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Original Research Paper

Comparative effectiveness of glatiramer acetate and interferon beta formulations in relapsing–remitting multiple sclerosis

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Abstract

Background: The results of head-to-head comparisons of injectable immunomodulators (interferon β, glatiramer acetate) have been inconclusive and a comprehensive analysis of their effectiveness is needed.
Objective: We aimed to compare, in a real-world setting, relapse and disability outcomes among patients with multiple sclerosis (MS) treated with injectable immunomodulators.
Methods: Pairwise analysis of the international MSBase registry data was conducted using propensity-score matching. The four injectable immunomodulators were compared in six head-to-head analyses of relapse and disability outcomes using paired mixed models or frailty proportional hazards models adjusted for magnetic resonance imaging variables. Sensitivity and power analyses were conducted.
Results: Of the 3326 included patients, 345–1199 patients per therapy were matched (median pairwise-censored follow-up was 3.7 years). Propensity matching eliminated >95% of the identified indication bias. Slightly lower relapse incidence was found among patients treated with glatiramer acetate or subcutaneous interferon β-1a relative to intramuscular interferon β-1a and interferon β-1b ($p \leq 0.001$). No differences in 12-month confirmed progression of disability were observed.
Conclusion: Small but statistically significant differences in relapse outcomes exist among the injectable immunomodulators. MSBase is sufficiently powered to identify these differences and reflects practice in tertiary MS centres. While the present study controlled indication, selection and attrition bias, centre-dependent variance in data quality was likely.

Keywords: Multiple sclerosis, treatment outcomes, patient registry, real-world date, propensity score, relapses, disability

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Introduction

Interferon β (IFNβ) and glatiramer acetate (GA) are commonly used in the treatment of relapsing–remitting multiple sclerosis (MS). While numerous randomised clinical trials (RCTs) generated seminal evidence about their efficacy relative to placebo, the evidence concerning their head-to-head comparisons is limited.[1–6] The high cost and assessment intensity of RCTs pose obvious limitations in relation to duration of existing RCTs. This translates into a limited power to detect treatment effect differences which are either of modest size or delayed. An example of such

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effects is the difference in relapse and disability outcomes in patients treated with IFNβ and GA. In particular, the observed differences in relapse activity, as shown in RCTs, are relatively small, and some of the conclusions drawn from RCTs are contradictory.[3,4] The only difference in disability outcomes was found between IFNβ-1b vs. IFNβ-1a IM, as the typical RCT duration of 2 years has potentially limited their power to detect changes in long-term disability accrual.[3]

The MSBase global clinical practice cohort accumulates longitudinal data from diverse populations over long time periods. Analyses based on such registries are well placed to evaluate treatment effectiveness in the context of real-world medication use, long-term follow-up, and a variety of clinical scenarios.[7] However, valid and unbiased conclusions can only be drawn on the precondition that appropriate procedures aiming at elimination of indication bias have been implemented. To this end, propensity score-based methods[8] have previously been used to generate quasi-randomised studies of MS outcomes.[9-11] We have recently demonstrated feasibility of propensity-based matching for evaluation of treatment effectiveness in the MSBase dataset, showing that two dosages of IFNβ-1a SC were equivalent in relapse rate and disability outcomes, thus mirroring the outcomes of the pivotal registration study.[12,13]

Here we present a propensity score-matched analysis comparing the effectiveness of IFNβ and GA preparations in a series of pairwise head-to-head cohort studies conducted in MSBase.

Patients and methods

The MSBase registry[14] is registered with WHO International Clinical Trials Registry Platform [ACTRN12605000455662], and was approved by the Melbourne Health Human Research Ethics Committee [2006.044], and by the local ethics committees in all participating centres (or exemptions granted, according to local regulations). If required, written informed consent was obtained from enrolled patients.

Database and study population

Longitudinal data from 21,938 patients (122,561 patient-years) were extracted from the MSBase registry in April 2013; 81% of patients were enrolled after year 2000 and 79% had their information updated since 2008.

Inclusion criteria reflected the criteria most commonly employed by RCTs and comprised diagnosis of MS or clinically isolated syndrome (using the 2005 or 2010 McDonald criteria[15,16]), relapsing MS course, therapy with IFNβ or GA as a first-ever disease-modifying agent, at least 6-month persistence on the initial therapy, time from initial symptoms to treatment start <10 years, at least one relapse recorded during the 2 years preceding the treatment initiation, and availability of the minimal dataset. The minimal dataset consisted of sex, age, date of first MS symptoms, dates of relapses, clinical MS course, disability at baseline quantified with Expanded Disability Status Scale (EDSS), and treating MS centre. Baseline EDSS was recorded within 6 months of treatment initiation. In addition, an on-treatment follow-up visit with EDSS recorded at least 6 months after the treatment initiation was required.[17]

All information was recorded as part of routine practice, using real-time or near real-time data entry in association with clinical visits. The MSBase protocol stipulates minimum annual updates of the minimum dataset, but patients with less frequent updates were not excluded from the analysis. Data entry portal was either the iMed patient record system or the MSBase online data entry system.

A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for >24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse.[18] Disability was scored by accredited scorers using EDSS (online Neurostatus certification was required at each centre), excluding any EDSS score recorded within 30 days of a previous relapse. Progression of EDSS was defined as an increase of ≥1 EDSS step (≥1.5 EDSS step if baseline EDSS was 0) sustained for ≥12 months. Onset of secondary progressive MS was defined as at least 1 year of disability progression with or without superimposed relapses following previous relapsing–remitting course,[17] and was assessed by the treating neurologists. Individual annualised relapse rate (ARR) was calculated as the overall number of recorded relapses between the treatment initiation and one of the following: discontinuation of therapy, end of follow-up, or 5 years from treatment initiation (whichever occurred first). The 5-year censoring was applied in order to ameliorate regression to mean,[12] which would predominantly impact ARR during long-sustained treatment. Categorised evaluations of magnetic resonance imaging (MRI) and cerebrospinal fluid were reported by treating neurologists and were used to better characterise the treatment cohorts.

Quality assurance procedures were followed. Only information from centres with at least 10 active records was used, as stipulated in the study protocol.

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A date of onset was required for all recorded events, including relapses, visits, changes in disease course, and changes in treatment. In addition, a series of automated procedures was applied to identify any invalid or inconsistent entries.

Statistical analysis

Treatment outcomes were analysed in a series of pairwise models comparing populations matched on their propensity of receiving either of the compared treatments. The hypotheses were postulated prior to inspection of the analysed data. The matching procedures were performed using R 3.0.2[19] with MatchIt[20] and Zelig[21] packages. Propensity scores were calculated using logistic regression models with the outcome variables representing allocation to either of the compared agents and the independent variables being age, sex, disease duration, ARR over two pre-treatment years, categorised EDSS, disease course, and MS centre. The individual propensity scores were calculated as weighted sums of coefficients of the variables with non-zero weights (at $p \leq 0.1$). Patients in the compared treatment group pairs were then matched in a variable 1–3:1 ratio using nearest neighbour matching without replacement and discarding from both groups the cases outside the 0.1 caliper (i.e. with no match within 0.1 standard deviation of the propensity score). Closeness of match was evaluated using cumulative and average propensity distances between the groups.[22] For each of the matched patient pairs, the common on-treatment follow-up period was determined as the shorter of the two individual follow-up periods. After assessing normality of data distribution, disease outcomes were compared between the propensity score-matched treatment groups. ARR (based on all relapses or relapses treated with corticosteroids) were compared using weighted mixed model with clusters for matched pairs. The proportions of patients free from relapses (censored latest at 5 years) or 12-month confirmed disability progression were evaluated with weighted frailty proportional hazards models. Proportionality of hazards was tested with Schoenfeld's global test and where violated, model with Weibull distribution was applied. All analyses were adjusted for the categorised number of T2 lesions (missing, 1–8, ≥9) recorded on baseline brain MRI. The hypotheses were tested at the $p \leq 0.05$ two-tailed level of statistical significance, after controlling false discovery rate within the primary analyses with Benjamini–Hochberg procedure.

Ad-hoc power estimation was carried out for the analyses of ARR and was expressed as the minimum detectable effect at $\alpha=0.05$ and $1-\beta=0.95$. Sensitivity analysis was carried out in a subpopulation of patients matched at a fixed 1:1 ratio. Hodges–Lehmann Γ for Rosenbaum bounds was estimated for the ARR analyses to evaluate the robustness of the results in relation to any non-recognised confounders of treatment assignation.[23,24]

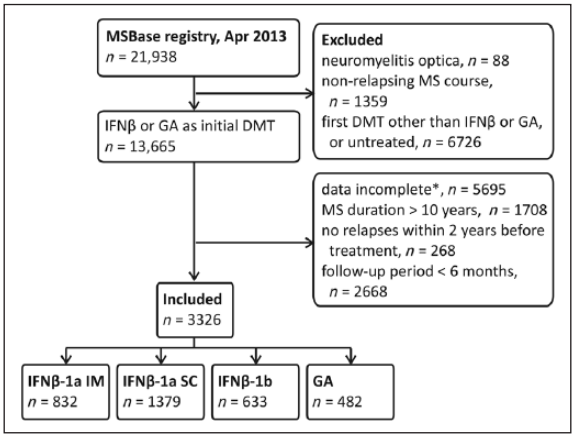

Figure 1. CONSORT chart of patient disposition.
*The majority of the patients excluded due to incomplete datasets did not have suitable baseline and/or follow-up disability information recorded (for the definition see the inclusion criteria in the Patients and methods section).
DMT: disease-modifying therapy; GA: glatiramer acetate; IFN: interferon; MS: multiple sclerosis; SC: subcutaneous.

Results

Out of the 21,938 screened patients, 3326 patients (with cumulative follow-up of 15,247 patient-years) from 49 MS centres in 22 countries (online eTable 1) fulfilled the inclusion criteria (for CONSORT diagram see Figure 1). Exclusion of patients was proportional across treatment groups. The median follow-up was 3.7 years (interquartile range 2.2–6.3), with mean gap between visits of 5.8–7.0 months. As shown in Table 1, the treatment groups differed in several baseline demographic and clinical characteristics. Allocation to therapy (and thus the calculated propensity score) was mostly determined by treating MS centre, followed by disability, pre-treatment relapse rate, MS course, and age. For instance, patients treated with IFNβ-1b were more frequently those with more severe disability compared with those initiated on other preparations, patients receiving IFNβ-1a IM were less disabled than those with IFNβ-1a SC or IFNβ-1b, and those on GA were older than those treated with IFNβ-1a SC or IM (see eTable 2). Patients were matched on their estimated probability of allocation to either compared medication (expressed as propensity score), with between 65 and 90% of the included patients retained in the subsequent head-to-head

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Table 1. Characteristics of the included patients.

	IFNβ-1a IM	IFNβ-1a SC	IFNβ-1b	GA
BASELINE				
patients, number (% females)	832 (71%)	1379 (70%)	633 (70%)	482 (73%)
age at treatment start, years	32.8 ± 10·0	33.5 ± 9.4	34.6 ± 9.4	35.1 ± 8.9
disease duration, years	2.9 ± 2.6	2.9 ± 2.6	2.9 ± 2.6	3.2 ± 2.7
baseline ARR	1.6 ± 1.1	1.8 ± 1.3	1.7 ± 1.1	1.6 ± 1.2
disease course				
CIS, number (%)	93 (11%)	59 (4%)	43 (7%)	23 (5%)
RRMS, number (%)	737 (89%)	1309 (95%)	581 (92%)	454 (94%)
RPMS, number (%)	2 (0.2%)	11 (0.8%)	9 (1%)	5 (1%)
disability, EDSS*	2 (1.0, 2.5)	2 (1.5, 3.0)	2 (1.0, 3.0)	2 (1.0, 2.5)
EDSS 0–1.5, number (%)	407 (49%)	510 (37%)	248 (39%)	203 (42%)
EDSS 2–3.5, number (%)	374 (45%)	705 (51%)	289 (46%)	237 (49%)
EDSS 4–8.5, number (%)	51 (6%)	164 (12%)	96 (15%)	42 (9%)
MS centres, number	43	45	40	39
Time on treatment, months*	41 (24, 69)	47 (28, 77)	45 (24, 84)	44 (25, 74)
MRI: hyperintense T2 lesions, number (%)				
availability	491 (59%)	831 (60%)	312 (49%)	270 (56%)
0	91 (19%)	141 (17%)	68 (22%)	75 (28%)
1–8	324 (66%)	572 (69%)	179 (57%)	145 (54%)
9+	76 (15%)	118 (14%)	65 (21%)	50 (19%)
MRI: contrast enhancing lesions, number (%)				
availability	425 (51%)	713 (52%)	236 (37%)	202 (58%)
no	324 (76%)	507 (71%)	191 (81%)	156 (77%)
yes	101 (24%)	206 (29%)	45 (19%)	46 (23%)
Cerebrospinal fluid, number (%)				
availability	332 (40%)	626 (35%)	180 (28%)	144 (30%)
abnormal	304 (92%)	543 (87%)	162 (90%)	122 (85%)
normal	28 (8%)	83 (13%)	18 (10%)	22 (15%)
STUDY END				
visit density (visits per year), median (quartiles)	2.1 (1.1, 4.0)	1.9 (1.0, 3.7)	1.7 (0.9, 3.5)	1.9 (1.0, 3.6)
further disease-modifying therapy, number (%)				
continued previous therapy†	247 (30%)	550 (40%)	223 (35%)	207 (43%)
switched to IFNβ-1a IM	0	40 (3%)	36 (6%)	13 (3%)
switched to IFNβ-1a SC	189 (23%)	0	16 (3%)	34 (7%)
switched to IFNβ-1b	32 (4%)	8 (0·6%)	0	14 (3%)
switched to GA	48 (6%)	117 (8%)	38 (6%)	0
switched to fingolimod	10 (1%)	22 (2%)	18 (3%)	14 (3%)
switched to teriflunomide	0	0	0	1 (0·2%)
switched to natalizumab	24 (3%)	69 (5%)	29 (5%)	15 (3%)
switched to mitoxantrone	1 (0.1%)	25 (2%)	10 (2%)	5 (1%)
enrolled in randomised trial	2 (0.2%)	0	1 (0.1%)	2 (0.4%)
stopped previous therapy‡	279 (34%)	548 (40%)	262 (41%)	177 (38%)
reason for treatment discontinuation/switch, number (%)				
data availability	251 (43%)	416 (50%)	141 (34%)	94 (34%)
lack of tolerability	40 (16%)	131 (31%)	60 (43%)	25 (27%)

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Table 1. (Continued)

	IFNβ-1a IM	IFNβ-1a SC	IFNβ-1b	GA
lack of effect	138 (55%)	150 (36%)	34 (24%)	36 (38%)
convenience / planned discontinuation	73 (29%)	135 (32%)	47 (33%)	33 (35%)

*median (interquartile range); otherwise mean ± standard deviation are shown.
†on-study follow-up was terminated at the last recorded visit.
‡discontinuation of previous therapy exceeding 3 months.
ARR: annualised relapse rate; CIS: clinically isolated syndrome; EDSS: Extended Disability Status Scale; GA: glatiramer acetate; IFN: interferon; IM: intramuscular; MRI: magnetic resonance imaging; MS: multiple sclerosis; RPMS: relapsing–progressive multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis; SC: subcutaneous.

comparisons. Average between-group differences in propensity scores were reduced by 96–97% (eFigure 1). The resulting six paired groups were closely matched on all recorded demographic and clinical parameters (Table 2). In addition, categorised MRI and cerebrospinal fluid variables (not included in the propensity calculations due to high proportion of missing data) did not markedly differ between the matched groups.

Average ARR recorded during the follow-up period ranged from 0.38 to 0.56 relapse/year (Table 3). Comparisons of ARR between the matched groups showed that patients treated with GA or IFNβ-1a SC experienced fewer relapses than those receiving IFNβ-1a IM or IFNβ-1b ($p \leq 0.001$). The observed mean differences were small (0.15–0.16 and 0.09–0.1 relapse/year for GA and IFNβ-1a SC, respectively). Between 38% and 52% of all relapses were treated with steroids (steroid-treated ARR 0.17–0.25), with no statistically significant differences between the compared therapies and only with a nearly significant trend observed between IFNβ-1a SC and IFNβ-1a IM (0.03 relapse/year, $p=0.07$). The proportion of relapse-free patients (Figure 2) was significantly higher for GA in comparison with either IFNβ-1a IM or IFNβ-1b (hazard ratio=1.36 and 1.48, respectively, $p \leq 0.02$). In addition, a marginally higher proportion of relapse-free patients was observed for IFNβ-1a IM in comparison with IFNβ-1b (hazard ratio=1.28, $p=0.05$). In contrast, we did not observe any differences in the proportions of patients free from 12-month sustained progression of disability (Figure 3, eFigure 2) in the analyses extending to 10 years.

The outcomes in the unmatched cohorts are shown in eTable 3 and eFigures 3–5. The sensitivity analyses within the groups matched in a 1:1 ratio retained 38% and 60% of patients from the primary analysis. With the exception of the proportion of relapse-free patients treated with IFNβ-1a IM vs. GA, the sensitivity analyses confirmed all observed effects (eTable 4). The Hodges–Lehmann sensitivity parameter (Γ) showed that the ARR analyses were resistant to a hypothetical unknown confounder of a magnitude of 10–40% of the propensity score, with the exception of the comparison of IFNβ-1a SC vs. IM, which was vulnerable to an unidentified confounder of any magnitude. The analysis of steroid-treated ARR was vulnerable to any unidentified confounders. The analysis of ARR contained 95% power to identify the minimum effect size of 0.07–0.15 relapse/year. Finally, the sensitivity analysis of the proportions of patients free from 12-month sustained disability progression did not find any significant differences between the compared therapies (eTable 5).

Discussion

In this analysis of clinical practice data, we have directly compared effectiveness of the injectable immunomodulatory agents (IFNβ and GA preparations) in 3326 closely matched patients using pairwise comparisons with on-treatment follow-up spanning up to 10 years. In this cohort the patients treated with IFNβ-1a SC or GA were at slightly but significantly lower risk of MS relapses than those treated with IFNβ-1a IM or IFNβ-1b, as demonstrated by ARR and the proportions of relapse-free patients. We have found no difference in the rate of the first 12-month confirmed disability progression events between the compared medications.

Our study confirms and extends the outcomes of several previously published head-to-head RCTs. The EVIDENCE trial and its extension showed superior effect of IFNβ-1a SC on relapse activity and active MRI lesions over a 2-year follow-up period compared with IFNβ-1a IM.[2] Another RCT in 90 patients suggested superior effect of IFNβ-1a SC on relapse activity compared with IFNβ-1a IM.[25] In the REGARD trial, no difference in the effect on relapse

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Table 2. Characteristics of the matched cohorts.

	IFNβ-1a IM	vs. IFNβ-1b	IFNβ-1a IM	vs. IFNβ-1a SC	IFNβ-1a IM	vs. GA	IFNβ-1b	vs. IFNβ-1a SC
matched patients, number (% females)	658 (71%)	427 (69%)	725 (71%)	1199 (69%)	628 (71%)	362 (72%)	525 (71%)	1001 (71%)
age, years	33.5 ± 10.2	33.8 ± 9.0	32.6 ± 10.9	33.1 ± 9.2	34.0 ± 9.8	34.6 ± 8.7	34.5 ± 9.5	34.1 ± 9.5
disease duration, years	2.9 ± 2.6	2.9 ± 2.6	2.9 ± 2.6	3.0 ± 2.6	3.1 ± 2.7	3.1 ± 2.6	2.9 ± 2.6	2.9 ± 2.6
baseline ARR	1.6 ± 1.1	1.7 ± 1.1	1.6 ± 1.1	1.7 ± 1.2	1.6 ± 1.1	1.6 ± 1.1	1.7 ± 1.2	1.8 ± 1.3
disease course								
CIS, number (%)	64 (10%)	29 (7%)	53 (7%)	54 (5%)	53 (8%)	22 (6%)	31 (6%)	44 (4%)
RRMS, number (%)	593 (90%)	397 (93%)	674 (92%)	1140 (94%)	573 (91%)	338 (93%)	485 (92%)	948 (95%)
RPMS, number (%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	5 (0.4%)	2 (0.3%)	2 (0.6%)	9 (2%)	9 (1%)
disability, EDSS*	2 (1, 2.5)	2 (1, 3)	2 (1, 2.5)	2 (1.5, 2.5)	2 (1, 2.5)	2 (1, 2.5)	2 (1.5, 3)	2 (1.5, 3)
EDSS 0–1.5, number (%)	283 (44%)	179 (42%)	333 (45%)	466 (39%)	277 (46%)	155 (43%)	190 (36%)	376 (38%)
EDSS 2–3.5, number (%)	319 (48%)	201 (47%)	349 (48%)	628 (52%)	312 (50%)	180 (49%)	256 (49%)	492 (49%)
EDSS 4–8.5, number (%)	46 (7%)	47 (11%)	51 (7%)	111 (9%)	39 (6%)	27 (7%)	79 (15%)	133 (13%)
Matched follow-up duration, months*	27 (17, 43)		29 (18, 45)		27 (16, 43)		28 (19, 47)	
MRI: hyperintense T2 lesions, number (%)								
availability	371 (56%)	220 (52%)	435 (59%)	727 (61%)	350 (56%)	203 (56%)	249 (47%)	568 (57%)
0	73 (20%)	50 (23%)	80 (18%)	118 (16%)	75 (21%)	63 (31%)	56 (22%)	112 (20%)
1–8	237 (64%)	128(58%)	293 (67%)	519 (71%)	211 (60%)	105 (52%)	143 (57%)	357 (63%)
9+	61 (16%)	42 (19%)	62 (14%)	90 (12%)	64 (18%)	35 (17%)	50 (20%)	99 (17%)
MRI: contrast enhancing lesions, number (%)								
availability	312 (47%)	165 (39%)	384 (52%)	628 (52%)	298 (47%)	150 (41%)	189 (36%)	468 (47%)
no	243 (78%)	135 (82%)	292 (76%)	452 (72%)	229 (77%)	116 (77%)	150 (79%)	335 (72%)
yes	69 (22%)	30 (18%)	92 (24%)	176 (28%)	69 (23%)	34 (23%)	39 (21%)	135 (28%)
Cerebrospinal fluid, number (%)								
availability	233 (35%)	133 (31%)	323 (44%)	567 (47%)	225 (36%)	112 (31%)	157 (30%)	391 (39%)
abnormal	214 (92%)	121 (91%)	295 (91%)	501 (88%)	205 (91%)	93 (83%)	144 (92%)	334 (85%)
normal	19 (8%)	12 (9%)	28 (9%)	66 (12%)	20 (9%)	19 (17%)	13 (8%)	57 (15%)

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Table 2. (Continued)

	IFNβ-1b	vs.	GA	IFNβ-1a SC	vs.	GA
patients, number (% females)	540 (71%)		354 (73%)	916 (73%)		431 (73%)
age, years	34.8 ± 9.4		35.1 ± 8.7	34.4 ± 9.5		34.9 ± 8.8
disease duration, years	2.9 ± 2.6		3.2 ± 2.7	2.9 ± 2.6		3.1 ± 2.6
baseline ARR	1.7 ± 1.2		1.6 ± 1.2	1.8 ± 1.3		1.7 ± 1.2
disease course						
CIS, number (%)	35 (6%)		18 (5%)	42 (5%)		22 (5%)
RRMS, number (%)	496 (92%)		331 (94%)	865 (94%)		404 (94%)
RPMS, number (%)	9 (2%)		5 (1%)	9 (1%)		5 (1%)
disability, EDSS*	2 (1, 3)		2 (1.5, 2.5)	2 (1.5, 2.5)		2 (1, 2.5)
EDSS 0–1.5, number (%)	217 (40%)		141 (40%)	379 (41%)		181 (42%)
EDSS 2–3.5, number (%)	257 (48%)		181 (51%)	443 (48%)		211 (49%)
EDSS 4–8, number (%)	66 (12%)		32 (9%)	94 (10%)		39 (9%)
Matched follow-up duration, months*		27 (17, 47)			28 (17, 44)	
MRI: hyperintense T2 lesions, number (%)						
availability	265 (49%)		193 (55%)	517 (56%)		243 (56%)
0	62 (23%)		47 (24%)	115 (22%)		57 (23%)
1-8	154 (58%)		108 (56%)	299 (58%)		137 (56%)
9+	49 (18%)		38 (20%)	103 (20%)		49 (20%)
MRI: contrast enhancing lesions, number (%)						
availability	201 (37%)		146 (41%)	409(45%)		191 (44%)
no	162 (81%)		113 (77%)	305 (75%)		149 (78%)
yes	39 (19%)		33 (23%)	104 (25%)		42 (22%)
Cerebrospinal fluid, number (%)						
availability	160 (30%)		119 (34%)	322 (35%)		135 (31%)
abnormal	147 (92%)		102 (86%)	269 (84%)		114 (84%)
normal	13 (8%)		17 (14%)	53 (16%)		21 (16%)

*median (interquartile range); otherwise mean ± standard deviation are shown.
ARR: annualised relapse rate; CIS: clinically isolated syndrome; EDSS: Extended Disability Status Scale; GA: glatiramer acetate; IFN: interferon; IM: intramuscular; RPMS: relapsing-progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

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Table 3. Annualised relapse rates in matched cohorts.

	all relapses			relapses treated with steroids		
	mean	SD	*p**	mean	SD	*p**
Glatiramer acetate vs.	0.38	0.63	10^{-5}	0.17	0.37	0.1
IFNβ-1a IM	0.53	0.81		0.24	0.57	
Glatiramer acetate vs.	0.40	0.66	10^{-4}	0.21	0.45	0.4
IFNβ-1b	0.56	0.73		0.23	0.49	
Glatiramer acetate vs.	0.39	0.60	0.2	0.20	0.44	0.8
IFNβ-1a SC	0.42	0.66		0.19	0.42	
IFNβ-1a SC vs.	0.44	0.58	10^{-4}	0.21	0.40	0.07
IFNβ-1a IM	0.53	0.78		0.24	0.52	
IFNβ-1a SC vs.	0.45	0.66	0.001	0.18	0.43	0.7
IFNβ-1b	0.55	0.73		0.21	0.48	
IFNβ-1a IM vs.	0.54	0.82	0.2	0.25	0.59	0.1
IFNβ-1b	0.53	0.71		0.22	0.43	

IFN: interferon; IM: intramuscular; SC: subcutaneous; SD: standard deviation.
*weighted mixed model adjusted for categorised baseline T2 lesion load; *p*-values were adjusted for multiple hypothesis testing.

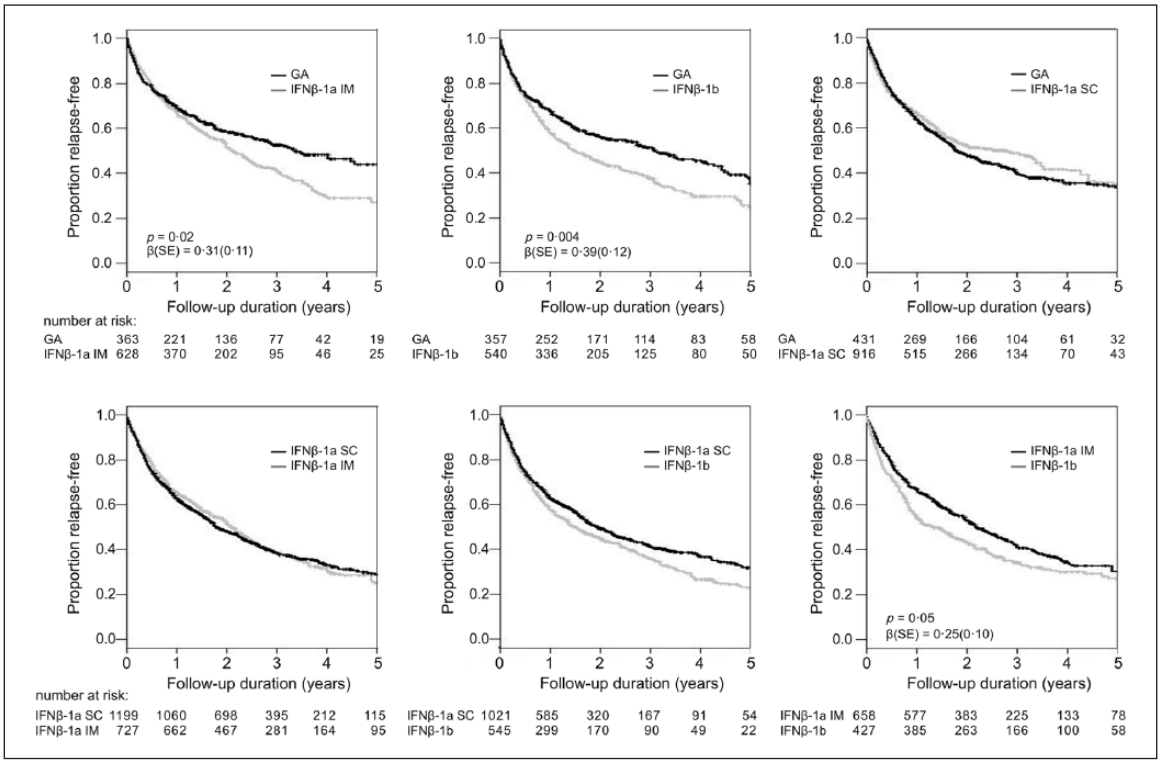

Figure 2. Proportions or patients free from relapses.
Proportions of relapse-free patients are shown for all pairwise comparisons of the studied therapies, within the propensity score-matched groups. Pairwise censoring was applied throughout. The comparisons were censored latest at 5 years from treatment onset; *p*-values indicate the outcomes of paired frailty models.
β: coefficient; GA: glatiramer acetate; IFN: interferon; IM: intramuscular; SC: subcutaneous; SE: standard error of coefficient.

activity was observed between patients treated with IFNβ-1a SC or GA. However, IFNβ-1a SC showed a more pronounced reduction of active T2 lesions, while GA was associated with reduction in brain

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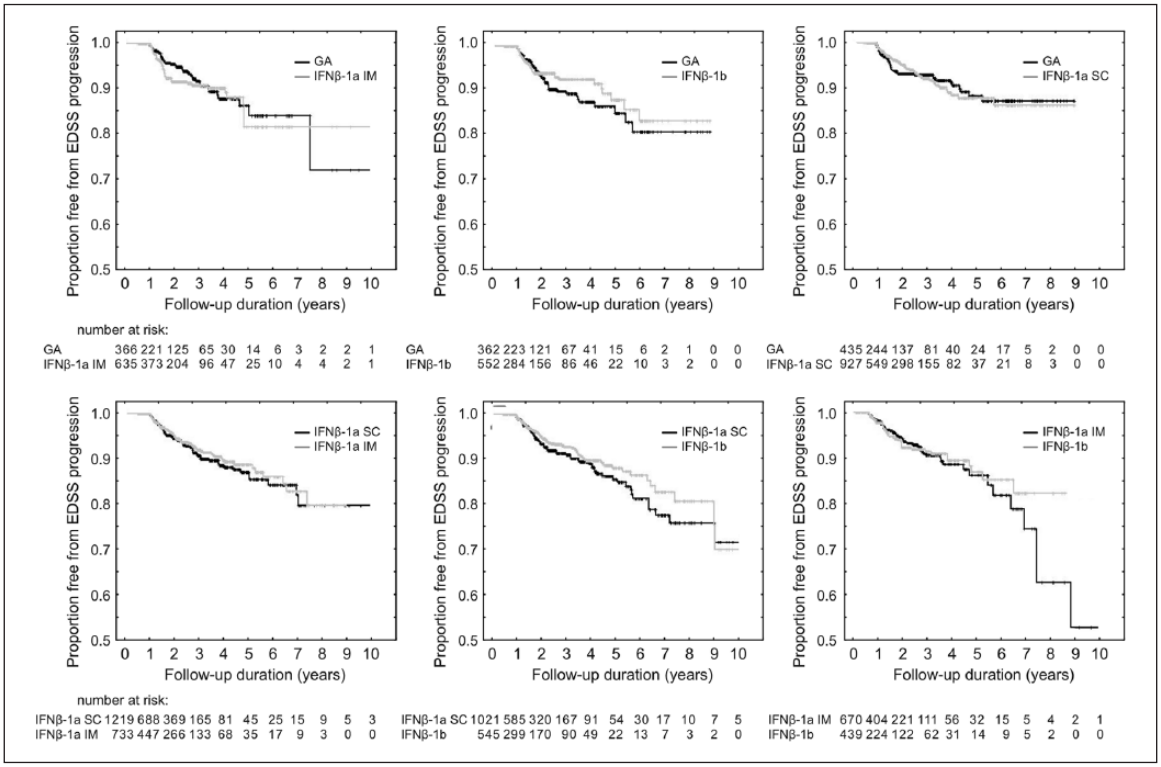

Figure 3. Proportions of patients with the first on-treatment disability progression event confirmed at 12 months.
Disability progression events are shown for all pairwise comparisons of the studied therapies, within the propensity score-matched groups. Pairwise censoring was applied throughout. Frailty proportional hazards models did not identify any differences between any of the pairwise comparisons.
EDSS: Expanded Disability Status Scale; GA: glatiramer acetate; IFN: interferon; IM: intramuscular; SC: subcutaneous.

atrophy.[5] The CombiRX trial showed that the effect of GA on relapse activity over 3 years was superior to that of IFNβ-1a IM.[6] In addition, an RCT in 141 patients showed a more pronounced effect of IFNβ-1a SC on new cortical demyelinating lesions than GA or IFNβ-1a IM.[26]

In contrast, our study did not confirm the results of some other RCTs. The BEYOND trial did not find any differences in ARR between GA and IFNβ-1b over 2 years, but showed superior effect of IFNβ-1b on change in T2 lesion volume and number of new T2 lesions.[1] The INCOMIN trial showed that the effect of IFNβ-1b on relapse and MRI activity was superior to that of IFNβ-1a IM.[3] In addition, an unmatched retrospective cohort study in 546 patients, which was not adjusted for baseline differences between patients, reported comparable treatment outcomes among all four injectable immunomodulatory therapies.[27] It is of interest that while several of these studies showed an association between interferon dosage and its therapeutic efficacy, our present analysis showed comparable effectiveness of low-dose IFNβ-1a IM and IFNβ-1b. A possible explanation may involve the role of neutralising antibodies, whereby IFNβ-1a IM administered once weekly is known to be less immunogenic than IFNβ-1a and IFNβ-1b administered subcutaneously multiple times per week.[28] However, it should be noted that our previous analysis comparing two doses of IFNβ-1a SC did not identify any dose-dependent effects.[22] It should also be noted that our analysis did not show any statistically significant differences in the frequency of steroid-treated relapses. Besides the lack of power determined by the relatively low steroid ARR, it could be speculated that this may reflect difference in the on-treatment relapse severity, of which steroid therapy may be indicative.

A recent Cochrane review including five trials comparing IFNβ and GA reported no differences in relapse and disability outcomes between the compared preparations at 2 years and a slightly lower ARR at 3 years in GA relative to IFNβ-1a IM (as shown in the CombiRX trial).[29] This suggests that any differences in relapse activity between the injectable immunomodulators are minimal and detectable only on sufficient follow-up duration. In their network meta-analysis, Filippini and colleagues used a combination of direct and indirect

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comparisons to estimate relative treatment efficacy among the commonly used disease-modifying therapies, including IFNβ and GA.[30] In agreement with our findings, the meta-analysis showed superiority of IFNβ-1a SC over the other IFNβ preparations in their effect on relapse outcomes. In addition, unlike our analysis, it reported superiority of IFNβ-1a SC over GA. Finally, the meta-analysis did not find any statistically significant differences in the disability endpoints, thus converging with our conclusions. The authors attributed this to the limited follow-up in the available RCTs (2–3 years). It is worth noting that in a number of instances, including the comparisons between GA vs. IFNβ-1a SC or IFNβ-1b, the quality of the evidence was deemed insufficient for a reliable comparison of relapse outcomes. Another systematic review, which analysed outcomes of the RCTs completed before 2010, reported a superior effect of IFNβ-1b on relapse activity when compared with IFNβ-1a SC.[31] Similarly to the meta-analysis, the review did not find any differences in the disability outcomes. Our study has confirmed that the injectable immunomodulatory therapies do not differ in their effects on accumulation of disability over extended follow-up in routine clinical practice, despite small differences in the effect on relapses.

Network meta-analysis assumes consistency between the compared trials, evaluated using visual inspection of forest plots or by I^2 statistic, whose power to detect important clinical and methodological effect modifiers is low.[30] Therefore, the outcomes of network meta-analyses may be susceptible to confounding introduced by the heterogeneity of indirectly compared trial populations. Our analysis used matched head-to-head comparisons with uniform inclusion criteria and follow-up protocol, and was therefore relatively resistant to population heterogeneity. To adjust for potential confounders of treatment indication, we used a previously validated propensity score-based procedure.[22] We used variable matching ratio, which is more efficient in eliminating indication bias than fixed ratio and leads to only a minimal increase in variance.[32] To eliminate any attrition bias (which favours therapy perceived as less effective), we have applied pairwise censoring, where any discontinuation of therapy or follow-up triggered censoring of both matched patients. ARR observed in this study was compatible with ARR reported in other contemporary studies.[33] In comparison with the previous RCTs, our study had greater power to evaluate disability outcomes, mainly due to the longer clinical follow-up (median 3.7 years).

The analysed data were collected as part of routine practice and therefore could be subject to selection, performance, or detection bias. The high similarity of the follow-up density between the treatment cohorts does not suggest presence of selection bias due to preferential inclusion of any therapy. Given that the present analysis lacked comparison against an untreated population (as we were unable to identify an unbiased natural-history cohort in the MSBase registry), the study was not affected by an immortal-time bias. Detection bias could have been introduced by the varying treatment preferences and follow-up protocols at the multiple contributing centres. MSBase is a prospective cohort study largely conducted at large university MS centres with certifications to conduct RCTs. We have applied the minimum data quality definitions to ameliorate detection bias but we acknowledge that we were unable to control the input quality at the level of a prospectively designed RCT. It should be noted that neither the previously conducted head-to-head trials were free from these biases, as they were conducted as open-label or single-blinded studies. On the other hand, our present analysis was free from attrition, reporting, or funding bias. Finally, it should be noted that the information about treatment safety for the analysed preparations was relatively incomplete and therefore not reported.

Our observations in a large MS clinical practice cohort suggest that subcutaneous IFNβ-1a and GA are associated with a slightly superior effect relative to intramuscular IFNβ-1a and IFNβ-1b on reducing frequency of relapses but not on delaying accumulation of irreversible neurological disability. Comparisons with newer therapies in the clinical practice setting are eagerly awaited.

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Conflict of interests

Alessandra Lugaresi is a Bayer Schering, Biogen Idec, Genzyme, Merck Serono Advisory Board Member. She received travel grants and honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva, research grants from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva, travel and research grants from the Associazione Italiana Sclerosi Multipla.

Cavit Boz did not declare any competing interests.

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