Nurses’ Perspective on Approaches to Limit Flu-Like Symptoms During Interferon Therapy for Multiple Sclerosis

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Background: Several interferon beta (IFNβ) formulations are approved for first-line use as disease-modifying therapies to treat patients with multiple sclerosis (MS). Systemic post-injection reactions, often termed flu-like symptoms (FLS), occur in approximately half of all patients treated with IFNβs and can affect adherence to therapy. These symptoms, which include pyrexia, chills, malaise, myalgia, and headaches, usually resolve within 24 hours or persist intermittently following each injection. Because FLS, which usually occur early in the treatment course and diminish over time, are a primary cause of nonadherence to IFNβ therapy, it is important to employ strategies that can attenuate these side effects.

Methods: To identify interventions effective in limiting FLS, a panel of United States–based nurses with expertise in MS patient care was convened and a literature review completed.

Results: Panel consensus was reached on specific interventions that can attenuate FLS. These prevention and mitigation strategies include dose titration, analgesia, and optimal injection timing, as well as other techniques that panel members have found useful in their clinical practice experience.

Conclusions: These measures, in addition to effective patient education, will help to reduce the incidence of FLS secondary to IFNβ therapy, improve patient medication adherence, and positively affect long-term clinical outcomes. Int J MS Care. 2014;16:55–60.

Multiple sclerosis (MS) is a chronic, progressive, neurodegenerative disease characterized by demyelination and the subsequent loss of both gray and white matter in the central nervous system. It is currently estimated that 2.5 million people worldwide, including 400,000 people in the United States, have MS. In the United States alone, approximately 200 people receive a diagnosis of MS each week. Treatment for relapsing-remitting MS is indicated to slow MS disease progression, minimize axonal damage, reduce the frequency and severity of relapses, delay the accumulation of irreversible neurologic damage, and

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lessen the disability associated with the disease. Moreover, in long-term studies of individuals diagnosed with a clinically isolated syndrome, which often precedes relapsing MS, the benefits of early intervention were sustained, whereas delayed treatment was not associated with comparable therapeutic benefits. In general, early therapeutic intervention is associated with better long-term clinical outcomes in MS.

Several therapeutic options are currently available to treat MS. Interferon beta is used in a number of different formulations as first-line MS therapy, based on its efficacy in slowing disease progression and in reducing the number and frequency of MS relapses. Interferons are members of a large class of glycoproteins, known as cytokines, that broadly activate immune cells and are involved in the upregulation of antigen presentation to T lymphocytes. However, these medications may have downstream effects that include aching muscles, fever, and a host of other systemic post-injection reactions, often referred to as flu-like symptoms (FLS).

Adherence to therapy is increasingly recognized as critical to improving long-term outcomes in MS patients, yet long-term adherence rates for MS treatment rarely exceed 75%. While convenience-related factors, such as dosing frequency, can affect adherence, tolerability issues also represent an important potential barrier to adherence. Thus, effective management of side effects is essential to maintain treatment and prevent disease progression.

Patients frequently report FLS as a concern, and untreated FLS negatively affect adherence to IFNβ therapy. However, such symptoms can often be effectively managed with minor lifestyle and medication modifications. Flu-like symptoms usually resolve within 24 hours after injection or persist intermittently following each injection; they typically diminish during the first few months of treatment and may cease completely over time.

Clinicians working with the MS population need to be proactive in assessing the tolerability of treatment and providing education and strategies for managing treatment-related symptoms while setting realistic expectations. The goal of the panel was to generate a consensus statement about FLS mitigation, primarily aimed at nursing staff working with MS patients.

Methods

A panel of nine United States–based expert MS nurses was convened and a literature review completed with the goal of generating a set of practice guidelines for nurses and other caregivers of MS patients on managing FLS secondary to IFNβ therapy. Five FLS—pyrexia, chills, malaise, myalgia, and headache—were examined. A number of possible interventions derived from clinical trials (Class 1 evidence), clinical reports (Class 2 evidence), or the experts’ own 100-plus cumulative years of clinical experience with MS patients (anecdotal evidence) were discussed. Consensus regarding each of the proposed interventions was obtained, and treatment recommendations were made to generate a best practice model for addressing the most common FLS reported by patients treated with IFNβ.

Results

The panel recommended combining early patient counseling regarding the possibility of developing FLS with specific interventions effective in limiting these injection-related reactions. Seven interventions were unanimously recommended by the panel, as described below and summarized in Table 1.

Titration

The panel agreed that the most effective and best-supported strategy to reduce FLS is dose titration during the initiation of IFNβ therapy. Dose-titration schedules are included in the prescribing information for IFNβ therapies currently approved for the treatment of MS and are supported by the results of several studies. A study of 98 patients randomized to either placebo or two different titration schedules of IFNβ-1b found that slower titration (reaching full dose on day 31) was associated with FLS in 32.9% of patients, while rapid titration (reaching full dose on day 15) was associated with FLS in 41.9% of patients. In an open-label pilot study of 47 patients, the combination of analgesics and quarter- or half-dose titration of intramuscular (IM) IFNβ-1a significantly reduced FLS during the first 2 weeks of therapy compared with analgesics alone. These findings were confirmed and extended by a larger, randomized, dose-blinded study assessing the frequency and severity of FLS in healthy volunteers using self-injecting IM IFNβ-1a with no titration or with one of two titration schedules. One group increased its dosage by a quarter-dose each week for 3 weeks, reaching full dose at week 4; the other group underwent a longer 6-week titration, starting at a quarter-dose with quarter-dose increases every 2 weeks, reaching full dose after week 6. Compared with no titration, the incidence
Table 1. Interventions for limiting the incidence of FLS

<table>
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<tr>
<th>Intervention</th>
<th>Consensus opinion</th>
<th>Comments</th>
<th>Evidence level</th>
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| Titration             | Highly effective  | • Recommend starting with quarter-dose and increasing to a full dose over a period of 4–6 weeks; no consensus regarding the optimum speed of titration  
• Product labels for all IFNβ therapies approved for the treatment of MS provide dose titration schedules | Class 1        |
| Analgesics            | Highly effective  | • Recommend starting with ibuprofen and using steroids only if NSAIDs provide insufficient relief  
• Product labels for all IFNβ therapies approved for the treatment of MS suggest that concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms | Class 1        |
| Interferon preparation| Effective         | • Lower incidence of FLS seen with lyophilized IFNβ; switching preparations recommended if FLS occur with prefilled syringe  
• Differences between preparations for FLS not addressed in product labels | Class 2        |
| Timing                | Effective         | • Consensus that patients should self-inject at night so that FLS occur during sleep  
• Evening administration preferred according to the product label for IFNβ-1b | Class 2        |
| Temperature           | Probably effective| • Consensus that patients have fewer FLS when medication is warmed to body temperature prior to use  
• Temperature of medication not addressed in product labels | Anecdotal      |
| Hydration             | Probably effective| • FLS better tolerated in patients who are well hydrated  
• Hydration of patients not addressed in product labels | Anecdotal      |
| Diet                  | Probably effective| • Better resistance to FLS seen in patients with good nutrition  
• Patient nutritional status not addressed in product labels | Anecdotal      |

Abbreviations: FLS, flu-like symptoms; IFNβ, interferon beta; NSAIDs, nonsteroidal anti-inflammatory drugs.

of FLS at the 4- to 6-hour time point and at the 12- to 15-hour time point was significantly reduced with both 3-week titration ($P < .001$ at 4–6 hours; $P = .006$ at 12–15 hours) and 6-week titration ($P = .023$ at 4–6 hours; $P = .027$ at 12–15 hours). The severity of FLS was reduced by 76% at 4–6 hours ($P < .001$) and by 37% at 12–15 hours ($P < .001$) with 3-week titration, while symptom severity was reduced by 50% at 4–6 hours ($P < .001$) and by 32% at 12–15 hours ($P = .002$) with 6-week titration, compared with no titration.  

Thus, there is compelling evidence in both healthy volunteer and MS patient populations that the incidence and severity of FLS can be reduced by carefully titrating IFNβ dosage as patients start therapy. The panel agreed that dose titration is critical to minimize FLS incidence when initiating any IFNβ therapy. Many participants on the panel customized the titration rate based on the patient’s tolerance and any reports of FLS during initiation of therapy.

**Analgesic Management of FLS**

For patients who experience ongoing FLS, there is good evidence that analgesics are effective in limiting symptom occurrence and severity. Concurrent use of analgesics and/or antipyretics to help ameliorate IFNβ-associated FLS is mentioned in the product labels for all IFNβ therapies currently approved for the treatment of MS. In clinical practice, clinicians recommend a variety of treatment protocols to prevent and mitigate FLS, including ibuprofen, naproxen, and oral steroids, as well as acetaminophen.

The panel reviewed three studies that attempted to determine the most effective analgesic for FLS management. When the efficacies of acetaminophen, ibuprofen, and the steroid prednisone were compared, no significant difference was found between the treatment options in the first month of therapy with IM IFNβ-1a. However, ibuprofen appeared to provide better control of symptoms immediately after IM IFNβ-1a injection than either acetaminophen or steroids. Similarly, Reess et al. compared acetaminophen and ibuprofen and found them equally effective at FLS management in patients initiating IM IFNβ-1a. Leuschen et al. compared the efficacy of naproxen, ibuprofen, and acetaminophen and found that the first two were more effective than the last at minimizing many of the physical symptoms associated with IM IFNβ-1a. However, none of these therapies was as effective as originally hypothesized.
for minimizing fatigue or for effectively managing joint and muscle pain.28

Based on these studies, the panel recommended that patients take ibuprofen or naproxen 1 hour prior to IM IFNβ-1a injection, as both compounds were shown to be better than acetaminophen at providing overall prophylaxis of FLS. In one clinical trial a course of steroids with acetaminophen significantly reduced FLS compared to acetaminophen alone; however, patients taking steroids should be carefully monitored, and steroids should generally not be used for long-term symptom management.27 Using low-dose oral steroids to help manage FLS-related pain was recommended only if no improvement was noticed with nonsteroidal anti-inflammatory drugs (NSAIDs).

Timing of Injections

Patient education regarding the potential impact of injection timing on the development of FLS is a key component of successful symptom management, especially during the first 6 months of therapy, when the risk of nonadherence is highest.29 Based on clinical reports,30–31 the panel recommended that IFNβ injections, in general, be administered in the evening to mitigate FLS. Patients are encouraged to determine when their symptoms peak and administer the injection at the appropriate interval prior to bedtime, thus allowing the worst of the side effects to occur during sleep and to fully resolve prior to waking. However, the panel underscored the importance of evaluating individual patients for alternate dosing times, especially in light of evidence that many patients suffered fewer FLS with morning injections.31 These data demonstrate the need for clinicians to counsel each patient to develop an individual routine that best allows the patient to manage any FLS, based on his or her own responses to IFNβ injection.

IFNβ Formulation

IFNβ therapies for MS are available in a number of different formulations, including prefilled syringes and lyophilized preparations (reconstituted immediately prior to injection).20–23 Flu-like symptoms have been reported in 59% to 88% of patients during the initial dosing period using prefilled syringe preparation22,32 and in 49% to 57% of patients receiving reconstituted formulations.20–23,30,32 In their clinical practice, members of the panel noted that a substantial number of their patients who were switched from lyophilized preparations to prefilled syringes experienced more FLS with the latter preparation. Therefore, the panel agreed that clinicians should consider evaluating the IFNβ formulation for those patients who continue to experience FLS despite following the dose-titrations, analgesic, and administration timing recommendations.

Solution Temperature

A review of the literature did not identify any formal reports on the effect of solution temperature on FLS, and this issue is not discussed in the prescribing information for the IFNβ products used to treat patients with MS.29–33 However, in the panel’s experience, the severity and duration of FLS are reduced when the prepared medication is near body temperature at the time of administration. Thus, to optimize solution temperatures, IFNβ therapies should be removed from the refrigerator several hours prior to dosing.31 Patients need to be cautioned that these medications should never be artificially warmed in hot water, in a microwave, or with another intense heat source, as they will lose potency. However, gently warming the solution by holding the vial or syringe in hands, axilla, or a pocket can safely bring the medication closer to a more comfortable temperature. While this evidence is anecdotal, the panel concluded that gently warming the solution prior to injection is associated with a reduced incidence of FLS in a substantial number of their patients and is, therefore, recommended, especially as no risks to the patients are incurred.

Hydration

Low-grade fever is often a significant component of FLS. Because fever can cause dehydration, it is important to counsel patients to hydrate themselves adequately, particularly during the period they experience FLS. Hydration is also important for many aspects of normal cognitive and physical functioning.30 Patients should be counseled on the importance of maintaining adequate fluid intake, as well as on the signs of dehydration, such as dry skin, headache, fatigue, irritability, confusion, and reduced urine output. As patients with MS experience urinary bladder symptoms including incontinence, urine leakage, and hesitancy, they may restrict their fluid intake to limit these bladder-related issues.35 These symptoms may exacerbate FLS in patients with fever resulting from IFNβ treatment. Maintenance of adequate hydration is particularly important in patients who inject during the evening, as restricting fluid intake
in the hours before sleep is often recommended to manage nocturia.

The panel recommended that MS therapy guidelines for injectable IFNβs emphasize the importance of patients maintaining adequate hydration, particularly prior to IFNβ injection, in order to minimize any effects of fever-induced dehydration. The guidelines should recognize that for patients who suffer from FLS and nocturia, fluid loading prior to evening injections may not be appropriate and alternative dosing times should be considered. This recommendation is not based on formal clinical trial data, but on the panel’s clinical experience in their efforts to mitigate discomfort during low-grade fever.

Diet

Finally, proper nutrition is critical for maintaining robust immune responses. While there is no evidence that a specific food can moderate FLS, it is axiomatic that maintenance of a healthy diet makes a large contribution to the body’s ability to withstand FLS. Proper nutrition that includes a reasonable combination of proteins, carbohydrates, and fats from fresh fruits and vegetables, grains, meats, fish, and dairy products has been associated with better health outcomes across all patient populations. Therefore, patients with MS can benefit by avoiding or limiting their intake of foods that are high in fat and sugar in the interest of their overall health. While no formal trials have been conducted on the effect of specific foods or diets on FLS, the panel felt that patients should be counseled on nutrition issues for overall health.

Discussion

As the maximal therapeutic benefit requires good adherence to therapy, it is essential to address factors that lead to patient nonadherence. Adverse events, including FLS, are a major cause of discontinuation of IFNβ-1a therapy in MS patients. The majority of currently approved first-line therapies are IFNβ formulations, which may cause such FLS as fatigue/malaise, chills, fevers, headaches, and myalgia that many patients find difficult to tolerate over long periods. Moreover, the relatively low rate of clinically relevant relapses that most MS patients experience makes long-term adherence more challenging, because the clinical benefit of treatment may not be readily apparent while FLS may continue to occur regularly.

Clinical trial data clearly show that effective management of FLS can increase patient adherence to IFNβ-based disease-modifying therapies (DMTs). Because FLS most often occur during therapy initiation, it is critical that patients be counseled on both the probability of symptoms and their mitigation. Because FLS can occur in long-term users of IFNβ-based DMTs as well, it is important to routinely monitor patient adherence so that clinical staff can intervene as necessary. Nurses should be prepared to discuss the probability of FLS with patients initiating IFNβ therapy and offer practical methods to limit these side effects. This counseling has been shown to be an important aspect of patient care, as adherence rates are higher in patients with realistic expectations of treatment-related side effects. In summary, nurses play a crucial role in ensuring the best long-term clinical outcomes in MS patients by working with patients to develop strategies that increase their overall compliance and adherence to therapy. The guidelines described will help health-care providers educate their patients on effective strategies to limit FLS and thus increase the probability of long-term adherence.

Practice Points

- Flu-like symptoms (FLS) associated with interferon beta (IFNβ) injections negatively affect patient adherence to therapy for MS, and strategies that limit FLS can improve adherence and, hence, overall clinical outcome.
- FLS can be mitigated by dose titration, use of analgesics, evening dosing, drug formulation, solution temperature, adequate hydration, and a nutritious diet.
- Overall adherence to IFNβ therapy can be significantly improved by working with patients to effectively incorporate all of these interventions into their daily routines and injection practices.

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