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Original article

Results of sustained long-term use of interferon beta-1a in a community-based cohort of patients with relapsing multiple sclerosis

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Abstract

Background:
Few studies have evaluated long-term efficacy of interferon beta-1a in large community-based cohorts.

Objective:
Evaluate time to relapse, relapse rate, and disability progression in patients treated with intramuscular interferon beta-1a.

Methods:
A retrospective review of medical records from 2000–2010 was performed. Adult patients with relapsing-remitting MS or clinically isolated syndrome treated with interferon beta-1a were included. Primary outcomes were time to relapse, annualized relapse rate, and changes in Expanded Disability Status Scale score. Other outcomes included factors associated with time to first relapse, risk of having a relapse while receiving interferon beta-1a, and discontinuation of therapy.

Results:
In total, 364 of 696 patients screened were enrolled, with a mean age of 51 $\pm$ 12.1 years, disease duration of 9.39 $\pm$ 7.02 years, and duration of therapy of 4.03 $\pm$ 2.56 years. Mean time to first on-therapy relapse was 5.58 $\pm$ 0.26 years, annualized relapse rate was 0.30 $\pm$ 0.55 years, and mean increase in sustained Expanded Disability Status Scale score was 0.018. Relapse risk was associated with higher baseline Expanded Disability Status Scale score, age at disease onset, and number of relapses in the 12 months prior to therapy initiation.

Conclusions:
This study demonstrates favorable clinical outcomes observed in a large community-based cohort, and serves to emphasize the continued therapeutic importance of interferon beta-1a, despite the development of newer agents with greater convenience of use, but also more potential risk of serious morbidity.

Introduction

Clinical trials have demonstrated that interferon beta-1a (IFNB) may control disease activity in relapsing forms of multiple sclerosis (RMS), reducing the risks of clinical relapse, disability progression, and worsening disease burden on brain magnetic resonance imaging (MRI), when compared to placebo-treated patients[1–3]. However, these are short-term studies, not exceeding 2 years' duration, and do not provide data on IFNB impact upon the long-term management of RMS. Several retrospective studies of long-term outcomes of intramuscular (IM) IFNB-treated patients have been reported[4–7], but the number of patients

has been small and a large percentage of patients were lost to follow-up. Furthermore, these patients had been originally recruited for controlled clinical trials, and, thus, were subject to potential selection bias, which might render them unrepresentative of patients treated in a community-based cohort. Our study is comprised of clinical data from a community-based cohort of continuously treated, and closely followed patients, in a single, large multiple sclerosis center. We conducted this study because we observed that our patients appeared to have a clinical response to IM IFNB which was superior to that expected from the results of earlier reported clinical trials.

Methods

A retrospective review of medical records of patients cared for by the Providence Multiple Sclerosis Center (PMSC) was conducted by two nurses who were experienced in chart review and data abstraction for patients with MS, covering the period from January 1, 2001 to December 31, 2010. All patients in the PMSC were diagnosed and cared for by neurologists who specialize in the management of MS. The search criteria used in the medical records were MS diagnosis, meeting the 2010 Revised McDonald Diagnostic Criteria[8], and IM IFNB use. Further review excluded subjects if they had more than one neurological diagnosis, had received IM IFNB as part of their participation in an investigational trial, had started IM IFNB therapy prior to initiating care at PMSC, had not had more than one visit to PMSC, did not have RMS, or had any documented gaps in IM IFNB use that were greater than 1 month. Outcome variables, following initiation of IM IFNB, included time to first relapse, annualized relapse rate, and disability progression, as measured by the Expanded Disability Status Scale (EDSS)[9]. Factors associated with risk of relapse and discontinuation of IM IFNB were also analyzed.

Baseline was defined as the time of IM IFNB therapy initiation. Relapse was defined as the onset of new or worsening neurological symptoms of at least 24 hours' duration, in the absence of fever or other signs of infection, in a patient who had been neurologically stable for at least 30 days prior to the acute event. Relapses were captured by patient self-report and confirmed by neurological assessment. As a standard practice in the PMSC, patients are instructed to call the center when they experience any new or worsening symptoms. Following the telephone encounter, patients whose symptoms are consistent with a relapse are brought back to the PMSC for further evaluation and, if a relapse has been confirmed, therapeutic intervention proceeds generally within 24 h of the clinic visit. Descriptive statistics were applied to examine the distribution of the data. *T*-test and chi-square test were used to compare the differences between the groups for continuous and categorical variables, respectively. Kaplan-Meier estimates were used to obtain the proportion of patients who had a relapse during the follow-up, and the estimated time to relapse for the cohort over the study period. Multivariate analyses for the predictors of time to first relapse were performed using Cox proportional hazard regression. Variables include in the model were EDSS at baseline, age at MS onset, number of relapses in the 12 months prior to start of IM IFNB, and time from diagnosis to start of IM IFNB. Each subject contributed relapse-free time from the start of IM IFNB therapy until the end of the study period or first on-therapy relapse. Patients were censored if they discontinued therapy or left the clinic prior to the end of the observation period. Multiple logistic regression was used to determine the factors associated with having a relapse while on IM IFNB therapy and the factors associated with discontinuation of therapy. The study was approved by the Providence Institutional Review Board for Human Research.

Results

Initial screening revealed 696 potentially eligible patients, but only 364 of them met the criteria to be included in the study. A total of 332 patients were excluded: 29 were enrolled in investigational drug trials; 40 did not have RRMS or CIS or had other neurological diagnoses; 203 did not start or sustain IFNB treatment during the study period; and 60 patients did not have regular office visits or complete medical records.

Baseline characteristics and patient outcomes are shown in Table 1. Age ranged from 20–87 years, 79.9% were female, and age of MS onset varied from 10–76 years. At baseline, 76.9% had RRMS and 23.1% had CIS. The demographic profile of this cohort is consistent with features found in the MS population of North America. Mean duration of disease was 9.4 years. The mean number of relapses in the 12 months prior to initiating IFNB therapy was 1.06. Mean and median baseline EDSS scores were 2.37 and 2.0, respectively, and 19% of subjects had received other disease-modifying therapies prior to initiation of IM IFNB therapy.

Over the observation period (4.7 ± 3.7 years), 44% of subjects had at least one relapse. The cohort had a mean and median time to first relapse after starting IM IFNB therapy of 5.58 and 5.25 years, respectively. ARR during the period of observation was 0.3 ± 0.55, and there was a mean increase from baseline EDSS of 0.018 (Table 1). There was no significant difference in ARR between RRMS and CIS patients (0.31 vs 0.25, $p = 0.40$) and, although there appeared to be a trend favoring longer interval to first relapse while taking IM IFNB in CIS patients, this result did not reach statistical significance (5.36 vs 6.16 years, $p = 0.12$). The estimated hazard of

Table 1. Baseline characteristics and patient outcomes.

Variable	Mean (SD) or %	*n*
Age, mean years (SD)	51.0 (12.1)	364
Female, %	79.9	291
MS pattern, %		
Relapsing Remitting MS (RRMS)	76.9	280
Clinically Isolated Syndrome (CIS)	23.1	84
Age at MS onset, mean years (SD)	41.6 (11.57)	364
Duration of disease, mean years (SD)	9.39 (7.02)	363
Number of relapses in 12 months prior, mean (SD)	1.06 (0.67)	364
Used other DMT prior to IFNβ1a, %	19.2	70
Time from diagnosis to start of IFNβ1a, %		
<1 year	67.3	245
≥1 year	31.3	114
EDSS, mean (SD)		
Baseline	2.37 (1.13)	364
End of observation	2.38 (1.39)	364
Change	0.018 (1.25)	364
Time to first on IFNβ1a relapse, mean years (SD)		
Overall	5.58 (0.26)	364
RRMS	5.36 (0.30)	280
CIS	6.16 (0.51)	84
Annualized relapse rate, mean (SD)		
Overall	0.30 (0.55)	364
RRMS	0.31 (0.56)	280
CIS	0.25 (0.48)	84
Relapsed while on IFNβ1a, %	44.0	160
Time on IFNβ1a, mean years (SD)	4.03 (2.56)	364
Discontinued IFNβ1a during observation, %	35.7	130
Reason for discontinuing IFNβ1a, %		
Side-effects	30.8	40
Breakthrough disease evidenced by relapse	23.1	30
Breakthrough disease evidenced by MRI changes	12.3	16
Pregnancy	10.8	14
Cost of IFNβ1a	8.5	11
Transition to progressive MS	3.1	4
Other	11.5	15

Table 2. Cox proportional hazard model: Risk of on-IFNβ1a relapse ($n = 361$).

Variable	Hazard ratio	95% CI	*p* Value
EDSS at baseline	1.17	1.01–1.35	0.03
Age at MS onset (years)	0.97	0.96–0.98	<0.001
# of relapses in 12 months prior to start of IFNβ1a	1.44	1.14–1.81	<0.01
Time from diagnosis to start of IFNβ1a			
<1 year (ref)			
≥1 year	0.62	0.41–0.92	0.02

on-therapy relapse increased with higher baseline EDSS (HR = 1.17, $p = 0.03$) and greater number of relapses in the 12 months preceding initiation of IM IFNB (HR = 1.44, $p = 0.002$). However, the risk of time to first on-IFNB relapse decreased if the patient was older at disease onset (HR = 0.97, $p < 0.001$) and had one or more years from time of diagnosis to initiation of IM IFNB (HR = 0.62, $p = 0.02$), as shown in Table 2. Table 3 demonstrates adjusted odds ratios (OR) of factors associated with having a relapse while receiving IM IFNB. For each relapse observed in the 12 months prior to IM IFNB therapy, there was a 62% increased odds of having a relapse while on IM IFNB ($p = 0.007$). Older age at disease onset (OR = 0.958, $p < 0.001$) reduced the odds of having a relapse. Duration of IM IFNB therapy also showed a trend to increase the odds of having a relapse while on therapy with a borderline *p* value of 0.05. Baseline EDSS, time from diagnosis to therapy initiation, previous DMT, or duration of disease did not affect the likelihood of having a relapse while on IM IFNB. One hundred and thirty patients (35.7%) discontinued IM IFNB therapy during the period of observation due to intolerance of side-effects ($n = 40$), clinical relapses ($n = 30$), MRI changes ($n = 16$), pregnancy ($n = 14$), cost of medication

Table 3. Factors associated with having an on-IFNβ1a relapse ($n = 364$).

Variable	Adjusted Odds Ratio	95% CI	*p* Value
Age at MS onset (years)	0.96	0.94–0.98	<0.001
# of relapses in 12 months prior to start of IFNβ1a	1.62	1.14–2.29	<0.01
Time on IFNβ1a	1.10	1.00–1.22	0.05
Time from diagnosis to start of IFNβ1a			
<1 year (ref)			
≥1 year	0.50	0.24–1.03	0.06
EDSS at baseline	1.20	0.97–1.48	0.10
Prior DMT			
No (ref)			
Yes	1.00	0.53–1.92	0.99
Duration of MS (years)	1.00	0.96–1.05	0.82

Table 4. Reported adverse events.

Adverse event	*n*	% of total sample
Flu-like symptoms	260	71.4%
Cutaneous injection reactions	23	6.3%
Infection		
Respiratory	152	41.8%
Urinary tract	51	14.0%
Flu	19	5.2%
Bacterial dermatitis	8	2.2%
Eye infection	4	1.1%
Herpes Zoster	4	1.1%
Herpes Simplex	1	0.3%
Other	17	4.7%
Depression		
Diagnosed after baseline	14	3.8%
Worsened on IM IFNβ1a	27	7.4%
Suicidal thinking	8	2.2%
Suicide attempts	2	0.5%
Suicide death	1	0.3%
Hepatic dysfunction		
LFT > 3 × ULN	4	1.1%
Cardiovascular		
Hypertension	1	0.3%
Tachycardia	3	0.8%
Heart failure[a]	1	0.3%
Cancer		
Breast[b]	3	0.8%
Colon	1	0.3%
Prostate	1	0.3%
Lung[c]	1	0.3%
Basal Cell	1	0.3%

[a]One death.
[b]Two deaths.
[c]One death.

($n = 11$), transition to progressive MS ($n = 4$), and undetermined reasons ($n = 15$) (Table 1).

Reported side-effects (Table 4) included flu-like symptoms ($n = 260$), cutaneous injection reactions ($n = 23$), infections ($n = 256$), psychiatric ($n = 52$), serious liver abnormalities ($n = 4$), and cardiovascular ($n = 5$), including one death from heart failure, and six cancer diagnoses, including two deaths from breast cancer and one death from lung cancer. Multiple logistic regression analysis showed that higher ARR (≥0.4) during IM IFNB therapy was the only significant factor for discontinuing the treatment during the observation period (OR = 7.646, $p < 0.0001$) (Table 5).

Discussion

Our study was initiated to better understand the clinical responsiveness of patients with RMS to treatment with IM IFNB in a large community-based cohort. It was our impression that the results of controlled investigational trials[1–3] may have under-estimated the clinical efficacy of IM IFNB, were of too short a duration, and possibly comprised of a cohort profile not representative of community-based MS patient populations. The PMSC is a regional MS center serving the entire State of Oregon and southwestern Washington State. The MS patients cared for are broadly representative of the geographic, socioeconomic, and ethnic characteristics of the region, and are seen in the clinic every 3–4 months for routine care. This retrospective analysis of all RMS patients over the age of 18 years, who had initiated therapy with IM IFNB while attending the PMSC, revealed a mean time to first relapse of 5.58 years, an ARR of 0.299, and mean EDSS increase of 0.018. Despite the difficulties inherent in trying to compare results in different trials, employing different patient populations, different study designs, and different investigators, our results do suggest that clinical control of disease activity, in our large community-based setting, is superior to that expected from the results of earlier controlled IFNB trials[1,3,10]. The risk of time to first on-IFNB relapse was associated with age of disease onset, the number of relapses during the 12 months prior to starting IM IFNB, and EDSS at the time IM IFNB was initiated. Surprisingly, and in contrast to previously published studies[11], patients with an interval of at least 1 year between MS diagnosis and initiation of IM IFNB were less likely to experience subsequent relapses compared to those who initiated therapy in less than a year. We do not have an explanation for this variance from the results of earlier studies. The side-effect profile observed was consistent with previously reported studies of

Table 5. Factors associated with discontinuation of IFNβ1a ($n = 364$).

Variable	Adjusted Odds Ratio	95% CI	*p* Value
ARR			
ARR = 0 (ref)			
ARR < 0.4	1.60	0.56–2.02	0.85
ARR ≥ 0.4	7.65	4.21–13.88	<0.001
Age at MS onset (years)	1.01	0.98–1.03	0.62
EDSS at baseline	1.00	0.82–1.30	0.78
# of relapses in 12 months prior to start of IFNβ1a	0.96	0.66–1.40	0.84
Time from diagnosis to start of IFNβ1a			
<1 year (ref)			
≥1 year	1.00	0.47–2.14	0.99
Prior DMT			
No (ref)			
Yes	1.47	0.74–2.93	0.27
Duration of MS (years)	1.00	0.95–1.04	0.84

IFNB[1–3], with the majority of subjects experiencing flu-like symptoms. There were 256 infection-related adverse events reported at some time during the course of therapy, primarily of the urinary ($n = 51$, 14%) and upper respiratory ($n = 152$, 41.8%) tracts. There were no serious or opportunistic infections or hematologic abnormalities encountered, and minor liver function abnormalities were infrequently observed. Serious adverse events were limited to one patient with heart failure, and seven patients with carcinoma, well within the range encountered in the general adult population.

Among the strengths of our study are the large size of our cohort, the frequency and duration of patient follow-up, the low patient attrition, and the absence of gaps in medical histories that have plagued other retrospective analyses of long-term IFNB use[4–7]. Furthermore, the only criterion used for initiating IM IFNB therapy was a diagnosis of RMS and, during the 2001–2010 period of this study, IFNB was the only medication used to initiate treatment of RMS in the PMSC, thus reducing or eliminating medication selection bias based upon disease severity or duration in determining whether patients received IFNB or another agent. There was no attempt made to compare the efficacy of IFNB to other agents used to treat RMS, but we would encourage similar, community clinic-based studies of other 'first-line' agents used to treat RMS to determine if they yield therapeutic results different from those obtained in their respective pivotal controlled trials.

However, our results should be interpreted with caution. Treatment was not blinded, there was no placebo or therapeutic comparator employed, and these results do not provide comparative efficacy data. Because 30 patients (8%) discontinued IM IFNB after a single relapse, there is risk of bias in the results due to censoring of poor responders. If these patients had continued IM IFNB, the mean ARR and EDSS may have been higher than was observed. The data also demonstrate that 50% of patients had remained relapse-free 5.25 years after starting IM IFNB. Although there is a possibility that some patients did not inform the clinic of possible relapse symptoms occurring between scheduled visits, there is no indication that our patient population acted any differently in this regard than subjects in other studies of medication efficacy in MS. Furthermore, this result does not appear to be affected by bias of study design or performance, and compares favorably with previously reported studies[2,12,13] in which data on time to first relapse was provided. Nevertheless, one must be very cautious when comparing results of different studies. In addition to the problems of different patient populations, selection criteria and investigators, there has been a trend towards reduction in relapse rates and disability progression, even in placebo-treated patients, in the more recently conducted trials of various agents[1–3,12–15]. If placebo-controlled trials of IFNB were conducted now, the results might be very different than those observed in the 1990s. Although MRIs were obtained, typically every 12 months in our clinic, and changes in MRI contributed to IM IFNB discontinuation in 16 subjects (4.4%), this was a study limited to the clinical impact of treatment of IFNB. We did not report MRI outcomes, in part, because a wide variety of MRI machines were used due to differing patient locales, differing insurance coverage, and the changes in MRI technology that occurred during the 2000–2010 period of observation.

Although new disease modifying therapies for MS have been approved[12–20], only two newly approved agents have been proved more efficacious than IFNB in a head-to-head comparison, and one of these studies was of only one year's duration[16,19,20]. Furthermore, the frequency and severity of potential adverse events seen with newer agents are a major potential source of concern[14,17–20], whereas IFNB use, in a large community cohort of MS patients, over many years, was associated with minimal risk of serious adverse events. The results of this study support a continued role for IFNB in the long-term treatment of RMS,

based upon its efficacy, and safety profiles when compared to newer agents.

Transparency

Declaration of funding
This study was funded by Biogen Idec.

Declaration of financial/other relationships
SC has disclosed that he serves on advisory boards for Biogen Idec, Novartis, and Sanofi Genzyme, has received research support from Biogen Idec, Novartis, Sanofi Genzyme, Opexa, Teva, Mallinckrodt and Roche, and has received speaker honoraria from Biogen Idec, Novartis, Sanofi Genzyme and Acorda. CC, EB, TS, LG, and MR have no relevant financial relationships to disclose. JDA Peer Reviewers on this manuscript have no relevant financial relationships to disclose.

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