Heterogeneity in Response to Interferon Beta in Patients With Multiple Sclerosis

A 3-Year Monthly Imaging Study

Annie W. Chiu, BS; Nancy Richert, MD, PhD; Mary Ehrmantraut, MS; Joan Ohayon, MSN; Shiva Gupta, MD; Giuseppe Bomboi, MD; Deycia Gaindh, AB; Fredric K. Cantor, MD; Joseph A. Frank, MS, MD; Henry F. McFarland, MD; Francesca Bagnato, MD, PhD

Objectives: To investigate the heterogeneity in magnetic resonance image (MRI) patterns of response to interferon beta across patients with multiple sclerosis or within an individual patient over time.

Design, Setting, and Patients: Fifteen patients with relapsing-remitting multiple sclerosis underwent monthly MRIs and clinical examinations (6-month pretherapy phase and 36-month therapy phase) and bimonthly neutralizing antibody tests. On each MRI, the total number of contrast-enhancing lesions was noted. Therapy MRI responders were defined as those with a reduction of 60% or more in the total number of contrast-enhancing lesions during each semester of therapy.

Intervention: Subcutaneous administration of interferon beta-1b, 250 µg, every other day for 3 years.

Main Outcome Measure: Reduction in the number of contrast-enhancing lesions.

Results: Eight patients (53.3%) were MRI responders and 7 (46.7%) were nonresponders. Of those 7, 3 (20.0%) had only an initial optimal reduction of the total number of contrast-enhancing lesions, 2 (13.3%) never reached an optimal response, and 2 (13.3%) had a delayed optimal response. No clear association between neutralizing antibody profile and MRI response was evident.

Conclusions: Multiple MRI evaluations disclose that approximately only half of the patients treated with interferon beta achieve and maintain a full response to the drug over time, although an additional small number of individuals may still restore an optimal response to the drug after an initial failure.


Magnetic resonance imaging (MRI) allows for unique visibility of inflammatory plaques, namely contrast-enhancing lesions (CELs), in patients with multiple sclerosis (MS).1 The CELs precede the occurrence of clinical relapses,2 which in turn are presumed to lead disease progression. Many clinical studies have demonstrated the ability of interferon beta to reduce CELs (for review, see the article by Clerico et al3). However, little is known regarding the heterogeneity of the MRI response profiles between patients or within an individual patient over time. While important for clinicians to tailor appropriate therapeutic intervention, this information is still missing probably because there is no uniform consent as to how to assess recombinant interferon beta responsiveness. Highly variable proportions of responder patients were observed depending on the definition of responders used, the study design, and the duration.4-12

In addition to the observed interpatient variability in the profile of response to interferon beta, it is unknown whether MRI responsiveness to interferon beta changes with time and disease progression and, if so, whether this is a patient-dependent phenomenon.

For editorial comment see page 19

In this study, the MRI profile’s responses to interferon beta were analyzed and described in detail in a cohort of 15 patients with relapsing-remitting MS who were imaged monthly for 3 years on therapy onset. The novel aspect of the study is the unique number of monthly

CME available online at www.jamaarchivescme.com and questions on page 11
MRIs performed in each subject, potentially disclosing information masked by approaches that have used less frequent measurements.

METHODS

STUDY DESIGN

This open-label study was performed at the National Institutes of Health, Bethesda, Maryland, with approval from the institutional review board. The study is based on the retrospective evaluation of monthly scores on the Expanded Disability Status Scale (EDSS)\textsuperscript{13} and MRIs of 15 patients with relapsing-remitting MS\textsuperscript{14} from a 6-month pretherapy phase (PTP) followed by a 36-month therapy phase (TP), for a total of 42 observations. No patients were treated with any immunomodulatory or immunosuppressive therapy (except for steroids given for acute relapse) before the first MRI. During the TP, patients received a 250-µg dose of subcutaneous interferon beta-1b every other day. Alterations in the EDSS score were defined as changes of 1.0 or more for patients who enrolled with a score of 5.0 or lower or changes of 0.5 or more for those who enrolled with an EDSS score of 5.5 or higher, and the alterations were confirmed during at least 2 examinations held 3 months apart.\textsuperscript{15,16}

Repeated bimonthly blood collections were also performed to evaluate neutralizing antibody (NAb) titers using the MxA assay as described previously.\textsuperscript{17}

IMAGING DATA

Forty-two consecutive precontrast and postcontrast T1-weighted MRIs and T2-weighted MRIs were obtained from each patient. The MRIs were performed on a 1.5-T magnet (General Electric Medical Systems, Milwaukee, Wisconsin) using a standard head coil as previously described.\textsuperscript{17}

At each monthly MRI, the total number of CELs on T1-weighted postcontrast scans was identified by an experienced neurologist (F.B.) and radiologist (N.R.).

DATA ANALYSIS

No significant monthly effect was seen (Friedman test statistic = 2.32, df = 8; \( P = .80 \)) in the total number of CELs during the PTP (see the distribution of the total number of CELs during the PTP and TP in the Figure).

Thus, the total number of CELs from the PTP was averaged within patients in a single mean value. Because 1 patient (patient 10) showed a higher number in the total number of CELs as compared with the others, the analysis was repeated excluding patient 10 from the group and produced similar results. Thereafter, the TP was divided into 6 epochs or semesters, each consisting of 6 consecutive months. The percentage of change in the total number of CELs per semester of TP with respect to the averaged value across the 6 months of the PTP was calculated with the following formula: \[
\left( \frac{B - A}{A} \right) \times 100,
\] where \( B \) is the value corresponding to a semester during the TP and \( A \) is the value corresponding to the PTP or baseline.

Based on previous work,\textsuperscript{4} responders were defined as those patients who maintained a reduction of 60% or more in activity of the total number of CELs during each semester of the TP. An independent \( t \) test was used to analyze differences in age, EDSS score, years with MS, and the mean total number of CELs during the PTP between responders and nonresponders.

RESULTS

HETEROGENEITY IN MRI RESPONSE TO INTERFERON BETA-1B

Table 1 and Table 2 summarize the demographic, clinical, and MRI characteristics of the patients during the study period. Eight patients (53.3%) had a reduction of 60% or more in activity of the total number of CELs during each semester and at almost every scan of the study (Table 2) and were therefore classified as responders. Three of the MRI responders had clinical relapses dur-
Two of these responders had a sustained progression in the EDSS score. The EDSS scores of these 2 patients shifted from 1.5 to 2.5 in patient 1 (in the absence of any relapse treated with steroids) and from 3.5 to 6.5 in patient 12 (in the presence of a clinical relapse treated with steroids and involving the spinal cord).

The other 7 patients (46.7%) were nonresponders. Each of these 7 nonresponders had at least 1 clinical exacerbation during the TP. In 4 patients, the occurrence of clinical relapse was associated with a sustained increase in the EDSS score. Within this nonresponder cohort, 2 patients (13.3%) failed to reach an average reduction of 60% or more in activity of the total number of CELs during the first semester of the TP but reached and maintained a reduction of 60% or more thereafter. Three patients (20.0%) showed an average optimal response during only the first semester but could not maintain sustained optimal reduction in activity of the total number of CELs. Within these 3 patients, 1 did not maintain an average reduction of 60% or more in the total number of CELs during only the second semester of the TP. Two nonresponders (13.3%) did not achieve a consistent reduction of 60% or more in activity of the total number of CELs during any semester of the TP.

Age, years with MS, EDSS score, and total number of CELs during the PTP were not different between responders and nonresponders, although a trend ($P = .09$) toward a higher mean total number of CELs during the PTP was observed in responders.

### Table 1. Demographic and Clinical Characteristics of Patients During the Study Period

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, ya</th>
<th>MS Duration, ya</th>
<th>EDSS Score</th>
<th>Relapses, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>End of TP</td>
</tr>
<tr>
<td>1/F/34.2</td>
<td>11.2</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>2/M/29.0</td>
<td>2.0</td>
<td>2.5</td>
<td>5.5</td>
</tr>
<tr>
<td>3/F/41.0</td>
<td>9.0</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>4/F/47.0</td>
<td>4.0</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>5/F/28.0</td>
<td>4.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>6/F/26.0</td>
<td>7.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7/F/23.0</td>
<td>4.0</td>
<td>5.0</td>
<td>2.5</td>
</tr>
<tr>
<td>8/F/45.0</td>
<td>2.0</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td>9/F/31.0</td>
<td>3.0</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>10/F/30.9</td>
<td>5.9</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>11/F/38.6</td>
<td>6.3</td>
<td>2.5</td>
<td>6.5</td>
</tr>
<tr>
<td>12/F/40.6</td>
<td>5.8</td>
<td>3.5</td>
<td>6.5</td>
</tr>
<tr>
<td>13/F/37.6</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>14/M/35.0</td>
<td>7.0</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>15/F/43.0</td>
<td>6.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PTP, pretherapy phase; TP, therapy phase.

* Age and MS duration refer to those at study entry.
* The EDSS score maintained over 2 months (ie, 3 visits) at or near the end of the study period.
* The total number of relapses treated with steroids.
* This patient had 2 exacerbations during the PTP, and the EDSS score collected at the time of enrollment reflects the presence of 1 of those exacerbations. Possible biases deriving from the data of this patient are discussed in the “Comment” section.
* This patient was in the relapsing-progressive phase of MS.

### Table 2. Number of Magnetic Resonance Imaging Scans Showing Lack of Response to Interferon Beta-1b in Each Patient in Comparison With the Presence or Absence of Neutralizing Antibodies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CELs in PTP, Mean (SD), Total No.</th>
<th>Scans, No. (%)</th>
<th>Month of Lack of MRI Response</th>
<th>Month of NAb Presence (Titer, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder patients(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.2 (1.9)</td>
<td>3 (8.3)</td>
<td>1, 10, 15</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>3.0 (1.7)</td>
<td>1 (2.7)</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>1.8 (2.2)</td>
<td>1 (2.7)</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>7.8 (4.2)</td>
<td>0</td>
<td>NA</td>
<td>4-18 (Titer, Range)</td>
</tr>
<tr>
<td>9</td>
<td>6.3 (2.4)</td>
<td>0</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>33.2 (29.7)</td>
<td>0</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>12.0 (8.0)</td>
<td>1 (2.7)</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>1.8 (1.0)</td>
<td>4 (11.1)</td>
<td>6, 7, 14, 15</td>
<td>None</td>
</tr>
</tbody>
</table>

Patients with $\geq$60% reduction in total No. of CELs by second semester of therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CELs in PTP, Mean (SD), Total No.</th>
<th>Scans, No. (%)</th>
<th>Month of Lack of MRI Response</th>
<th>Month of NAb Presence (Titer, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.5 (1.0)</td>
<td>7 (19.4)</td>
<td>1-3, 5-7, 24</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>1.7 (2.0)</td>
<td>6 (16.6)</td>
<td>1-6</td>
<td>None</td>
</tr>
</tbody>
</table>

Patients with $\geq$60% reduction in total No. of CELs only during first semester of therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CELs in PTP, Mean (SD), Total No.</th>
<th>Scans, No. (%)</th>
<th>Month of Lack of MRI Response</th>
<th>Month of NAb Presence (Titer, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>10.5 (2.0)</td>
<td>9 (25.0)</td>
<td>11-14-19, 22</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>0.7 (0.8)</td>
<td>20 (55.5)</td>
<td>1, 8, 12, 14-18, 22, 23, 26-30, 32-36</td>
<td>13, 26, 27 (&lt;1:400)</td>
</tr>
<tr>
<td>8</td>
<td>3.3 (2.9)</td>
<td>8 (22.2)</td>
<td>1, 7, 8, 10, 11, 21-23</td>
<td>13, 17, 21, 22, 24, 26 (&lt;1:400)</td>
</tr>
</tbody>
</table>

Patients who never reached $\geq$60% reduction in total No. of CELs

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CELs in PTP, Mean (SD), Total No.</th>
<th>Scans, No. (%)</th>
<th>Month of Lack of MRI Response</th>
<th>Month of NAb Presence (Titer, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>3.3 (2.6)</td>
<td>26 (72.2)</td>
<td>1, 6, 7, 12-14, 17-36</td>
<td>3-34 (Titer, Range)</td>
</tr>
<tr>
<td>14</td>
<td>1.2 (1.6)</td>
<td>25 (69.4)</td>
<td>5-7, 9, 11, 12, 15-27, 29-33, 36</td>
<td>3-32 (Titer, Range)</td>
</tr>
</tbody>
</table>

Abbreviations: CELs, contrast-enhancing lesions; MRI, magnetic resonance imaging; NA, not applicable; NAb, neutralizing antibody; PTP, pretherapy phase.

* Response indicates a reduction of 60% or more in the total number of CELs.
* Patients with a reduction of 60% or more in the total number of CELs at each semester of therapy.
* Titers were 1:400 or higher between months 8 and 14 for patient 7, between months 13 and 24 for patient 10, and between months 9 and 25 for patient 14.
To our knowledge, our descriptive study provides for the first time a detailed long-term analysis of MRI patterns of patients undergoing long-term interferon beta-1b therapy. The results show that on a close monthly MRI inspection, approximately half of the patients fail therapy from an MRI perspective. Also, we show that an additional small proportion of patients may not be necessarily recognized as MRI nonresponders during the first semester of therapy, and frequent radiological monitoring is advised during the first year of therapy. Multiple MRIs, beyond the first 6 months of therapy, also disclose a small proportion of patients with a delayed but eventually sustained response to interferon beta and provide compelling information regarding the clinical outcome of patients during the course of a longer trial.

Neither MRI nor clinical parameters at the beginning of the study could segregate responders vs nonresponders. Because the number of patients is small, any definitive conclusion is precluded. However, it is noteworthy that contradictory results were obtained when examining the power of baseline characteristics in predicting outcome to therapy.\(^6,7,9,10,18,19\) In our cohort of patients, a trend was visible in that responders presented a higher disease activity in terms of the total number of CELs during the PTP. One might argue that changes due to interferon beta-1b administration may be more easily identified in patients with a higher total number of CELs during the PTP. However, on close inspection of the data, one can see that although a few responders had quite a higher total number of CELs, overall the total number of CELs among different responder types demonstrated a heterogeneous distribution.

The NAbs appeared in 5 of the patients (33.3%) as early as the third month of therapy and decreased in titers during the third year of therapy. The occurrence of NAbs was generally low in MRI responders and more prominent in nonresponders. However, no clear association between the NAb profile and MRI activity could be clearly identified within each NAb-positive patient.\(^17\)

Possible limitations of this study need to be addressed before drawing conclusions. Besides the small number of patients, this was an open-label study that lacked a systematic analysis of potential effects of steroids given for clinical relapses. However, it was shown previously that steroids given for acute relapse likely do not affect the long-term response to interferon beta\(^10,25\) and that while persistently low enhancement is seen in the follow-up scans of patients treated with steroids and interferon beta, a rebound increase in the number and volume of CELs may be observed in patients who are not receiving interferon beta.\(^20\) Finally, care needs to be taken with respect to patient 7. This patient experienced 2 clinical relapses during the PTP. It is likely that part of the optimal MRI response to interferon beta-1b might be the result of some regression to the mean associated with the relative increase of the total number of CELs during the PTP. While worth mentioning, we do not think the data per se would form a bias in the interpretation of our results.

Accepted for Publication: February 18, 2008.
Published Online: November 10, 2008 (doi:10.1001/ archneur.66.1.noc80047).
Correspondence: Francesca Bagnato, MD, PhD, Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bldg 10, Room 5C103, 10 Center Dr, Bethesda, MD, 20892-1400 (bagnatof@ninds.nih.gov).

Author Contributions: Study concept and design: Gupta and Bagnato. Acquisition of data: Richert, Ehrmantraut, Ohayon, Frank, and McFarland. Analysis and interpretation of data: Chiu, Richert, Gupta, Bomboi, Gaindh, Cantor, and Bagnato. Drafting of the manuscript: Chiu, Gupta, Cantor, McFarland, and Bagnato. Critical revision of the manuscript for important intellectual content: Chiu, Richert, Ehrmantraut, Ohayon, Bomboi, Gaindh, Frank, McFarland, and Bagnato. Statistical analysis: Chiu, Gupta, McFarland, and Bagnato. Obtained funding: McFarland. Administrative, technical, and material support: Ehrmantraut, Gaindh, and Cantor. Study supervision: Frank, McFarland, and Bagnato.

Financial Disclosure: None reported.

Funding/Support: This work was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health. Dr Bomboi’s contribution was sustained by a public-private partnership supported jointly by the Università La Sapienza, Rome, Italy, and a grant from the Bayer-Schering Pharmaceuticals Group.

Additional Contributions: Roger S. Stone, BS, from the Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of
Health provided data management and storage. All of the patients and their family are acknowledged for their time, patience, and cooperation.