Management Strategies for Flu-Like Symptoms and Injection-Site Reactions Associated with Peginterferon Beta-1a
Obtaining Recommendations Using the Delphi Technique

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Background: Flu-like symptoms (FLSs) and injection-site reactions (ISRs) have been reported with interferon beta treatments for multiple sclerosis (MS). We sought to obtain consensus on the characteristics/management of FLSs/ISRs in patients with relapsing-remitting MS based on experiences from the randomized, placebo-controlled ADVANCE study of peginterferon beta-1a.

Methods: ADVANCE investigators with a predefined number of enrolled patients were eligible to participate in a consensus-generating exercise using a modified Delphi method. An independent steering committee oversaw the development of two sequential Delphi questionnaires. An average rating (AR) of 2.7 or more was defined as consensus a priori.

Results: Thirty and 29 investigators (ie, responders) completed questionnaires 1 and 2, respectively, representing 374 patients from ADVANCE. Responders reported that the incidence/duration of FLSs/ISRs in their typical patient generally declined after 3 months of treatment. Responders reached consensus that FLSs typically last up to 24 hours (AR = 3.17) and have mild/moderate effects on activities of daily living (AR = 3.34). Patients should initiate acetaminophen/nonsteroidal anti-inflammatory drug treatment on a scheduled basis (AR = 3.31) and change the timing of injection (AR = 3.28) to manage FLSs. Injection-site rotation/cooling and drug administration at room temperature (all AR ≥ 3.10) were recommended for managing ISRs. Patient education on FLSs/ISRs was advocated before treatment initiation.

Conclusions: Delphi responders agreed on the management strategies for FLSs/ISRs and agreed that patient education is critical to set treatment expectations and promote adherence. Int J MS Care. 2016;18:211–218.

Adherence to multiple sclerosis (MS) disease-modifying therapies, such as interferons, has been linked to improved treatment outcomes and reduced health-care costs.1,2 Reasons for poor patient adherence to prescribed MS therapies include frequency of administration and adverse events, such as flu-like symptoms (FLSs) and injection-site reactions (ISRs), associated with interferon beta treatments.3–8 Peginterferon beta-1a is a pegylated form of interferon beta-1a approved for the treatment of relapsing forms of MS. The safety and efficacy of peginterferon beta-1a 125 μg administered subcutaneously every 2 or 4 weeks...
was evaluated during the 2-year, double-blind, randomized, placebo-controlled (year 1 only) ADVANCE study in patients with relapsing-remitting MS. Results from year 1 demonstrated that the use of peginterferon beta-1a 125 μg subcutaneously every 2 or 4 weeks significantly reduced the relapse rate, risk of relapse, disability progression, and number of magnetic resonance imaging brain lesions compared with placebo. The most common adverse events in ADVANCE were FLSs and ISRs.

Because FLSs and ISRs may lead to reduced adherence and treatment discontinuation, a better understanding of the impact and management of FLSs and ISRs associated with peginterferon beta-1a therapy could promote improved patient adherence and could potentially affect treatment outcomes. The Delphi technique, which is a widely accepted method that uses iterative rounds of questionnaires to build consensus, has previously been used to identify practice patterns and obtain recommendations for symptom management in patients with MS.

The objective of this study was to obtain expert consensus on the characteristics, impact, and management of FLSs and ISRs associated with peginterferon beta-1a therapy based on experiences in the ADVANCE study using a modified, two-round, sequential Delphi technique.

Methods

The ADVANCE study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and local regulatory requirements. Approval for the study protocol was obtained from local ethics committees. Written informed consent was obtained from each patient before any evaluations were conducted for eligibility. The methods and results of the ADVANCE study have previously been published. Briefly, patients aged 18 to 65 years with an Expanded Disability Status Scale score between 0.0 and 5.0 and a confirmed diagnosis of relapsing-remitting MS, as defined by the McDonald criteria, were included in the study. Patients were randomized to receive peginterferon beta-1a 125 μg subcutaneously every 2 or 4 weeks or placebo at 183 sites worldwide.

A steering committee (n = 4) composed of expert MS clinicians with substantial experience with peginterferon beta-1a (JH, DC, SDN, and DH) was responsible for overseeing the development of two questionnaires and provided input into the criteria for investigator participation. ADVANCE investigators involved in direct patient care at a site in the ADVANCE study with a pre-defined number of patients were offered the opportunity to participate. Because the United States and Western Europe had fewer patients enrolled in ADVANCE but a good geographic representation was desired for this expert panel, the following inclusion criteria were applied: ADVANCE sites with two or more enrolled patients in the United States and Western Europe (France, Germany, Spain, and the United Kingdom) or ten or more patients in the rest of the world.

Both questionnaires were Web-based (http://www.surveymonkey.com), with access provided through an e-mail link. Participants were offered a monetary incentive to complete the survey. The first questionnaire consisted of 150 questions and was designed to help us better understand the frequency, duration, impact, and management of FLSs and ISRs in patients with MS treated with peginterferon beta-1a. Participants were asked to review their clinical findings from the phase 3 trial to accurately respond to all the questions on the questionnaire. Four question formats were used: yes/no, multiple choice, ranking, and open ended. Both qualitative and quantitative techniques were used to analyze the results. For some questions, investigators (ie, responders) were asked to provide responses for two separate periods: 0 to 3 months of treatment (within the first 3 months of treatment) and more than 3 months of treatment.

After completion of questionnaire 1 and analysis of the data, questionnaire 2 was designed to reach consensus on specific issues, clarify best practices, and generate consensus recommendations for the management of these adverse events. Questionnaire 2 consisted of 15 Likert scale questions. The results of questionnaire 1 were summarized and aggregated into a preliminary consensus and presented to responders before each question in questionnaire 2. The steering committee defined consensus a priori as at least 70% agreement for questionnaire 1 (when applicable) and an average rating (AR) of 2.7 or more based on a 4-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree) for questionnaire 2.

Results

Responder Demographics

Questionnaire 1 responses were received between February 26 and May 4, 2014, and questionnaire 2 responses between September 15 and October 22, 2014. From the 183 sites that participated in ADVANCE, 84 investigators met the inclusion criteria and were invited to participate. Of 50 ADVANCE investigators who agreed to participate, 30 (ie, responders) completed questionnaire 1 and 29 also completed questionnaire 2.
reported greater FLSs in women. However, additional responses indicated that some responders had enrolled only female patients. On questionnaire 2, all the responders reached consensus (AR ≥ 2.7) that FLSs typically begin within 24 hours after dose administration (AR = 3.72), and most agreed that FLSs typically last 24 hours or less (AR = 3.17). A total of 79% of responders (n = 23) agreed (AR = 2.90) that FLSs may last up to 3 days, with 3% (n = 1) strongly disagreeing with this statement (Table 1).

In the first questionnaire, 29 of 30 responders reported ISRs in one or more of their patients, with 79% of responders reporting no sex difference and 17% reporting greater ISRs in women. Injection-site reactions were reported in a typical patient after every dose or most doses by 69% of responders during 0 to 3 months of therapy versus 45% after 3 months of therapy (Figure 2A). Erythema (86% and 76%) and pain (3% and 17%) were the most prevalent subgroups of ISR reported by responders during 0 to 3 months and after 3 months of therapy, respectively. Because responses regarding onset and duration of ISRs varied (Figure 2B and C), no follow-up questions were included in questionnaire 2.

Severe FLSs and ISRs

Eleven responders reported severe FLSs and two reported severe ISRs in one or more of their patients during ADVANCE. The severity of FLSs and ISRs with peginterferon beta-1a therapy was reported to be similar to or less severe compared with that of other intramuscular or subcutaneous disease-modifying drugs by more than 52% of responders.

Impact of FLSs and ISRs on Patients’ Lives

In the first questionnaire, 86% of responders reported that FLSs cause a 4- to 7-point (moderate) disruption in patients’ daily activities on a scale from 0 (none) to 10 (severe) during 0 to 3 months, with 89% reporting a 1- to 4-point (mild) disruption after 3 months (Figure 3). In questionnaire 2, responders reached consensus that FLSs have only a mild-to-moderate effect on activities.
of daily living (ADLs) for most patients during 0 to 3 months of treatment (AR = 3.34) and a minimal effect after 3 months (AR = 3.00). One (3%) and nine (31%) responders, respectively, disagreed with these statements (Table 1).

Most responders reported that the overall impact of ISRs on patients’ daily activities was not substantial; 25 (86%; 0–3 months) and 29 (100%; after 3 months) of 29 responders answered 0 to 3 on a scale from 0 (none) to 10 (severe) on questionnaire 1. A total of 72% of responders reported ISRs in their patients to be similar or less severe compared with standard interferon beta treatments. In questionnaire 2, responders reached the consensus that ISRs have only a minimal effect on ADLs for most patients (AR = 3.48), with one responder disagreeing with this statement (Table 1).

### Management of FLSs and ISRs

In questionnaire 1, all the responders reported that they recommend or encourage the use of prophylactic therapy to prevent or manage FLSs as recommended in the study protocol: acetaminophen or ibuprofen before each injection and for the 24 hours after each injection, and additional doses as necessary after 24 hours following injection (Table 2). Fourteen percent of responders also reported that they recommended additional pharmacologic therapy (pentoxifylline, naproxen sodium, and meloxicam), and 32% reported that they recommended nonpharmacologic interventions for managing

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**Figure 2.** Responder-reported frequency (A), onset (B), and duration (C) of flu-like symptoms (FLSs) and injection-site reactions (ISRs)
FLSs to their patients. Nonpharmacologic interventions included altering injection timing, rest, cold water showers/baths or cooling of the injection site, caffeine, and administrating peginterferon beta-1a at room temperature. Most responders (57%) reported that their patients did not need additional treatment for FLSs compared with current recommendations for FLSs with standard interferon beta treatments (owing to the question format, no additional details were provided).

Although only 10% of responders reported that they advised their patients to use pharmacologic therapy (acetaminophen, topical diphenhydramine, and topical dimethindene) to manage ISRs, nearly all (97%) had recommended the use of nonpharmacologic interventions (Table 2). The most commonly advised interventions were rotation of the injection site (93%), patient education (59%), and warming of peginterferon beta-1a to room temperature (52%).

In questionnaire 2, responders reached a consensus on the recommended management strategies for FLSs and ISRs and agreed that patients who begin treatment should be advised to take acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID; AR = 3.79), use it on a scheduled basis (AR = 3.31), and for as long as FLSs to their patients. Nonpharmacologic interventions included altering injection timing, rest, cold water showers/baths or cooling of the injection site, caffeine, and administrating peginterferon beta-1a at room temperature. Most responders (57%) reported that their patients did not need additional treatment for FLSs compared with current recommendations for FLSs with standard interferon beta treatments (owing to the question format, no additional details were provided).

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### Table 1. Delphi responder answers to questionnaire 2

<table>
<thead>
<tr>
<th>Question</th>
<th>Responders, No. (%) (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FLSs during the first 3 mo of treatment have only a mild-to-moderate effect on ADLs for most patients</td>
<td>Strongly agree</td>
</tr>
<tr>
<td></td>
<td>11 (38)</td>
</tr>
<tr>
<td>2. FLSs have only a minimal effect on ADLs after the initial 3 mo of treatment</td>
<td>9 (31)</td>
</tr>
<tr>
<td>3. Patients beginning treatment should receive verbal education that includes information about the frequency, severity, and management of FLSs</td>
<td>28 (97)</td>
</tr>
<tr>
<td>4. FLSs begin ≤24 h after dose administration</td>
<td>21 (72)</td>
</tr>
<tr>
<td>5. FLSs generally last up to 24 h after peginterferon beta-1a administration</td>
<td>8 (28)</td>
</tr>
<tr>
<td>6. FLSs may last up to 3 d after peginterferon beta-1a administration</td>
<td>4 (14)</td>
</tr>
<tr>
<td>7. Patients beginning treatment with peginterferon beta-1a should be advised to take acetaminophen/NSAIDs to manage FLSs</td>
<td>23 (79)</td>
</tr>
<tr>
<td>8. Patients beginning treatment should be advised to use acetaminophen or an NSAID on a scheduled basis</td>
<td>13 (45)</td>
</tr>
<tr>
<td>9. For patients who experience FLSs associated with drug administration, the use of acetaminophen/NSAIDs should be continued as long as needed</td>
<td>16 (55)</td>
</tr>
<tr>
<td>10. Changing the time of peginterferon beta-1a injection can be recommended as a way to manage FLSs</td>
<td>11 (38)</td>
</tr>
<tr>
<td>11. ISRs associated with peginterferon beta-1a administration have a minimal effect on ADLs for most patients</td>
<td>15 (52)</td>
</tr>
<tr>
<td>12. Patients who begin treatment should receive education that includes information about the frequency, severity, presentation, and management of ISRs</td>
<td>24 (83)</td>
</tr>
<tr>
<td>13. Injection-site rotation for peginterferon beta-1a should be advised as a means of managing ISRs</td>
<td>24 (83)</td>
</tr>
<tr>
<td>14. Cooling the injection site after peginterferon beta-1a injection is an effective way to manage ISRs</td>
<td>10 (34)</td>
</tr>
<tr>
<td>15. Peginterferon beta-1a should be administered at room temperature to mitigate ISRs, as indicated on the product label</td>
<td>14 (48)</td>
</tr>
</tbody>
</table>

Abbreviations: ADLs, activities of daily living; FLS, flu-like symptom; ISR, injection-site reaction; NSAID, nonsteroidal anti-inflammatory drug. An average rating of 2.7 or more was defined as consensus.
Typically, FLSs occur within 6 hours after injection, dissipate within 24 hours, and are most prevalent during the first 6 months of treatment.\(^{10,17,18}\) Consistent with this and based on the experiences in the ADVANCE study, the frequency and duration of FLSs generally declined after 3 months of treatment in a typical patient treated with peginterferon beta-1a. The responders reached the consensus that FLSs typically begin within 24 hours of drug administration and generally last up to 24 hours. Responders also agreed that for some patients, symptoms may last up to 3 days. However, the possibility of an artifact in the reported 48- to 72-hour duration cannot be ruled out; FLSs that begin in the evening of day 1 and last until the evening of day 2 may be reported to last 48 hours instead of 24 hours. Consequently, one responder (3%) strongly disagreed and five (17%) disagreed that FLSs may last up to 3 days. Because of the question design, it was not clear whether these responders disagreed because they believed that FLSs do not last up to 3 days or because they believed that FLSs may last more than 3 days.

**Figure 3.** Responder-reported impact of flu-like symptoms (A) and injection-site reactions (B) on patients’ lives

Responders reported disruption in their typical patients’ lives on a scale from 0 (none) to 10 (severe).

Discussion

The purpose of this study was to obtain expert consensus on the characteristics, impact, and management of FLSs and ISRs associated with peginterferon beta-1a therapy based on the investigators’ experiences in the ADVANCE study. Both FLSs and ISRs are common adverse events with interferon beta treatments for MS, including peginterferon beta-1a.\(^{5,6,9,16}\) Flu-like symptoms are burdensome and associated with poor treatment adherence and discontinuation of treatment.\(^{4,7,8,10}\) In this study, Delphi responders agreed that for most patients treated with peginterferon beta-1a, FLSs have a mild-to-moderate effect on ADLs during 0 to 3 months of treatment. Consistent with the reduced incidence of FLSs over time, the impact of FLSs on patients’ lives seems to decrease and to have only a minimal effect on ADLs after 3 months of treatment.

Several management strategies for FLSs associated with interferon beta treatment have been suggested, including prophylactic over-the-counter (OTC) medica-
Consequently, ISRs are associated with peginterferon beta-1a therapy. The reported incidence, onset, and duration of ISRs varied, and no consensus was obtained on the characteristics of ISRs in patients treated with peginterferon beta-1a. However, most responders (97%) agreed that ISRs generally have only a minimal effect on ADLs.

Several studies have suggested that ISRs can be managed with injection-site practices such as massage, cooling the injection site before or after injection, and pharmacologic therapy, such as diphenhydramine and topical corticosteroids. In the present study, Delphi responders recommended that patients be advised to rotate the injection site, cool the injection site after injection, and administer peginterferon beta-1a at room temperature to manage or prevent ISRs. Pharmacologic therapy (acetaminophen, topical diphenhydramine, or topical dimethindene) was recommended by only a few responders (10%).

All Delphi responders agreed that educating patients about the characteristics and management of FLSs and ISRs before treatment initiation is critical. In previous studies, patient education and counseling was associated with high adherence and low treatment discontinuation due to FLSs and ISRs in patients with MS treated with injectable MS therapies. Additionally, setting realistic expectations regarding MS treatment and adverse events was associated with improved adherence. Because FLSs and ISRs are linked to treatment discontinuation and low adherence in patients with MS, setting realistic treatment expectations is critical and should be done.

## Table 2. Responder-reported management strategies for FLSs and ISRs used in the ADVANCE study

<table>
<thead>
<tr>
<th>Therapy</th>
<th>FLSs</th>
<th>ISRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologic</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Additional pharmacologic</td>
<td>Acetaminophen, ibuprofen</td>
<td>Acetaminophen, diphenhydramine, or dimethindene</td>
</tr>
<tr>
<td>Not applicable</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Nonpharmacologic</td>
<td>Pentoxifylline, naproxen sodium, meloxicam, amphetamine, or amantadine</td>
<td>Not applicable</td>
</tr>
<tr>
<td>32</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

Responders’ suggestions included:
- Rotating the injection site (93%)
- Educating patients (99%)
- Warming medication to room temperature (52%)
- Applying ice to the site after injection (34%)
- Injection before bedtime (34%)
- Avoiding certain sites for injection (17%)
- Warming medication to body temperature (7%)
- Injection early in the day (7%)
- Applying heat (7%)

Abbreviations: FLS, flu-like symptom; ISR, injection-site reaction. These recommendations were provided in an open-ended response. No percentages were obtained because not all responders provided details.

- The results of this study highlight the importance of educating patients about the characteristics and management of flu-like symptoms and injection-site reactions associated with peginterferon beta-1a therapy.
- It is vital that patients have realistic treatment expectations and understand the timing and impact of flu-like symptoms and injection-site reactions and how these adverse events can be reduced and prevented by using over-the-counter medications and other self-care practices.
- Overall, these results provide a consensus gained from investigators with substantive experience in MS and may have an effect on patient adherence to therapy and, ultimately, influence treatment outcomes with peginterferon beta-1a.
before treatment initiation. Addressing concerns about treatment-related adverse events and educating patients about proper strategies to prevent and manage FLSs and ISRs could lower injection-related fears and treatment anxiety and, thus, increase adherence to peginterferon beta-1a therapy and ultimately improve treatment and patient outcomes.

Limitations of this study include its survey nature and that it asked responders to refer to data collected a few years earlier during a clinical study. In addition, only a limited number of Delphi responders participated in this study, and their observations were based on the number of patients enrolled in a clinical study. These results should be confirmed in clinical practice after gaining more real-world experience with peginterferon beta-1a.

Management of the adverse effects of injectable medications in MS has been well documented in the literature, particularly those encountered with interferon products administered subcutaneously. The present study reinforces the previous literature using a newly approved interferon product with an emphasis on the importance of patient education related to peginterferon beta-1a therapy. Before treatment initiation, it is vital to set realistic expectations regarding treatment and possible adverse events and to highlight the timing and impact of FLSs and ISRs and how these can be reduced and prevented by using OTC medications and other self-care practices. This is the first study to provide consensus agreement on management strategies for FLSs and ISRs associated with peginterferon beta-1a treatment. Overall, these results provide a consensus gained from investigators with substantive experience in MS and may have an effect on patient adherence to peginterferon beta-1a therapy and, ultimately, influence treatment and patient outcomes.

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References