Swiss analysis of multiple sclerosis: a multicenter, non-interventional, retrospective cohort study of disease-modifying therapies

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Abstract: BACKGROUND: There is a scarcity of reports comparing efficacy and tolerability of the multiple sclerosis (MS) disease-modifying therapies [DMTs; intramuscular interferon- 1a (IM IFN -1a), subcutaneous (SC) IFN -1a, SC IFN -1b, SC glatiramer acetate (GA)] in a real-world setting. METHODS: This multicenter, non-interventional, retrospective cohort study analyzed data from 546 patients with clinically isolated or relapsing-remitting MS constantly treated with one DMT for 2 years. Annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) scores, and DMT tolerability were assessed. RESULTS: Demographic data were comparable across DMTs. There were no significant differences between DMT groups in ARR during study year 1 ($p = 0.277$) or study year 2 ($p = 0.670$), or in EDSS change between years 1 and 2 ($p = 0.624$). Adverse events were frequent (39-56%) in all groups. Flu-like symptoms were less frequent with GA treatment (2.3% vs. IM IFN -1a, 46.7%; SC IFN -1a, 39.8%; SC IFN -1b, 25.8%; $p < 0.05$). Injection site reactions were less often reported with IM IFN -1a (10.5% vs. SC IFN -1a, 33.9%; SC IFN -1b, 38.3%; GA, 26.1%; $p < 0.05$). CONCLUSIONS: All DMTs showed comparable effects on MS relapse rate and EDSS change, with IM IFN -1a and GA being more tolerable with respect to injection site reactions and flu-like symptoms, respectively.

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Swiss Analysis of Multiple Sclerosis (SAME): Multicenter, Noninterventional, Retrospective-Cohort Study of Disease-Modifying Therapies

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Abstract

Background: Few reports exist comparing the efficacy and tolerability of the multiple sclerosis (MS) disease-modifying therapies (DMTs) intramuscular interferon beta-1a (IM IFNβ-1a), subcutaneous (SC) IFNβ-1a, SC IFNβ-1b, and SC glatiramer acetate (GA) in a real-world setting. **Methods:** This multicenter, noninterventional, retrospective cohort study analyzed data from 546 patients with clinically isolated syndrome or relapsing-remitting MS treated on a consistent basis with one DMT for ≥2 years. Annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) score, and DMT tolerability were assessed. **Results:** Demographic data were comparable across DMTs. There were no significant differences between groups in ARR during study year 1 ($p = 0.277$) or study year 2 ($p = 0.670$) or in EDSS change between years 1 and 2 ($p = 0.624$). Adverse events included flu-like symptoms (IM IFNβ-1a, 46.7%; SC IFNβ-1a, 39.8%; SC IFNβ-1b, 25.8%; GA, 2.3%) and injection-site reactions (IM IFNβ-1a, 10.5%; SC IFNβ-1a, 33.9%; SC IFNβ-1b, 38.3%; GA, 26.1%). **Conclusions:** All DMTs showed comparable effects on MS relapse rate and EDSS change during the study period, with IM IFNβ-1a and GA being most tolerable with respect to injection-site reactions and flu-like symptoms, respectively.

Introduction

The efficacy and tolerability of injectable interferon beta (IFNβ) and glatiramer acetate (GA) as first-line disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS) have been validated in pivotal phase 3 trials [1–5]. Across several clinical studies, IFNβ and GA reduced the mean patient MS relapse rate by approximately one-third [1–4] and decreased magnetic resonance imaging (MRI) T2-weighted (T2) brain lesion volume and the number of gadolinium-enhancing (Gd+) brain lesions compared with placebo [5–6]. However, the relative efficacy of these immunomodulatory therapies cannot be determined by a simple comparison between past trial results because of differences among trials in study methodology, outcome criteria, and patient populations.

Previous DMT comparative studies have typically evaluated two of the four commercially available injectable therapies [7–10]. Two large, pharmaceutical industry–sponsored head-to-head trials showed that self-injectable subcutaneous (SC) IFNβ was not superior to GA with regard to clinical efficacy outcomes over 2 years [7–8]. There have also been two reported head-to-head trials that showed superior efficacy for SC IFNβ compared with intramuscular (IM) IFNβ in lengthening the time to the first clinical relapse on study [9–10]. In addition, study populations in phase 2 and 3 clinical trials may not represent the general population in which the studied drugs will be used after approval, and it is thus well recognized that clinical trial results may be only partially reproducible in general clinical practice.

Several open-label, postmarketing, observational studies have reported similar efficacy for the three different IFNβ preparations [11–19], but only a few have compared these DMTs and GA [20–21]. Although there is one report in the literature comparing the effects of all four different immunomodulatory therapies on MS disease progression in patients with relapsing-remitting MS (RRMS), the study groups were quite imbalanced and the reported differences in hazard ratios between the DMTs were attributed to selection bias [22]. Multicenter clinical data comparing the use of all four injectable DMTs in patients with clinically isolated syndrome (CIS) or RRMS have not previously been reported. We present the results of a retrospective study comparing the efficacy, safety, and tolerability of the three IFNβ preparations and GA in patients with CIS or RRMS in a real-world setting.

Methods

Patients

The Swiss Analysis of Multiple Sclerosis (SAME) study was a multicenter, noninterventional, retrospective cohort study that analyzed data from patients treated at 30 centers in Switzerland with either one of the IFNβ formulations or GA on a consistent basis for at least 2 years. The inclusion criteria were age between 18 and 65 years at first visit, diagnosis of either CIS or RRMS according to the 2005 revised McDonald criteria [23], and treatment with the same DMT for the previous 2 years. Availability of patient demographic information, medical history, and the results of neurological examinations were required for inclusion in the study. All patients who met these criteria from June to October 2010 were included. Eligible patients had received continuous treatment with one of four first-line DMTs (IM IFNβ-1a 30 μg [Avonex®], SC IFNβ-1a 22/44 μg [Rebif®], SC IFNβ-1b 250 μg [Betaferon®], or GA 20 mg [Copaxone®]) at standard doses for at least 2 years (i.e., the study period). Use of any MS treatment for any duration was allowed prior to the study period. Study exclusion criteria were DMT treatment less than 2 years, an interruption in DMT therapy during the study period, therapy that did not include a first-line DMT, or the occurrence of an MS relapse during the 4 weeks immediately prior to enrollment in SAME. All patients provided informed consent, and the study was approved by each study site's institutional review board or clinical research ethics committee.

Study design

The SAME study was a multicenter, noninterventional, retrospective cohort study that analyzed data from patients treated at one of 30 MS centers in Switzerland with an IFNβ or GA for at least 2 years. The study period was defined as 24 months of continuous use of the same DMT and was divided into the two time intervals of the first 12 months (year 1) and the second 12 months (year 2) of the study period (Fig. 1).

The primary study endpoint was annualized relapse rate (ARR) for years 1 and 2. The secondary endpoint was change in patient Expanded Disability Status Scale (EDSS) score from year 1 to year 2. In addition, adverse events (AEs) during the 2-year study period were collected in all patients. For each patient, participating investigators completed a case report form that requested information on patient demographic and clinical data, including date of birth, gender, date of CIS or RRMS diagnosis, preparation and dose of the DMT, first treatment after MS diagnosis prior to the start of the SAME study period (i.e., "initial therapy"), number of relapses, and EDSS scores. MRI scans were performed based on clinical need.

Participating study sites entered data using a secure, Web-based tool created for the study that ensured the quality of the data collection and also allowed for consolidated monitoring. Study endpoints were the number of relapses (categorized as 0, 1, 2, or ≥3), the change in EDSS score, and treatment-associated AEs (categorized into flu-like symptoms, injection-site reactions [redness, inflammation, necrosis, and lipoatrophy], and other) during SAME study years 1 and 2. A relapse was defined, according to widely accepted international diagnostic and therapeutic guidelines [23], as newly developed neurological symptoms or reactivation of preexisting neurological deficits for a minimum of 24 hours in the absence of an increase in body temperature or infections, or as symptoms occurring at least 30 days after the preceding episode.

Statistical analyses

The planned analysis compared the number of relapses, EDSS score, and change in EDSS score between treatment groups. In addition, patients who had switched to DMT before the study (the “switch” group) were compared with those for whom DMT was the first treatment (the “no-switch” group). Because of the non-normal distribution of the outcomes, comparisons used nonparametric tests (U-tests, Kruskal-Wallis one-way analysis of variance, and chi-square tests, as appropriate). Bonferroni post hoc tests were conducted for comparisons that showed overall significant differences. Results were considered significant at $p < 0.05$. Treatment differences in AEs were analyzed using chi-square tests, with significance accepted when $p < 0.05$.

Results

A total of 546 subjects were enrolled in SAME. Patient demographic data were similar across all four treatment groups (Table 1). The overall mean age at enrollment (± standard deviation) was 44 ± 10.5 years, and the majority of patients (70%) were women. Ninety percent of patients presented with RRMS. Disease duration was largely comparable across treatment groups for CIS patients, though RRMS patients treated with SC IFNβ-1b had a longer disease duration than patients treated with IM IFNβ-1a ($p < 0.05$ [post hoc test]; Table 1). There were no significant differences between groups in relapse rate or EDSS score during

years 1 or 2 (Fig. 2; Fig. 3; Table 1). In addition, change in EDSS score from year 1 to year 2 did not differ significantly between treatment groups ($p = 0.624$ [Kruskal-Wallace one-way analysis of variance]).

A total of 88 patients (22 on IM IFNβ-1a, 16 on SC IFNβ-1a, 8 on SC IFNβ-1b, and 42 on GA) had used a different DMT prior to SAME. When patients receiving a DMT as their first drug (458 patients) and those receiving a DMT as their second drug (88 patients) were compared, the two groups did not differ in age, gender, or proportion of patients with RRMS or CIS (Table 1). Patients who had switched to a DMT had a longer disease duration and higher EDSS scores both during year 1 and 2 than those who had originally received a DMT. The EDSS change between year 1 and 2 was, however, comparable between groups ($p = 0.0472$ [Mann-Whitney U test]).

MRIs were performed for 148 patients (27.1%) and 226 patients (41.6%) during SAME study years 1 and 2, respectively. For the majority of patients (75% in year 1 and 65% in year 2), MRIs were performed as part of routine disease monitoring, with the remainder of procedures (25% and 35%, respectively) performed following evidence of MS disease activity. Given the small proportion of patients who had MRI results at both years 1 and 2, we did not perform detailed statistical analysis or further evaluation of these data.

Overall patient reports of treatment-related AEs did not differ significantly ($p = 0.052$) between treatment groups, although some group differences in specific AEs were evident (Table 2). The predominant AEs were flu-like symptoms and local injection-site reactions. Reports of flu-like symptoms differed significantly between IM IFNβ-1a and both SC IFNβ-1b ($p < 0.001$) and GA ($p < 0.001$); between SC IFNβ-1a and both SC IFNβ-1b ($p = 0.017$) and GA ($p < 0.001$); and between SC IFNβ-1b and GA ($p < 0.001$). However, patients on IM IFNβ-1a experienced significantly fewer injection-site reactions ($p < 0.001$) than patients on the other three DMTs, with redness and inflammation the most commonly reported injection-site reactions. Necrosis was associated with SC IFNβ-1a and SC IFNβ-1b, but not with IM IFNβ-1a or GA. Slight lipoatrophy was associated with SC IFNβ-1a, SC IFNβ-1b, and GA, but not with IM IFNβ-1a. Patient-reported fatigue did not differ significantly between treatment groups.

Discussion

This 2-year, multicenter, retrospective, observational study demonstrated that, in a selected real-world MS population of nearly 550 patients, the four first-line DMTs for the treatment of MS had a similar impact on

ARR and disability progression. There were no major differences in AEs between patients receiving the different DMTs, although the prevalence of injection-site reactions and flu-like symptoms seemed to be lower with IM IFNβ-1a and GA, respectively. To our knowledge, this is the first report of a study simultaneously comparing the efficacy and side effects of these four first-line DMTs in a large cohort of patients affected with RRMS and CIS in a multicenter real-world setting.

The SAME study showed comparable efficacy for all four injectable DMTs in preventing MS relapses and disability progression (as indicated by change in EDSS score) during the study period. In addition, a separate analysis on the key clinical endpoints (ARR and EDSS), stratified into patients receiving the DMT as their first drug and those receiving it as their second drug, indicated that the latter group was more severely affected in terms of disability. However, ARR and disability progression over 2 years did not differ between the 2 groups.

These results are in line with other short- and long-duration real-world postmarketing studies [11–21]. In contrast, two previous head-to-head trials, EVIDENCE [9] and INCOMIN [10], showed superior efficacy for SC IFNβ compared with IM IFNβ in terms of time to the first clinical MS relapse on study. However, differences between treatment groups in patient baseline characteristics, variation in MS therapies prior to study initiation, the absence of a placebo comparator group, failure to randomize for treatment allocation, regression to the mean, and possible selection bias may limit the utility of those data.

The current study evaluated an MS patient cohort during a 2-year period of uninterrupted first-line MS therapy. Given that the majority (87%) of patients in the SAME study had been on the same DMT for many years, we suggest that these patients represent a stable, real-world MS patient population. In the current study, all of the AEs reported by patients were expected, and they occurred at similar frequencies as in previous reports [24].

The study has several limitations that should be taken into account when interpreting its results. We examined a large group of patients (546 patients in 30 Swiss centers), representing approximately 10% of the estimated Swiss MS population, in real-world clinical practice settings. Patients on stable DMT treatment for at least 2 years in such settings most likely represent long-term responders to DMTs or patients with low disease activity; they may differ from the general population of MS patients. To further explore potential differences among patients, we also compared patients who had been switched to DMTs, i.e., were switched due to reasons of tolerability or efficacy, with those for which DMTs were the first treatment. Given the

specific study protocol, we had no information as to why patients had switched treatment. However, our results indicated that although patients who had switched treatment were more severely affected by disability, change over the 2-year period did not differ between the groups. The low number of patients who had switched (13%), however, precluded us from comparing different treatments within this group. A related limitation involves the retrospective study design: Since we did not include patients who discontinued DMT treatment before 2 years, we cannot make any statements about safety and tolerability based on the study. However, in patients who stayed on their DMT, AE rates were comparable to previous study reports. In general, randomized studies have a better research design, since bias can be introduced in open-label, nonrandomized studies that cannot be overcome by any statistical methods [25]. However, it is not always feasible to conduct randomized trials, and alternative study designs will inevitably need to be utilized. Benson et al. [26] reported that the estimates of treatment effects from observational studies and randomized controlled trials are similar. The value of observational studies should therefore not be underestimated since phase 4 studies and retrospective chart reviews can also reveal important differences among drugs in the same class that were not detected in controlled phase 2 or 3 clinical trials [17]. Taken together, in a selected patient population, the four injectable DMTs showed comparable efficacy and safety with differences in tolerability.

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Conflicts of Interest

Claudio Gobbi has received honoraria from Bayer Schering, Biogen-Dompé, Merck Serono, Novartis, and Teva. Chiara Zecca has received honoraria from Bayer Schering, Merck Serono, Novartis, and Teva. Michael Linnebank has received grants or honoraria from Abbott, Bayer, Biogen-Dompé, Desitin, Merck, Novartis, Pfizer, Sanorell, and Teva. Stefanie Müller has received honoraria, travel grants, research grants,

and personal compensation from Bayer Healthcare, Biogen-Dompé, Merck Serono, Novartis, sanofi-aventis, and Teva. Xiaojun You is an employee of Biogen Idec Inc. Emanuela Villiger and Martin Traber are employees of Biogen-Dompé AG. Rosetta Meier is a former employee of Biogen-Dompé AG.

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Table 1. Patient demographic and clinic characteristics

		DMT					Switch vs no switch		
	All DMTs	IM INFβ-1a	SC INFβ-1a	SC INFβ-1b	GA	p value	DMT as first therapy	Switch to DMT	p value
Patients, n (%)	546 (100)	105 (19)	186 (35)	167 (30)	88 (16)	—	458 (84)	88 (16)	—
Gender, n (%) males	164 (30)	24 (23)	61 (33)	52 (31)	27 (31)	0.339[a]	139 (30)	25 (28)	0.716[a]
Age, mean ± SD	44.0 ± 10.5	43.6 ± 11.5	43.6 ± 10.3	45.0 ± 10.4	43.4 ± 9.9	0.530[b]	43.9 ± 10.5	44.3 ± 10.4	0.772[b]
Diagnosis, n (%)									
RRMS	492 (90)	92 (88)	175 (94)	145 (87)	80 (91)		410 (89)	82 (79)	
CIS	54 (10)	13 (12)	11 (6)	22 (13)	8 (9)	0.106[a]	48 (11)	6 (7)	0.292[a]
Disease duration, years, median (IQR)									
RRMS	4.3 (3.0–7.4)	6.0[c] (3.7–11.3)	7.5 (5.7–11.7)	9.5[c] (4.8–15.2)	7.6 (4.3–12.8)	0.007[d]	7.3 (4.4–11.8)	11.7 (6.9–15.5)	<0.001[e]
CIS	7.6 (4.3–12.8)	4.5 (3.0–6.8)	5.5 (3.7–7.3)	3.4 (2.8–4.8)	8.1 (3.4–13.0)	0.244[d]	4.1 (2.9–6.8)	6.7 (3.1–11.7)	0.459[e]
No. of relapses, n (%)									
Year 1									
0	438 (80)	83 (79)	142 (76)	141 (84)	72 (82)	0.277[a]	371 (81)	67 (76)	0.294[a]
≥1[f]	108 (20)	22 (21)	44 (24)	26 (16)	16 (18)		87 (19)	21 (24)	
Year 2									
0	413 (76)	79 (75)	136 (73)	129 (77)	69 (78)	0.670[a]	355 (77)	58 (66)	0.066[a]
1	105 (19)	21 (20)	38 (20)	33 (20)	13 (15)		81 (18)	24 (27)	
≥2[g]	28 (5)	5 (5)	12 (7)	5 (3)	6 (7)		22 (5)	6 (7)	
EDSS, median (IQR)									
Year 1	2 (1.5–3.0)	2 (1.5–3.0)	2.25 (1.5–3.5)	2 (1.5–3.5)	2.5 (1.5–3.0)	0.196[d]	2 (1.5–3)	2.5 (1.5–3.5)	0.019[e]
Year 2	2 (1.5–3.5)	2 (1.0–3.0)	2 (1.5–3.5)	2 (1.5–4.0)	2.5 (1.3–3.0)	0.167[d]	2 (1.5–3.5)	2.5 (2–4)	0.009[e]

SD = standard deviation; IQR = interquartile range. [a] Chi-square test. [b] Analysis of variance. [c] Post-hoc comparison, adjusted $p < 0.05$ for pairwise comparison. [d] Kruskal-Wallis one-way analysis of variance. [e] Mann-Whitney U test. [f] Only eight patients had two or more relapses during year 1. [g] Only three patients had three or more relapses during year 2.

Table 2. AEs during SAME (after 2 years)

	DMT					
	IM INFβ-1a	SC INFβ-1a	SC INFβ-1b	GA	All DMTs	p value[a]
AEs, n (%)						
All AEs	59 (56.2)	102 (54.8)	89 (53.3)	34 (38.6)	284 (52.0)	0.052
Flu-like symptoms	49 (46.7)	74 (39.8)	43 (25.8)	2 (2.3)	168 (30.8)	<0.001
Injection-site reactions[b]	11 (10.5)	63 (33.9)	64 (38.3)	23 (26.1)	161 (29.5)	<0.001
Redness	10 (9.5)	56 (30.1)	59 (35.3)	16 (18.2)	141 (25.8)	
Inflammation	4 (3.8)	19 (10.2)	19 (11.4)	3 (3.4)	45 (8.2)	
Necrosis	0 (0.0)	4 (2.2)	8 (4.8)	1 (1.1)	13 (2.4)	
Lipoatrophy	0 (0.0)	10 (5.4)	11 (6.6)	7 (8.0)	28 (5.1)	
Other	12 (11.4)	18 (9.7)	10 (6.0)	13 (14.8)	53 (9.7)	0.135

[a] Treatment differences in AEs were analyzed using chi-square tests, with significance accepted when $p < 0.05$. [b] Individual patients recorded one or more types of injection-site reactions.

Fig. 1. SAME study timeline.

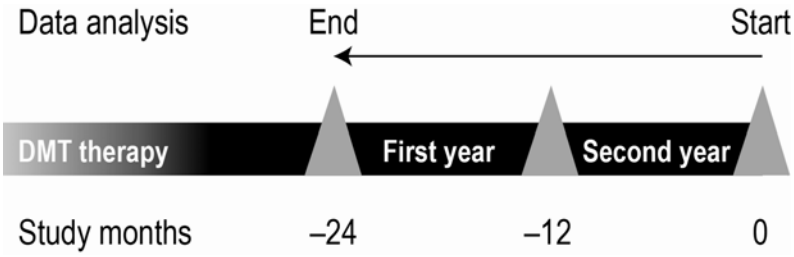

Fig. 2. Number of relapses during SAME, year 1 (A) and year 2 (B).

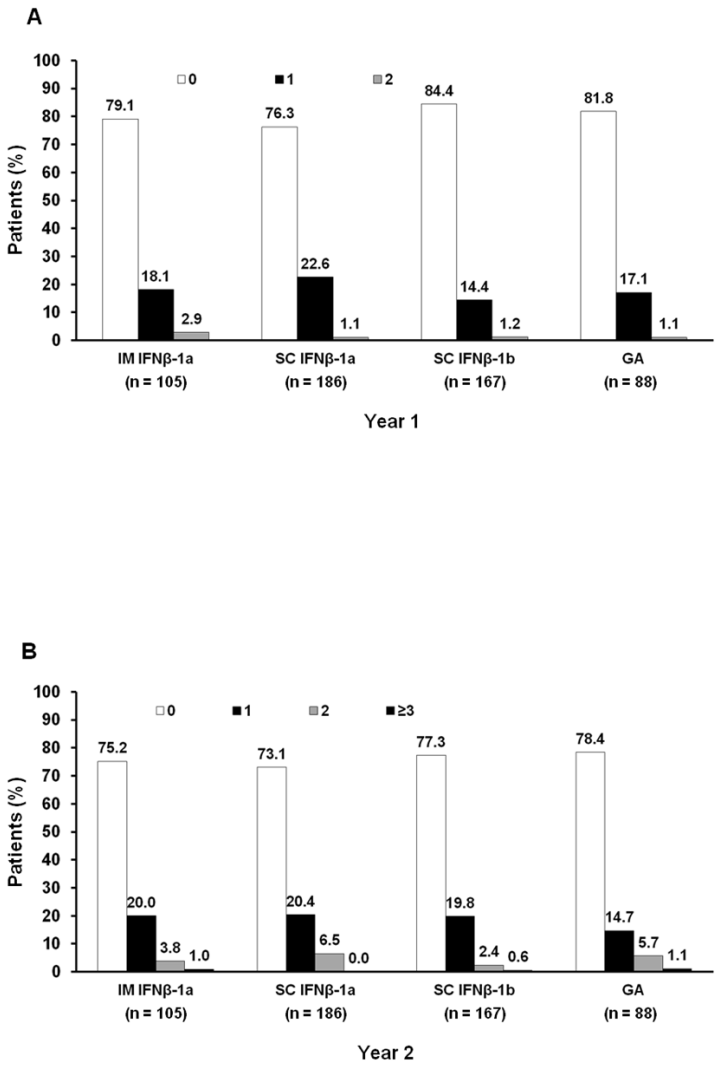

Fig. 3. Median EDSS score during SAME, year 1 (A) and year 2 (B).