Enhanced Benefit of Increasing Interferon Beta-1a Dose and Frequency in Relapsing Multiple Sclerosis

The EVIDENCE Study

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Background: The EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) Study demonstrated that patients with multiple sclerosis (MS) who initiate interferon beta-1a therapy with 44 µg 3 times weekly (TIW) were less likely to have a relapse or activity on magnetic resonance imaging (MRI) compared with those who initiate therapy at a dosage of 30 µg 1 time weekly (QW).

Objective: To determine the effect of changing the dosage from 30 µg QW to 44 µg TIW in this extension of the EVIDENCE Study.

Design/Patients: Patients with relapsing MS originally randomized to interferon beta-1a, 30 µg QW, during the comparative phase of the study changed to 44 µg TIW, whereas patients originally randomized to 44 µg TIW continued that regimen. Patients were followed up, on average, for an additional 32 weeks.

Main Outcome Measure: The within-patient pretransition to posttransition change in relapse rate.

Results: At the transition visit, 223 (73%) of 306 patients receiving 30 µg QW converted to 44 µg TIW, and 272 (91%) of 299 receiving 44-µg TIW continued the same therapy. The posttransition annualized relapse rate decreased from 0.64 to 0.32 for patients increasing the dose (P < .001) and from 0.46 to 0.34 for patients continuing 44-µg TIW (P = .03). The change was greater in those increasing dose and frequency (P = .047). Patients converting to the 44-µg TIW regimen had fewer active lesions on T2-weighted MRI compared with before the transition (P = .02), whereas those continuing the 44-µg TIW regimen had no significant change in T2 active lesions. Patients who converted to high-dose/high-frequency interferon beta-1a therapy had increased rates of adverse events and treatment terminations consistent with the initiation of high-dose subcutaneous interferon therapy.

Conclusions: Patients receiving interferon beta-1a improved on clinical and MRI disease measures when they changed from 30 µg QW to 44 µg TIW.

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P HARMACOLOGICAL DATA AND many clinical trials demonstrate a dose effect of interferon in relapsing multiple sclerosis (MS), suggesting that a higher dose given more than once weekly leads to superior efficacy outcomes. By contrast, doubling the dose administered once weekly seems not to have such added benefit. The EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) Study, a direct comparison of the relative efficacy of 2 different dosing regimens of interferon beta-1a, found significant benefit on relapse and magnetic resonance imaging (MRI) measures for high-dose/high-frequency interferon beta-1a therapy after 48 weeks, benefits that were sustained up to 64 weeks. Data are limited, however, regarding the effects of changing from low-dose weekly to high-dose/high-frequency interferon treatment. Following completion of the comparative phase of the EVIDENCE Study, patients receiving low-dose weekly therapy were given the opportunity to convert to 44 µg 3 times weekly (TIW), permitting prospective assessment of this issue.

METHODS

PATIENTS

In the EVIDENCE Study, 677 interferon-naive patients with definite relapsing remitting MS and Expanded Disability Status Scale scores of 0 to 5.5 were enrolled at 56 centers worldwide. Patients were randomly assigned...
to receive subcutaneous interferon beta-1a (Rebif; Serono International SA, Geneva, Switzerland), 44 µg TIW, or intramuscular interferon beta-1a (Avonex; Biogen Idec, Cambridge, Mass), 30 µg 1 time weekly (QW) for a median of 62 weeks. At the completion of the comparative phase of the study, 299 (88%) of 339 patients originally randomized to the 44-µg TIW regimen and 306 (91%) of 338 patients originally randomized to the 30-µg QW regimen continued to receive therapy. All patients were then offered the opportunity to receive the high-dose/high-frequency regimen for an additional interval, permitting an assessment of the impact of a change in therapy. The patients continuing the 44-µg TIW regimen from the start of the study provided a concurrent assessment of no change in treatment. Approval was obtained from the institutional review boards or ethics committees of all participating institutions before study continuation, and written informed consent was obtained from all patients before continuing beyond the transition visit.

PROCESSES

The transition visit was the point at which patients completed their participation in the comparative phase of the study. At the transition visit, patients converting to the subcutaneous 44-µg TIW regimen underwent a complete neurological examination and proton-density T2-weighted MRI. Subsequent clinical assessments occurred every 24 weeks and as needed for relapse assessments. The MRI procedures were repeated at 12 or 24 weeks after transition (depending on the date of the last pretransition MRI) and then every 24 weeks. Although patients and examiners were not blinded to the initial treatment assignments after the transition, MRI assessments remained fully blinded. Blood samples were obtained every 12 weeks for hematologic, biochemical, and thyroid function testing and every 24 weeks for neutralizing antibody (NAb) titers as described previously.11 A relapse was defined as the appearance of a new symptom or worsening of an old symptom, accompanied by an appropriate objective change on results of the neurological examination that lasted at least 24 hours in the absence of fever and was preceded by at least 30 days of clinical stability or improvement. Corticosteroids (intravenous methylprednisolone sodium succinate, 1.0 g/d for 3 days) were prescribed previously.13 A relapse was defined as the appearance of a new symptom or worsening of an old symptom, accompanied by an appropriate objective change on results of the neurological examination that lasted at least 24 hours in the absence of fever and was preceded by at least 30 days of clinical stability or improvement. Corticosteroids (intravenous methylprednisolone sodium succinate, 1.0 g/d for 3 days) were permitted to treat relapses, and study-related MRI was performed before beginning methylprednisolone therapy or at least 7 days after the last dose. Magnetic resonance imaging was performed according to a protocol under the direction of the University of British Columbia MS/MRI Research Group.

OUTCOME MEASURES

The preplanned primary outcome measure was the annualized relapse rate, comparing the within-patient change from the 24-week interval immediately prior to transition to the posttransition interval. The group continuing the 44-µg TIW regimen from the start of the study served as a reference point for outcomes in patients with no change in therapy in addition to providing further data on safety and immunogenicity of interferon. The proportion of patients remaining free of relapses during weeks 0 to 24 of the comparative phase compared with the posttransition interval was a secondary outcome measure.

Preplanned secondary MRI end points included pretransition to posttransition change in the number of new, enlarging, or reappearing lesions on T2-weighted MRI (hereafter referred to as T2 active lesions) per patient per scan, the proportion of T2 active scans per patient, and the proportion of patients without T2 active scans. All MRI analyses were performed by radiologists unaware of treatment allocation in the University of British Columbia MS/MRI Research Group.

The effect of NAb on relapse and MRI measures was assessed by comparing subgroups with (NAb+) and without (NAb−) NAb, with NAb positivity defined as a value of at least 20 neutralizing U/mL at any time. The NAb assays were performed in the same manner before and after the transition.10

Safety evaluations included the recording of new-onset adverse events, withdrawals due to adverse events, serious adverse events, and monitoring of laboratory abnormalities after transition. Grading of laboratory abnormalities was based on the World Health Organization (WHO) system, in which grade 1 of elevated alanine aminotransferase (ALT) levels is less than 2.5 times the upper limit of the reference range (ULR); grade 2 is 2.5 to 5 times the ULR; and grade 3 is 5 to 20 times the ULR. For white blood cell count, grade 1 is below normal but greater than 3 × 10³/µL, grade 2 is greater than 2 × 10³/µL but no more than 3 × 10³/µL, and grade 3 is more than 1 × 10⁴/µL but no more than 2 × 10⁴/µL.

STATISTICAL CONSIDERATIONS

Analyses were performed on all patients who entered the posttransition phase. Statistical tests were 2 sided and were performed at the 5% significance level. Demographic and disease characteristics at transition were presented by treatment group. The annualized relapse rate was derived by dividing relapse count by time in the study (in years) and analyzed using the Wilcoxon signed rank test to compare pretransition and posttransition rates within treatment groups. We compared between-group and within-group pretransition to posttransition changes using 2-sided Wilcoxon rank sum tests. Each of the other continuous efficacy end points was analyzed using similar methods. The proportions of patients remaining relapse free and without T2 active lesions were summarized by period for each treatment group and analyzed using the McNemar test for a significant pretransition to posttransition distribution shift within each treatment group.

Outcomes based on NAb status were analyzed in the same fashion as overall analyses. To determine whether longer observation would alter conclusions regarding the impact of NAb development on efficacy, we performed a secondary analysis including only patients in the study for at least 72 weeks.

All patients who entered the posttransition interval were included in the safety analyses. Patients withdrawing prematurely from the study were listed and summarized by the primary reason for withdrawal for each treatment group.

We performed all analyses using SAS software, version 6.12 (SAS Institute, Cary, NC), and P<.05 denoted statistical significance.

RESULTS

PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

Of 605 patients still receiving therapy at the end of the comparative phase of the EVIDENCE Study, 272 (91%) of the 299 receiving subcutaneous interferon beta-1a, 44 µg TIW, and 223 (73%) of the 306 receiving intramuscular interferon beta-1a, 30 µg QW, entered the posttransition phase (Figure 1). Patients from 6 centers (25 patients originally randomized to 44 µg TIW and 22 randomized to 30 µg QW) did not participate in the posttransition phase of the study. Patients otherwise deciding not to continue included 2 in the group originally randomized to the 44-µg TIW regimen and 61 in the group randomized to the 30-µg
In the original study, 2 sites did not conduct MRI, such that 27 of 677 patients never underwent MRI. Of the 495 patients continuing after the transition, 67 patients (n=34 for 44 µg TIW and n=33 for 30 µg QW) had missing MRI films or had unusable films owing to imager change or imaging errors.

Comparisons between patients entering and not entering the posttransition phase are shown in Table 1.

In the group originally randomized to the 30-µg QW regimen, patients not entering the posttransition phase were more likely to be relapse free and had a lower pretransition relapse count compared with those converting to higher-dose therapy. Looked at differently, 98 (68%) of 145 patients who were relapse free before the transition converted to the 44-µg TIW regimen compared with 125 (78%) of 161 who were not relapse free. Despite these differences in clinical measures, there were no differences in pretransition T2 active lesions between these 2 groups (Table 1).

The median posttransition time in the study was 34 weeks (range, 0.1-45 weeks) and was almost identical for both treatment arms, as was all pretransition and posttransition time in the study (median, 96 weeks; range, 56-128 weeks).

EFFICACY

Patients converting from the 30-µg QW to the 44-µg TIW regimen had a 50% relative reduction in relapse rate (Figure 2 and Table 2) when the immediate 24-week pretransition interval was compared with the posttransition interval (P<.001). The group continuing the 44-µg TIW regimen also had a reduction in relapse rate (26%; P=.03). The change in relapse rates was greater in patients changing from the lower-dose to the higher-dose, more frequently administered interferon regimen than those receiving that regimen from study start (P=.047).
In patients converting from the low-dose QW interferon regimen, 180 (81%) of 223 remained relapse free during the interval after they initiated high-dose/high-frequency therapy. For those continuing the 44-µg TIW regimen from the start of the study, 223 (82%) of 272 remained relapse free after the transition.

The MRI outcome measures are presented in Table 2. Similar to relapse outcomes, MRI posttransition outcomes improved significantly in patients converting from the 30-µg QW to the 44-µg TIW regimen (P = .02), but not in patients continuing the 44-µg TIW regimen from the original randomization (Table 2). Again, the between-group difference significantly favored patients switching from low-dose to high-dose/high-frequency therapy (P = .02). As patients converted to high-dose/high-frequency treatment, T2 active lesions and the proportion of active scans per patient decreased, but the proportion of patients without active scans did not change.

### NEUTRALIZING ANTIBODIES

Of the 495 patients continuing after the transition, 487 had NAb data available in both the pretransition and posttransition phases. In the pretransition period, NAb developed in 72 (27%) of 268 before the transition; 60 (22%) of 272 remaining relapse free after the transition.

Figure 2. Annualized relapse rate for patients continuing treatment after the transition comparing within-patient rates during the pretransition interval with those during the posttransition period. The change in relapse rate is significantly greater for patients changing their dosage regimen than for those continuing the regimen unchanged (P = .047). QW indicates 1 time per week; TIW, 3 times weekly.

Outcomes based on NAb status demonstrated no significant impact on relapses in either group, but NAb− patients had fewer T2 active lesions (Table 3). A sensitivity analysis, including only patients receiving therapy for at least 18 months, provided similar results.

### SAFETY AND TOLERABILITY

Treatment was generally well tolerated in both groups, although more patients changing to high-dose/high-frequency treatment stopped therapy for adverse events (13 patients vs 2 patients). Principal causes for stopping therapy were injection site pain (n = 2), injection site inflammation (n = 2), elevated liver enzyme levels (n = 3), and influenza-like symptoms (n = 2). Skin necrosis was reported in 3 patients, none of whom required treatment discontinuation or plastic surgery. Patients converting to the 44-µg TIW regimen, compared with those receiving the 30-µg QW regimen, also experienced new or worsening adverse events involving injection site reactions and asymptomatic liver and white blood cell abnormalities (Table 4), consistent with the higher dose and change in route of administration. New or worsening flu-like symptoms occurred infrequently after increasing the interferon dose and frequency. Of 758 new-onset events in converting patients, 71% were mild, 27% were moderate, 2% were severe, and 0% were very severe events, based on WHO classification guidelines. For continuing patients, of 483 new-onset events, 64% were mild, 34% were moderate, 2% were severe, and 0.2% were very severe. Twelve serious adverse events were reported in 10 (2%) of 495 patients, of which only asymptomatic grade 3 ALT level elevation (5-20 times ULR), was considered by the investigator to be related to interferon treatment.

Asymptomatic laboratory abnormalities (whether or not they were considered to be adverse events) were noted in both groups. Elevated ALT levels were noted in 52% of patients converting to the 44-µg TIW regimen, including 41% grade 1, 7% grade 2, and 4% grade 3. In patients continuing the 44-µg TIW regimen, 24% had elevated ALT levels, including 22% at WHO grade 1 and 2% at WHO grade 2. These proportions were lower than those observed when interferon-naïve patients initiated 44-µg TIW therapy at the start of the study (65% total) but higher than when patients initiated therapy at 30 µg QW (41% total). The most common white blood cell abnormality was leukopenia, noted in 22% of patients converting to the 44-µg TIW regimen (14% grade 1, 7% grade 2, and <1% grade 3) and in 13% of patients continuing it (10% grade 1, 2% grade 2, and <1% grade 3). As with ALT abnormalities, these proportions were lower than those observed when interferon-naïve patients initiated the 44-µg TIW regimen at the start of the study (27%) but higher than those when patients initiated the 30-µg QW regimen (9%) at the start.

Of patients converting from the 30-µg QW to the 44-µg TIW regimen, 13 (5.8%) stopped therapy because of adverse events during the posttransition phase.
The randomized, controlled, assessor-blinded comparative phase of the EVIDENCE Study demonstrated significant benefits on relapse and MRI measures of disease activity in patients with relapsing MS receiving interferon beta-1a, 44 µg TIW compared with 30 µg QW, during an average of 64 weeks.10,11 The posttransition extension of the EVIDENCE Study, during which all patients received the 44-µg TIW regimen, provides supportive data demonstrating that patients converting from 30 µg QW to 44 µg TIW achieve significant reductions in relapse rate and T2 lesion activity with the increasing interferon beta-1a dose and frequency. Patients switching to 44 µg TIW showed a 50% reduction in relapse rate after the change in therapy. Patients continuing on therapy also experienced a reduction in relapse rate, suggesting that a component of the observed rate reduction is due to either the natural history of the disease or a regression to the mean. Nevertheless, the reduction in relapse rate was significantly greater (50% vs 26%) in the group switching therapies, indicating that switching to high-dose/high-frequency therapy had a clinical impact over and above any effect of these considerations. Similarly, the MRI outcomes in the postransition period improved significantly in patients switching from 30 µg QW to 44 µg TIW, but not in patients continuing to receive 44 µg TIW, and again, the between-group difference favored the group switching to high-dose/high-frequency therapy.

We must consider the possible impact of methodological limitations on the conclusions drawn from these results. In the postransition phase, all patients received 44 µg TIW and, consequently, clinical assessors were aware of their treatment assignments. Furthermore, at transition, all study participants were informed of the results of the comparative phase of the EVIDENCE Study. Both aspects could potentially bias the posttransition clinical assessments. However, the fact that clinical observations are consistent with the blinded MRI results supports the claim of the enhanced efficacy of the 44-µg TIW regimen. In addition, the postransition relapse rates and the proportions who were relapse free for both groups are virtually identical, further suggesting the lack of any systematic bias in the study.

Dropouts at transition might also have affected our results. On average, patients receiving the 30-µg QW regi-
men who chose to convert to 44 µg TIW had a higher pretransition relapse rate and were less likely to be relapse free compared with those who chose to discontinue the study (Table 1). This is not surprising because it is expected that patients who are doing well receiving low-dose weekly interferon would be less motivated to change therapy than those with active disease.

Bias could work 2 ways in this setting. Patients with ongoing active disease receiving low-dose therapy might be resistant to interferon therapy in general, biasing against seeing a difference once therapy was changed. On the other hand, such patients may also have greater potential to show improvements than those with less active disease.

Patients converting to high-dose/high-frequency interferon beta-1a therapy experienced an increase in interferon-related adverse effects. Most notable was an increase in injection site events consistent with the change in route of administration. The increase in asymptomatic laboratory abnormalities was modest, with little impact on adherence to therapy. The increase in asymptomatic laboratory abnormalities was modest, with little impact on adherence to therapy. The increase in asymptomatic laboratory abnormalities was modest, with little impact on adherence to therapy. The increase in asymptomatic laboratory abnormalities was modest, with little impact on adherence to therapy.

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Table 4. Proportions of Patients With New or Worsening Adverse Events Comparing Pretransition and Posttransition Intervals

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>44-µg TIW Continuation</th>
<th>30-µg QW to 44-µg TIW Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretransition</td>
<td>Posttransition</td>
</tr>
<tr>
<td>No. of patients with adverse events</td>
<td>339</td>
<td>272</td>
</tr>
<tr>
<td>Injection-site disorders, %</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>Inflammation</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Influenzalike symptoms, %</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Liver function abnormality, %</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase level elevation, %</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell abnormality, %</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: QW, 1 time per week; TIW, 3 times per week.
* Grades are explained in the “Outcome Measures” subsection of the “Methods” section.

CONCLUSIONS

This study adds to data indicating that high-dose/high-frequency interferon beta-1a therapy (44 µg TIW) provides greater therapeutic benefit on relapse and MRI measures than a low-dose, less frequent (30-µg QW) regimen, regardless of whether therapy is used in interferon-naive patients or those already receiving therapy. Although the posttransition follow-up was relatively brief, these results suggest that increasing the interferon beta-1a dose and frequency can rapidly reduce ongoing disease.
The EVIDENCE Study Group for the posttransition phase includes the following centers and investigators: United States: G. Garmany, P. Brownstone, and J. Lee (Alpine Clinical Research Center, Boulder, Colo); C. Blake, I. Chang, S. Gulevich, G. McIlvenna, L. McLaughlin, D. Shacklett, and D. Solsberg (Blake Neurology, Englewood, Colo); M. Kaufman, A. Dietrich, G. Evans, and B. Hawick (Carolinas Medical Center, Charlotte, NC); R. Hurwitz, V. Chihikuri, W. Davis, J. Hurwitz, R. Link, J. MacFalla, J. Morganlander, L. Poole, J. Provenzale, M. Rozear, and S. Wyne (Duke University Medical Center, Durham, NC); M. Picone, C. Finn, D. Habif, S. Kamin, and B. Johnson (Gimble MS Center at Holy Name Hospital, Teaneck, NJ); C. Markowitz, L. Balcer, L. Desiderio, and M. Mills (Hospital of the University of Pennsylvania, MS Center, Philadelphia); D. Mattson, J. Fleck, L. Hayward, C. Hingetgen, D. Jackson, and M. Phillips (Indiana University Medical Center, Indianapolis); J. Rosenberg, A. Blumenfeld, R. 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activity in patients receiving low-dose weekly therapy. These findings are consistent with a growing body of literature on the interferon dose response from preclinical work, pharmacokinetic and pharmacodynamic data,1-3,14 and clinical trials.4-8,15

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