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: A Multicenter, Non-Interventional, Retrospective Cohort Study of Disease-Modifying Therapies

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Key Words
Multiple sclerosis · Disease-modifying therapies · Swiss Analysis of Multiple Sclerosis study · Efficacy · Safety

Abstract
Background: There is a scarcity of reports comparing efficacy and tolerability of the multiple sclerosis (MS) disease-modifying therapies [DMTs; intramuscular interferon-β1a (IM IFNβ-1a), subcutaneous (SC) IFNβ-1a, SC IFNβ-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 IFNβ-1a, 46.7%; SC IFNβ-1a, 39.8%; SC IFNβ-1b, 25.8%; $p < 0.05$). Injection site reactions were less often reported with IM IFNβ-1a (10.5% vs. SC IFNβ-1a, 33.9%; SC IFNβ-1b, 38.3%; GA, 26.1%; $p < 0.05$). ***Conclusions:*** All DMTs showed comparable effects on MS relapse rate and EDSS change, with IM IFNβ-1a and GA being more tolerable with respect to injection site reactions and flu-like symptoms, respectively.

Introduction

The efficacy and tolerability of injectable interferon-β (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 average patient MS relapse rate by approximately one third [1–4] and decreased magnetic resonance imaging (MRI) T2-weighted brain lesion volume and the number of gadolinium-enhancing brain lesions compared with placebo [5, 6]. However, the comparative efficacy of these immunomodulatory therapies remained uncertain, since it cannot be derived from past trial results because of differences in study methodology, outcome criteria, and patient populations among trials.

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Previous DMT comparative studies have typically evaluated only 2 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 2 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]. However, 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 therefore well recognized that clinical trial results may only be 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]. There is only 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); however, the study groups were quite imbalanced, and the reported differences in hazard ratios between the DMTs were attributed to selection bias [22]. So far, 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 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, non-interventional, retrospective cohort study that included patients constantly treated for at least 2 years with either one of the IFNβ or GA at 30 centers in Switzerland. The inclusion criteria were age between 18 and 65 years at first visit, a diagnosis of either CIS or RRMS according to the 2005 revised McDonald criteria [23], and treatment with the same DMT for the last 2 years. Availability of patient demographic information, medical history, and 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 <2 years, 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.

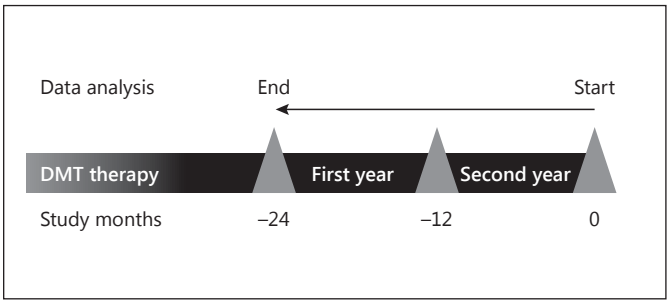

Fig. 1. SAME study timeline.

Study Design

The SAME study was a multicenter, non-interventional, 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).

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 Expanded Disability Status Scale (EDSS) scores. MRI scans were performed according to clinical need and in only a limited number of patients (27%, data not shown). 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.

The primary study end point was the annualized relapse rate for years 1 and 2 (categorized as 0, 1, 2, or ≥3). 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 h in the absence of an increase in body temperature or infections, or as symptoms occurring at least 30 days after the preceding episode. The secondary end point was change in patient EDSS score from year 1 to year 2. In addition, treatment-associated adverse events (AEs) during SAME study years 1 and 2 were collected in all patients [categorized into flu-like symptoms, injection site reactions (redness, inflammation, necrosis, and lipoatrophy), and other].

Table 1. Patient demographic and clinical characteristics

	All DMTs	DMT				p value	Switch vs. no switch		p value
		IM IFNβ-1a	SC IFNβ-1a	SC IFNβ-1b	GA		DMT as first therapy	switch to DMT	
Patients	546 (100)	105 (19)	186 (35)	167 (30)	88 (16)	–	458 (84)	88 (16)	–
Males	164 (30)	24 (23)	61 (33)	52 (31)	27 (31)	0.339[a]	139 (30)	25 (28)	0.716[a]
Age, years	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									
RRMS	492 (90)	92 (88)	175 (94)	145 (87)	80 (91)	0.106[a]	410 (89)	82 (79)	0.292[a]
CIS	54 (10)	13 (12)	11 (6)	22 (13)	8 (9)		48 (11)	6 (7)	
Median disease duration, years									
RRMS	7.7 (4.8–12.8)	6.0 (3.7–11.3)[c]	7.5 (5.7–11.7)	9.5 (4.8–15.2)[c]	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	4.3 (3.0–7.4)	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]
Number of relapses									
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)	
Median EDSS									
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]

Values for age are expressed as mean ± SD. Figures in parentheses indicate percentages or interquartile range. [a] χ^2 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 8 patients had two or more relapses during year 1. [g] Only 3 patients had three or more relapses during year 2.

Statistical Analyses

The planned analysis compared the number of relapses, EDSS score, change in EDSS score, and frequency of AEs 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 χ^2 tests, as appropriate). Bonferroni post hoc tests were conducted for comparisons that showed overall significant differences. Results were considered significant at $p < 0.05$.

Results

A total of 546 subjects were enrolled in SAME. Patient demographic 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 (fig. 2) or EDSS score during years 1 or 2 (fig. 3 and 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-Wallis 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 different DMTs 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 2 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 ($p = 0.472$, Mann-Whitney U test).

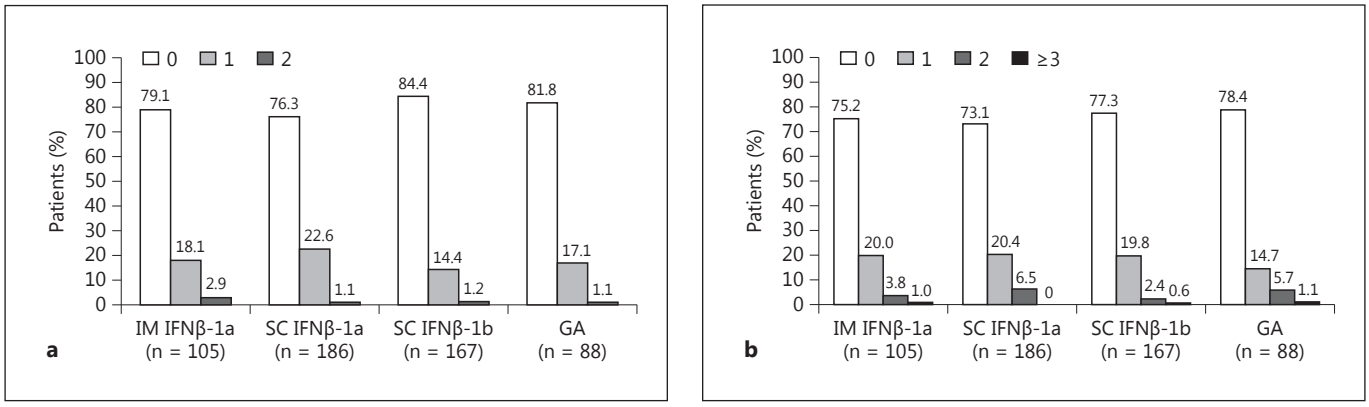

Fig. 2. Number of relapses during SAME. **a** Year 1. **b** Year 2.

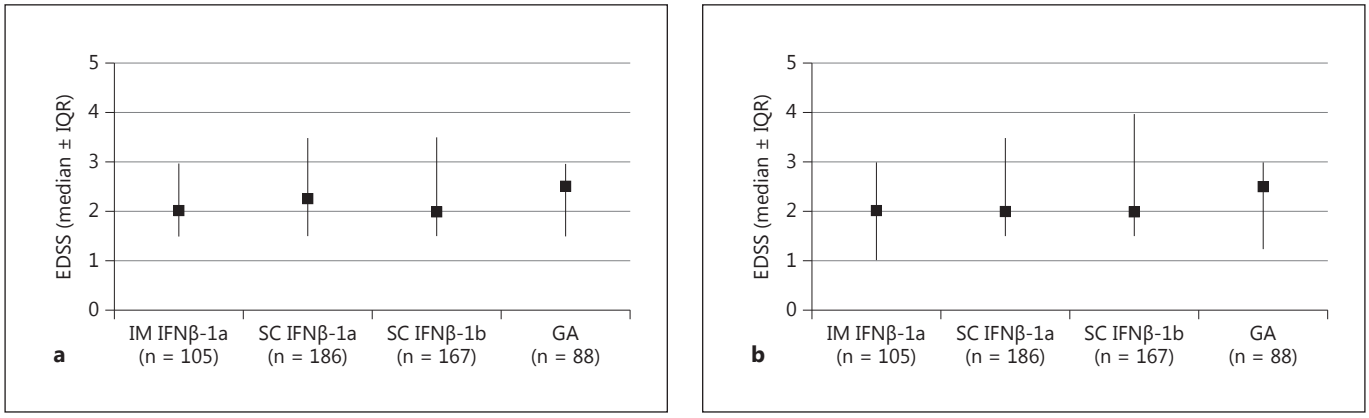

Fig. 3. Median EDSS score during SAME. **a** Year 1. **b** Year 2.

Table 2. AEs during 2-year DMT in MS

AEs	DMT					p value[a]
	IM IFNβ-1a	SC IFNβ-1a	SC IFNβ-1b	GA	all DMTs	
Any 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	4 (2.2)	8 (4.8)	1 (1.1)	13 (2.4)	
Lipoatrophy	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 χ^2 tests, with significance accepted when $p < 0.05$. [b] Individual patients recorded one or more types of injection site reactions. Percentages are given in parentheses.

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 were significantly less frequent with GA compared to all other DMTs and SC IFNβ-1b compared to IM IFNβ-1a and SC IFNβ-1a (adjusted $p < 0.05$ for all post hoc comparisons). On the other hand, 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 being the most commonly reported injection site reactions.

Discussion

This multicenter, retrospective, observational study in a selected real-world MS population of nearly 550 patients demonstrated that the four first-line DMTs for the treatment of MS had a similar impact on annualized relapse rate and disability progression (as indicated by change in EDSS score) during the 2-year study. 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 study that simultaneously compared the efficacy and side effects of these four first-line DMTs in a large cohort of patients affected by RRMS and CIS in a multicenter real-world setting. Our study population of 546 patients from 30 Swiss centers represents approximately 10% of the estimated Swiss MS population. 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 selected, stable, real-world MS patient population. In addition, we conducted a separate analysis that stratified the group into patients receiving the DMT as first- or second-line treatment and showed that the latter group, as expected, was more severely affected in terms of disability. However, relapse rate and disability progression over 2 years did not differ between the 2 groups. All of the AEs reported by patients were expected, and they occurred at similar frequencies as in previous reports [24].

These results are in line with other short- and long-term real-world postmarketing studies [11–21]. Nevertheless, 2 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, absence of a placebo comparator group, regression to the mean, and possible selection bias may limit the utility of those data.

The study has several limitations that should be taken into account when interpreting its results. The first and most important limitation is represented by the retrospective nonrandomized study design. In general, randomized studies have a better research design, since possible biases cannot be fully overcome by statistical methods in open-label, non-randomized studies [25]. However, it is not always feasible to conduct randomized trials, and alternative study designs will inevitably need to be utilized. Benson and Hartz [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]. In addition, in Switzerland all DMTs are approved first-line treatments for MS patients. The official administrative recommendations do not differ among DMTs, and there are no guidelines that preferentially recommend one specific DMT for these patients. Therefore, we can tentatively assume that all DMTs in our study were prescribed with the same a priori probability in MS patients.

Second, patients on stable DMT treatment for at least 2 years in the SAME study most likely represent long-term responders to DMTs or patients with low disease activity; they may differ from the general population of MS patients. As a consequence, we cannot generalize our results to the entire MS population. Finally, the absence of a systematic MRI follow-up precludes from identifying differences in subclinical disease activity, which is more sensitive than clinical parameters only.

To conclude, in a real-world setting in a selected MS patient population the four injectable DMTs showed more similarities than differences in the efficacy and safety of the treatment of MS during a 2-year study period.

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Disclosure Statement

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 Borter and Martin Traber are employees of Biogen-Dompé AG. Rosetta Meier is a former employee of Biogen-Idec AG.

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