functional worsening and reduce relapse in OSMS which is distinct from NMO.

Table 1. Clinical and laboratory findings of 6 OSMS patients treated with IFNβ-1b.

<table>
<thead>
<tr>
<th>OSMS patient</th>
<th>Age (y)/sex</th>
<th>Onset Age (y)</th>
<th>Brain MRI McDonald’s criteria</th>
<th>Relapse before IFNβ-1b/y</th>
<th>Relapse after IFNβ-1b/y</th>
<th>EDSS at nadir (before IFNβ-1b)</th>
<th>Optic neuritis/Spinal cord lesions+/&lt;3VS</th>
<th>OCB/AQP4 Ab</th>
<th>Brain lesions</th>
<th>Other therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/F</td>
<td>27</td>
<td>Fulfilled</td>
<td>2/13</td>
<td>0/2</td>
<td>2.5/1.5</td>
<td>Mild/ C5, T6-7</td>
<td>+/−</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>52/F</td>
<td>39</td>
<td>Fulfilled</td>
<td>4/4</td>
<td>0/9</td>
<td>6.0/6.0</td>
<td>Severe/ T5</td>
<td>+/−</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>43/F</td>
<td>30</td>
<td>Fulfilled (Severe)/6</td>
<td>3/10</td>
<td>2/7</td>
<td>3.0/2.0</td>
<td>Mild/ C2, C3-4</td>
<td>+/−</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>58/M</td>
<td>32</td>
<td>Not fulfilled</td>
<td>5/20</td>
<td>1/6</td>
<td>8.0/7.0</td>
<td>Sever/ T8</td>
<td>+/−</td>
<td>+</td>
<td>AZT (50mg/day)</td>
</tr>
<tr>
<td>5</td>
<td>43/M</td>
<td>39</td>
<td>Not fulfilled</td>
<td>2/1</td>
<td>0/3</td>
<td>2.0/0</td>
<td>Mild/ C1-2</td>
<td>+/−</td>
<td>−</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>36/F</td>
<td>26</td>
<td>Not fulfilled</td>
<td>7/7</td>
<td>1/3</td>
<td>2.0/3.0</td>
<td>Mild/ C2, C2-3, C3-4, C4-5, T10-11</td>
<td>+/−</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

Y, years; IFNβ-1b, interferon-beta-1b; EDSS, expanded disability status scale; VS, vertebral segment; C, cervical myelitis; T thoracic myelitis; OCB, oligoclonal IgG bands; AQP4, aquaporin-4; AZT, azathioprine.
although the favorable outcome needs to be confirmed in larger-scale studies. Oligoclonal IgG band is an important laboratory finding in the diagnosis of MS, but some MS patients are oligoclonal IgG band-negative. Therefore, it is interesting to know whether IFNβ-1b therapy is effective in OSMS patients without oligoclonal IgG band as well. However, despite our search, we could not find any OSMS patient without oligoclonal IgG band in our institutions. Seronegativity for anti-AQP4 antibody and no longitudinally extended spinal cord lesions were the key findings to distinguish OSMS from NMO. The brain lesions in three of our six patients did not fulfill the brain MRI findings in the McDonald criteria, but brain lesions are commonly seen in NMO as well as MS. Previous reports showed that brain MRI detected lesions in more than half of NMO patients (Pittock et al. 2006, Nakashima et al. 2006). Many brain lesions in NMO are nonspecific, but about 10% are MS-like lesions (Pittock et al. 2006). Thus brain MRI findings alone may not be helpful in the differential diagnosis of MS and NMO.

The therapeutic efficacy of IFNβ-1b in our patients appears to be comparable to that in previous reports on MS, suggesting that from the therapeutic point of view, OSMS defined in the present study is just a type of MS despite its unique clinical presentation. A previous Japanese clinical trial of IFNβ-1b in MS showed that ARR in “then OSMS” declined after therapy, but the difference was not statistically significant (Saida et al. 2005). Those patients with “OSMS” were perhaps the mixture of MS with optic-spinal presentation and NMO.

A Japanese collaborative study showed that patients with MS with optic-spinal presentation are increasing while those of NMO are essentially unchanged in number in recent years (Nakashima et al. 2007). The recent surge of such OSMS as those defined in the present study probably reflects steadily increased prevalence of MS in Japan (Osoegawa et al. 2009), and neurologists are expected to see and treat more patients with such OSMS from now on although it is unknown what percentage of those OSMS patients have received IFNβ so far.

Thus, making a diagnosis of “genuine” OSMS is important not to miss the opportunity for treating the patients with appropriate disease-modifying drugs for MS early in the course of disease, especially in countries where NMO is relatively common.

**Conclusions**

Although optic neuritis and myelitis are cardinal mani-
festations in both OSMS and NMO, “genuine” OSMS that we defined with the clinical and laboratory criteria is distinct from NMO. The present study suggests that IFN-β is efficacious in inhibiting functional worsening and reducing relapse rate in the “genuine” OSMS. In contrast, similar to previous reports, IFN-β did not show therapeutic efficacy in our patients with NMO. Distinction between “genuine” OSMS and NMO is crucially important from therapeutic point of view.

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Conflict of Interest

Yuko Shimizu, Kazuo Fujihara, Tatsuro Misu, Ichiro Nakashima, Kazumasa Yokoyama, and Yasuto Itoyama received honorarium for giving lectures on multiple sclerosis, and Kazuo Fujihara, Tatsuro Misu, and Ichiro Nakashima received research support from Bayer Yakuhin.

References


