Injectable Multiple Sclerosis Medications

A Patient Survey of Factors Associated with Injection-Site Reactions

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Although injection-site reactions (ISRs) occur with US Food and Drug Administration–approved injectable disease-modifying therapies (DMTs) for multiple sclerosis, there are currently few reports of real-world data on ISR management strategies or possible correlations between ISRs and patient demographics, disease characteristics, and missed injections. Patient-reported data on the use of DMTs, patient demographic and disease characteristics, missed injections, and ISR reduction strategies were collected via e-mail, a patient registry (www.ms-cam.org), and a Web-based survey. Of the 1380 respondents, 1201 (87%) indicated that they had used injectable DMTs, of whom 377 (31%) had used intramuscular (IM) interferon beta-1a (IFNβ-1a), 172 (14%) had used subcutaneous (SC) IFNβ-1a, 183 (15%) had used SC IFNβ-1b, and 469 (39%) had used glatiramer acetate (GA). The majority of respondents were older (73% were ≥40 years), female (79%), married or living with a partner (72%), white (94%), and nonsmoking (82%). Injection-site reaction incidence, grouped according to severity, varied among DMTs, with IM IFNβ-1a causing significantly ($P < .001$) fewer mild, moderate, or severe ISRs than the other therapies. Female sex and younger age were significantly ($P < .05$) associated with more moderate ISRs among users of IM IFNβ-1a, SC IFNβ-1b, and GA. Nonwhites reported severe ISRs more often than whites. For all DMTs injection-site massage and avoidance of sensitive sites were the most frequently used strategies to minimize ISRs. These data may help identify patients with characteristics associated with a higher risk for ISRs, allowing health-care professionals to provide anticipatory guidance to patients at risk for decreased adherence or discontinuation. ***Int J MS Care.* 2012;14:46–53.**

Between 1993 and 2002, four injectable disease-modifying therapies (DMTs) were approved by the US Food and Drug Administration (FDA) for use in multiple sclerosis (MS) therapy: subcutaneous interferon beta-1b (SC IFNβ-1b; Betaseron, Bayer HealthCare Pharmaceuticals, Wayne, NJ), intramuscular (IM) IFNβ-1a (Avonex, Biogen Idec, Inc, Cambridge, MA), SC IFNβ-1a (Rebif, Serono, Inc, Rockland, MA), and SC glatiramer acetate (GA; Copaxone, Teva Neuroscience, Inc, Kansas City, MO).[1-4] A fifth injectable DMT (SC IFNβ-1b; Extavia, Novartis Pharmaceuticals Corp, East Hanover, NJ) received FDA approval in 2009, after this study was completed.[5] Multiple clinical trials have shown that treatment with these injectable DMTs reduces the frequency of relapses and slows disease progression.[6-9] Although the MS treatment armamentarium is changing with the addition of infused and oral therapies that have recently become available or will be available soon, injectable DMTs remain critical in the treatment of this disease.

One limitation of injectable DMT use for MS is the relatively high rate of treatment discontinuation, estimated to range from 24% to 40% over periods of 2 to 5 years.[10-13] Among the patient-provided reasons for discontinuing therapy are the side effects of DMTs, specifically injection-site reactions (ISRs). In one report, the primary reasons for discontinuation among the 14% of patients who discontinued IFNβ therapy after experiencing associated side effects were ISRs (16%),

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(21%).[11] Another study found that among patients taking GA, ISRs were the most important side effect leading to discontinuation.[14] Skin reactions influence not only discontinuation rates, but also adherence rates. Indeed, approximately 12% of missed injections may be related to pain at the injection site or other skin reactions.[14] Not surprisingly, skin reactions are less common and appear to be less likely to cause discontinuation in users of the IM injectable therapy.[1-5,14,15]

Injection-site reactions as a side effect of injectable DMTs have important implications for both discontinuation and adherence. However, few large patient surveys have reported effective strategies for managing ISRs. Moreover, little is known about the relationships between ISRs and patient demographic variables, disease characteristics, and the frequency of missed injections.

Methods

Study Design

Self-reported patient data on ISR occurrence and use of injectable DMTs were collected using e-mail, a patient registry (www.ms-cam.org), and a Web-based survey instrument. The observational online survey collected descriptive information regarding the use of injectable DMTs, ISRs, disease characteristics, and how respondents with MS addressed the challenges presented by DMT-associated ISRs. For the purposes of this study, the population of interest was patients with MS who were using injectable DMTs. However, given that the respondents were from a self-selected registry that may not be completely representative of this population of interest, any generalizations based on the results should take account of this limitation.

Data Collection

Data were collected from a registry of patients with MS that has been maintained by the Rocky Mountain MS Center since June 2000. At the time of the reported survey, there were approximately 18,000 individuals with self-reported MS in the registry. This registry contains e-mail addresses and related unique, anonymous identifiers in a privately held, protected file. Individual patient participants also are given the opportunity to create passwords so that they can log into the server. These methods of data collection ensure both patient anonymity and secure information transfer and have previously been described in detail.[16]

MS registry participants were recruited through a [illegible] Center (www.mscenter.org) and National Multiple Sclerosis Society (www.nationalmssociety.org) websites. To a lesser extent, patients also learned about this registry through in-office clinic visits or by attending programs presented by clinicians affiliated with the Rocky Mountain MS Center. Typically, registrants were referred to www.ms-cam.org for MS-specific information pertaining to an evidence-based approach to integrative medicine. Thus, it is likely that users registered at www.ms-cam.org to gain access to such information and to participate in survey research. Because the results of Rocky Mountain MS Center surveys are made available to MS registry participants, the opportunity to learn about the experiences of others with MS is an incentive for patients to register. All data collected using patient self-reports and responses from individual registrants remain anonymous.

This Multiple Sclerosis–Injection Site Reaction (MS-ISR) survey was initiated through e-mails sent to the subset of registered patients who had expressed interest in participating in surveys and also demonstrated an ability to complete administered surveys. The methodology and specific content of the MS-ISR survey were approved by a local institutional review board. A subset of these data was previously presented in a preliminary format.[17] The MS-ISR survey instrument was designed by the authors and carefully reviewed by clinicians subspecializing in MS, although it did not undergo preliminary patient testing and evaluation prior to its administration. Patients who received regular medical care and who self-identified as having used injectable DMTs were asked about a number of other factors that might contribute to their ISRs, such as injectable medication used and time on current medication. Respondents were also asked to indicate whether they had tried any of ten possible strategies, compiled from multiple sources as well as the authors' own clinical experience, to prevent or relieve their ISRs. In addition, respondents were asked about their use of autoinjectors. For the purpose of this survey, no attempt was made to validate the effectiveness of any of these strategies. Disability data were also collected using the Patient-Determined Disease Steps model.[18,19]

Although ISRs are universally recognized to be an issue with the use of injectable DMTs for MS, the term currently has no standard definition, nor is there any widely accepted method for grading the severity of ISRs. In the present survey, respondents were asked to [illegible]

ISRs (rarely, sometimes, or often) and the seriousness of these ISRs according to three categories: 1) "mild"—usually transient and involving heat, redness, swelling, and/or bruising; 2) "moderate"—possibly not transient, involving discomfort, and involving itching, pain, lumps, dimpling, and/or skin sores; and 3) "severe"—including scabs, crusting around wound, infection, and/or necrosis. The categories mild, moderate, and severe were not mutually exclusive, as respondents could have experienced one or more of the three different ISR categories. Thus, individual patients may be counted in more than one ISR category depending on their individual symptoms.

Statistical Analyses

All analyses were performed using SPSS, version 17 (SPSS, Inc, Chicago, IL). Prior to analyses, data were examined for data entry and coding errors. Out-of-range and statistical outliers were also checked and, where possible, corrected. If data could not be corrected, they were treated as missing. Descriptive statistics were generated, including medians, means, standard deviations, minimums, and maximums; categorical variables were expressed as percentages. To assess possible associations between two variables, Pearson correlation coefficients were calculated for interval data, Spearman rank correlation coefficients were calculated for ordinal data, and point-biserial correlation coefficients were calculated for dichotomous variables. An independent-sample *t* test (or its nonparametric counterpart) was used to compare means between two groups, and a dependent-sample *t* test (or its nonparametric counterpart) was used to compare two means within a group. A one-way analysis of variance test, with or without repeated measures, was used to compare more than two means. Post hoc, pairwise multiple comparisons were performed using the Bonferroni adjustment. Chi-square analysis was used to assess differences in percentages or proportions.[20]

Results

Data for the MS-ISR survey were collected in 2007, with a total of 1380 eligible patients with MS providing responses. However, 179 (13%) respondents did not provide information on DMT use, leaving 1201 responses for analysis. Not all respondents answered all questions; thus, the number of patient responses to each question is a subset of the total number of 1201 useful

Analysis of patient-reported ISRs showed significant associations between use of injectable DMTs and reports of ISRs, induced discomfort following injection, and severe ISRs (Table 2). Intramuscular IFNβ-1a use was associated with significantly fewer reported ISRs than the other DMTs for all three severity categories, with 82% of patients receiving IM IFNβ-1a experiencing mild side effects ($P < .001$), 73% experiencing moderate side effects ($P < .001$), and 2% experiencing severe side effects ($P < .001$). Also, users of IM IFNβ-1a missed fewer injections because of skin reactions than users of the other DMTs. In comparison, patients receiving SC IFNβ-1a, SC IFNβ-1b, or GA reported a higher incidence of mild (99%, 94%, and 98%, respectively), moderate (91%, 78%, and 90%, respectively), and severe (7%, 15%, and 9%, respectively) ISRs.

For IM IFNβ-1a, SC IFNβ-1b, and GA, female sex and younger age were significantly associated with moderate ISRs, including perceptions of discomfort. Female users of IM IFNβ-1a and GA reported more transient ISRs than did male users (Table 3). Also, nonwhite patients receiving IM IFNβ-1a, SC IFNβ-1a, and GA reported more severe reactions than whites. Smoking, therapy duration, and disability level were not significantly associated with any category (transient, discomfort-causing, or serious) of skin reactions.

The specific strategies used to manage ISRs were similar among users of each of the four injectable DMTs, with a group of six management strategies constituting the top five strategies for all four injectable DMTs (Table 4). The top two management strategies, injection-site massage and avoidance of sensitive injection sites, were identical across all four injectable DMTs. In addition, of the 55% of all respondents who used SC autoinjectors, 24% reported that autoinjectors ameliorated their ISRs.

Discussion

Multiple studies and clinical experience have demonstrated that ISRs are a common side effect of injectable DMTs.[21-23] It is also clear from the present data set and multiple other reported studies that less severe ISRs are reported with IM IFNβ-1a than with the other injectable DMTs for MS.[14,24,25] Our findings on the frequency of ISRs (Table 2) generally conform with what has previously been reported and underscore the deleterious effect that ISRs have on treatment continuation and

Table 1. Demographics for 1201 respondents using one of the four FDA-approved injectable DMTs

Variable	Number	Percentage
Age, y		
<40	322	27
≥40	878	73
Gender		
Male	250	21
Female	946	79
Marital status		
Single	178	15
Married/living with partner	862	72
Divorced	133	11
Widowed	23	2
Race		
White	1122	94
Nonwhite	75	6
Smoking status		
Yes	217	18
No	974	82
Education level		
Less than high school	5	<1
High school	295	25
Associate degree	206	17
Bachelor degree	384	32
Graduate degree	294	25
Regional residence		
Eastern US	404	34
Midwestern US	256	21
Southern US	156	13
Western US	289	24
Eastern Canada	11	1
Central Canada	10	1
Western Canada	17	1
Other	58	5
Employment status		
Yes	707	59
No	482	41
Disease step[a]		
No disability	204	17
Mild disability	416	35
Moderate disability	161	13
Early cane	175	15
Late cane	84	7
Bilateral support	69	6
Wheelchair-bound	61	5
Unclassifiable	29	2

Variable	Number	Percentage
MS provider		
MS center or MS clinic	261	22
Neurologist's office	892	74
Primary-care physician	31	3
Other	17	1
Injectable DMT		
IM IFNβ-1a	377	31
SC IFNβ-1a	172	14
SC IFNβ-1b	183	15
GA	469	39
Time on current DMT, y		
IM IFNβ-1a		
<2	99	26
≥2	278	74
SC IFNβ-1a		
<2	143	83
≥2	29	17
SC IFNβ-1b		
<2	63	34
≥2	120	66
GA		
<2	175	37
≥2	294	63
Did ISRs cause missed injections?		
IM IFNβ-1a		
Yes	12[b]	4
No	295	96
SC IFNβ-1a		
Yes	32	19
No	138	81
SC IFNβ-1b		
Yes	13	8
No	160	92
GA		
Yes	73	16
No	384	84
Provider of injectable DMT instruction		
Neurologist	123	11
Physician (not neurologist)	8	<1
Nurse		
Office	107	9
Home health care	387	34
Pharmaceutical	339	29
MS specialist	191	17

	Mean (SD)	Range
Years since symptom onset	15.0 (9.2)	3–52
Years since MS diagnosis	10.6 (6.5)	3–56

Abbreviations: DMT, disease-modifying therapy; FDA, US Food and Drug Administration; GA, glatiramer acetate; IFNβ-1a, interferon beta-1a; IFNβ-1b, interferon beta-1b; IM, intramuscular; ISR, injection-site reaction; MS, multiple sclerosis; SC, subcutaneous; SD, standard deviation.
[a]No disability—functionally normal with no limitations on activity or lifestyle; mild disability—mild signs or symptoms; moderate disability—main feature is a visibly abnormal gait; early cane—uses a cane or other form of unilateral support for greater distances, but can walk at least 25 feet without it; late cane—unable to walk 25 feet without a cane or other form of unilateral support; bilateral support—requires bilateral support to walk 25 feet; wheelchair-bound—essentially confined to wheelchair.
[b]$p < .001$

Table 2. Perceived injection-site reaction severity with different DMTs

DMT	Perceived injection-site reaction severity		
	Mild	Moderate	Severe
IM IFNβ-1a	82% (306/374)[a]	73% (266/366)[a]	2% (9/364)[a]
SC IFNβ-1a	99% (169/171)	91% (153/168)	7% (11/169)
SC IFNβ-1b	94% (170/181)	78% (135/174)	15% (25/170)
GA	98% (456/465)	90% (409/455)	9% (40/449)

Abbreviations: DMT, disease-modifying therapy; GA, glatiramer acetate; IFNβ-1a, interferon beta-1a; IFNβ-1b, interferon beta-1b; IM, intramuscular; SC, subcutaneous.
Note: Responses were from patients reporting ever having experienced an ISR while on an injectable DMT. Individual patients may be counted in more than one ISR category depending on their individual symptoms.
[a]Significantly different from other DMTs, $P < .001$.

tinued study of these side effects and their causes and for continued patient education to alleviate symptoms, maintain compliance, and positively affect long-term MS outcomes.

Regarding associations among demographic characteristics and ISRs, the present results elaborate on previous findings reported by other investigators by identifying new associations and challenging a few previously proposed associations. In accordance with other studies,[15,27,28] the present data suggest that females report more moderate ISRs than do males. However, this specific finding was not apparent with SC IFNβ-1a, possibly as the result of a ceiling effect, with a high frequency of moderate side effects being reported by almost all users of that drug. This study also revealed two demographic associations that, to our knowledge, have not been previously reported. First, younger patients (<40 years of age) had more frequent complaints of discomfort with injections. Again, this specific association was not apparent with patients receiving SC IFNβ-1a, possi-

Table 3. Perceived transient, discomfort-causing, or serious injection-site reactions by select demographic variables

Variable	IM IFNβ-1a			SC IFNβ1a		
	Transient	Discomfort	Serious	Transient	Discomfort	Serious
Sex						
Male	61% (49/80)	62% (49/79)	3% (2/79)	100% (34/34)	91% (29/32)	13% (4/32)
Female	87% (255/292)[a]	76% (216/285)[b]	2% (7/283)	99% (134/136)	91% (123/135)	5% (7/131)
Age, y						
<40	88% (84/95)	98% (84/86)	3% (3/89)	100% (61/61)	95% (58/61)	7% (4/61)
≥40	22% (68/305)	67% (181/269)[a]	3% (8/240)	98% (108/110)	89% (95/107)	7% (7/103)
Smoking						
Yes	83% (57/69)	71% (49/69)	4% (3/69)	100% (23/23)	96% (22/23)	9% (2/23)
No	82% (247/302)	73% (215/294)	2% (6/292)	99% (144/146)	90% (129/143)	6% (9/139)
Disability						
0 or 1	77% (56/73)	75% (54/72)	4% (3/71)	14% (3/22)	80% (20/25)	14% (3/22)
≥2	83% (241/289)	72% (203/282)	2% (6/281)	14% (20/145)	77% (112/146)	14% (20/145)
Therapy duration, y						
<2	80% (78/98)	69% (66/95)	4% (4/94)	99% (141/143)	91% (130/143)	7% (10/139)
≥2	83% (228/276)	74% (200/271)	2% (5/270)	100% (28/28)	92% (23/25)	4% (1/25)
Race						
White	83% (285/344)	71% (240/336)	2% (6/334)	99% (154/156)	92% (140/153)	4% (6/149)
Nonwhite	70% (19/27)	85% (23/27)	11% (3/27)[c]	100% (15/15)	87% (13/15)	33% (5/15)[a]

Abbreviations: GA, glatiramer acetate; IFNβ-1a, interferon beta-1a; IFNβ-1b, interferon beta-1b; IM, intramuscular; SC, subcutaneous.
Note: Responses were from patients reporting ever having experienced an injection-site reaction while on an injectable disease-modifying therapy. Individual patients may be counted in more than one injection-site reaction category depending on their individual symptoms.
[a]$P < .001$.
[b]$P < .05$.

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