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ORIGINAL RESEARCH

Subcutaneous Interferon-β1a Does Not Increase the Risk of Stroke in Patients with Multiple Sclerosis: Analysis of Pooled Clinical Trials and Post-Marketing Surveillance

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ABSTRACT

Introduction: Previous studies suggest that multiple sclerosis (MS) patients have a greater stroke risk than the general population but there is limited evidence of stroke risk in patients receiving disease-modifying treatment. We assessed stroke risk in MS patients treated with subcutaneous interferon-β1a (sc IFN-β1a) using pooled data from clinical trials and post-marketing surveillance.

Methods: Seventeen phase II–IV Merck KGaA-sponsored trials of sc IFN-β1a were assessed to estimate the stroke incidence rate (IR) and IR ratio (IRR) per 100 patient-years (PY), and associated 95% confidence intervals (CI). The association of treatment duration with stroke was assessed through a Cox model. IR, IRR, and hazard ratio (HR) were adjusted by age, sex, presence of any comorbidity, and MS duration. Individual case safety reports were retrieved from the Global Patient Safety Database. The reporting rates of stroke were calculated and classified as medically confirmed or non-medically confirmed according to the source of each report.

Results: In 17 clinical trials, 4412 patients were treated with sc IFN-β1a for a total of 10,622 PY and 1055 patients with placebo for 2005 PY. The IR/100 PY (95% CI) of stroke was 0.025 (0.004, 0.150) in sc IFN-β1a patients and 0.051 (0.008, 0.349) in placebo patients. The IRR for sc IFN-β1a vs placebo was 0.486 (0.238, 0.995) and the HR was 0.496 (0.235, 1.043) for time to stroke-related event for sc IFN-β1a treatment at any dose compared with placebo. Among sc IFN-β1a patients, the IRR in those treated for < 2 years was 0.602 (0.159, 2.277) and for ≥ 2 years 0.469 (0.196, 1.124). Analysis of the safety database showed that the overall reporting rate for stroke was 13.286/10,000 PY.

Conclusion: Safety data from both clinical trial and post-marketing settings indicate that treatment with sc IFN-β1a does not increase stroke risk in patients with MS.

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Keywords: Subcutaneous interferon-β1a; Risk; Multiple sclerosis; Neurology; Stroke

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INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system (CNS) caused by inflammatory demyelination that leads to the progression of neurologic disability. The most common MS disease course is relapsing–remitting MS (RRMS), which is characterized by distinct attacks of neurological symptoms followed by periods of complete or partial remission [1].

Comorbidity is an area of growing interest for patients with MS as evidence suggests that comorbidity contributes to disability progression, reduced quality of life, and diagnostic complications [2]. A meta-analysis of population-based studies showed that stroke was one of the comorbidities with the highest incidence in patients with MS [3].

A stroke occurs when the supply of blood to the brain is inhibited, depriving the brain of oxygen and resulting in brain cell death [4]. The incidence of stroke in several European countries and the USA ranges from 114 to 350 cases per 100,000 persons per year, while its prevalence ranges from 1.5% to 3% [4]. In a meta-analysis that included two population-based studies, the incidence of any stroke in patients with MS was estimated at 2.73 per 100,000 [95% confidence interval (CI) 2.51, 2.95], with moderate heterogeneity between studies (I^2 47.7), and the prevalence was 3.28 per 100,000 (95% CI 0, 8.98; I^2 97.4) [5–7]. In both studies the incidence of any stroke and ischemic stroke was greater in patients with MS compared with the general population. Several further studies have also shown that compared to the general population, there is a higher prevalence of any stroke or ischemic stroke in the MS population [8–11]. Multiple reports of cerebral venous thrombosis (CVT) in patients with MS have also been made; however, the pathogenesis underlying the occurrence of CVT in MS patients remains unclear. Most of the cases reported underwent a lumbar puncture and intravenous corticosteroid treatment a few days before the clinical presentation of CVT. The use of oral contraceptives, a risk factor for CVT, may also have played a role [12–15].

It has been suggested that the risk for overall stroke is increased in patients with MS during the initial year of diagnosis [6, 16, 17]. Furthermore, two of these studies showed that this increased risk persists beyond the first year, albeit at a rate that is lower than for the initial year [6, 17].

Beta interferons (IFN) have shown effectiveness at treating RRMS during large randomized clinical trials by reducing the frequency of exacerbations and inhibiting disability progression as assessed by sustained change on the Expanded Disability Status Scale. They are widely prescribed and are generally well tolerated with a well-established, favorable safety profile [18–21]. However, to date, only one population-based study using health administrative data in British Columbia has evaluated the risk of stroke in patients treated with IFN-β (all formulations) [22].

The aim of this study was to assess the risk of stroke in MS patients treated with sc IFN-β1a and its association with treatment duration using pooled data from clinical trials and post-marketing surveillance.

METHODS

This study presents analyses of pooled data from sc IFN-β1a clinical trials and data from the Global Patient Safety Database.

This article is based on previously conducted studies and does not contain data collected by any of the authors.

Pooled Data From sc IFN-β1a Clinical Trials

Data from 17 Merck-KGaA-sponsored phase II–IV trials on sc IFN-β1a for MS were pooled for evaluation (Table 1). Data from trials were included in this analysis regardless of MS subtype (clinically isolated syndrome, RRMS, primary progressive MS, and secondary progressive MS), sc IFN-β1a dose, formulation, or follow-up duration. Patients receiving other interferon formulations were excluded.

In order to summarize patient characteristics without duplication, patients were stratified

Table 1 Main characteristics of key clinical trials included in the pooled analysis

Study number, acronym	Design	Placebo arm	sc IFN-β1a	Study duration	No. pts. treated (placebo[a]/sc IFN-β1a)	MS subtype
Data on file, Merck KGaA Study 6613	Randomized, open-label study with 6 months untreated lead-in followed by 6 months of treatment	No	sc IFN-β1a 11 μg or 33 μg tiw	1 year	0/68	RRMS
Data on file, Merck KGaA Study 8000 Extension	Extension study of 6613	No	sc IFN-β1a 11 μg or 33 μg tiw	18 months		RRMS
7480 ETOMS [26]	Randomized, double-blind, placebo-controlled	Yes	sc IFN-β1a 22 μg qw	2 years; 2-year extensions	154/154	CIS
6789 PRISMS [18]	Randomized, double-blind, placebo-controlled	Yes, option to switch	sc IFN-β1a 22 μg or 44 μg tiw	2 years	187/373	RRMS
22930 Long-term follow-up (LTFU) of study 6789 (PRISMS) [27]	Open-label, single visit between year 8 and 9 of original treatment in PRISMS	No, switch from 6789	Any commercial treatment or off treatment at LTFU visit	8-year extension		RRMS
7999 OWIMS [28]	Randomized, double-blind, placebo-controlled	Yes	sc IFN-β1a 22 μg or 44 μg qw	48 weeks; 2-year extension	100/193	RRMS
6954 SPECTRIMS [29]	Randomized, double-blind, placebo-controlled	Yes	sc IFN-β1a 22 μg or 44 μg tiw	3 years; 3-year extension	205/413	SPMS
6976 Nordic SPMS [30]	Randomized, double-blind, placebo-controlled	Yes, switch to 22 μg	sc IFN-β1a 22 μg	3 years, 1-year extension; 44 μg tiw offered to all extension II (no data from II)	178/186	SPMS

Table 1 continued

Study number, acronym	Design	Placebo arm	sc IFN-β1a	Study duration	No. pts. treated (placebo[a]/sc IFN-β1a)	MS subtype
21125 EVIDENCE [31]	Randomized, open-label, assessor-blinded, parallel-group study, comparative[b]	No	sc IFN-β1a 44 μg tiw	48 weeks; extension (up to 45 weeks post-transition)	0/339	RRMS
24735 REGARD [32]	Randomized, open-label, parallel-group study, comparative[c]	No	sc IFN-β1a 44 μg tiw	96 weeks	0/383	RRMS
Rebif® New Clone (484-39)–/Rebif® New Formulation (RNF; HSA-free formulation)						
24810, r-hIFN Beta-1a (Rebif®) Using Clone 484-39 EMEA NABs (NCT00367484)	Single-arm, open-label	No	sc IFN-β1a 22 μg or 44 μg tiw	48 weeks	0/460	RRMS
25632 The RNF Study [33]	Single-arm, open-label, historical comparison	No	sc IFN-β1a 44 μg tiw	96 weeks	0/260	RRMS
27025 REFLEX [21]	Randomized, double-blind, placebo-controlled	Yes	sc IFN-β1a 44 μg tiw or sc IFN-β1a 44 μg ow	24 months	171/344	CIS
28981 REFLEXION [34]	Double-blind, extension study to 27025	Yes, option for switch	sc IFN-β1a 44 μg tiw or sc IFN-β1a 44 μg ow	36 months (total 60 months of observation since randomization into REFLEX)		CIS
27178 IMPROVE [35]	Randomized, double-blind, placebo-controlled	Yes	sc IFN-β1a 44 μg tiw	16 weeks, 24-week extension	60/120	RRMS

Table 1 continued

Study number, acronym	Design	Placebo arm	sc IFN-β1a	Study duration	No. pts. treated (placebo[a]/sc IFN-β1a)	MS subtype
27571 TRANSFER [36]	Randomized, two-arm, open-label	No	sc IFN-β1a 44 μg tiw (RNF vs. original formulation)	4 weeks, 4-week safety follow-up (Rebif® HSA-free formulation continued), and long-term extension (until commercial availability of Rebif® HSA-free formulation)	0/116	RRMS
28733 RebiSmart™ [37]	Single-arm, open-label	No	RNF 44 μg tiw (e-device)	12 weeks	0/106	RRMS

CIS clinically isolated syndrome, *RRMS* relapsing–remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *RNF* rebif new formula, *HSA* human serum albumin

[a] Includes patients who were on placebo and switched to sc IFN-β1a

[b] Comparator was Avonex® 30 μg qw, only patients randomized to start on sc IFN-β1a were included in this analysis

[c] Comparator was Copaxone® 20 μg qd, only patients randomized to start on sc IFN-β1a were included in this analysis

into three groups according to the treatment received: cohort A comprised patients treated with sc IFN-β1a only (n = 3515), cohort B comprised patients treated with placebo only (n = 158), and cohort C comprised patients treated with placebo followed by sc IFN-β1a (n = 897). For analysis, patients who switched to sc IFN-β1a (cohort C) were considered as placebo patients until the start of sc IFN-β1a and as sc IFN-β1a patients following the switch. Stroke-related events that occurred before the start of sc IFN-β1a were analyzed alongside placebo-only events (cohort B) whereas stroke-related events that occurred after the start of sc IFN-β1a were analyzed alongside sc IFN-β1a-only events (cohort A).

Patient characteristics of the three cohorts, summarized in Table 2, included age at inclusion, sex, treatment duration (stratified in two groups: < 2 years; ≥ 2 years), MS disease duration in years, and baseline comorbidities, as identified from each patient's medical history, including history of prior stroke, hypertension, cardiovascular disease, diabetes, and obesity. The resulting groups used to assess the risk of stroke were those ever treated with sc IFN-β1a [cohort A + cohort C; n = 4412 patients, 10,622 patient-years (PY)] and those ever treated with placebo (cohort B + cohort C; n = 1055 patients, 2005 PY). The customized Standard MedDRA Query (SMQ) of central nervous system vascular disorders (20000060)—Scope Narrow for Stroke (MedDRA version 20.0) was used to retrieve 93 preferred terms corresponding to the medical concept of stroke (ischemic central nervous system vascular conditions; hemorrhagic central nervous system vascular conditions; central nervous system vascular disorders, not specified as hemorrhagic or ischemic; conditions associated with central nervous system hemorrhagic and cerebrovascular accidents). The selection was based on the underlying pathogenesis, type, etiology anatomical

Table 2 Patient characteristics

	Cohort A (sc IFN-β1a only; *n* = 3515)	Cohort B (placebo only; *n* = 158)	Cohort C (placebo then sc IFN-β1a; *n* = 897)
Female, *n* (%)	2408 (68.5)	105 (66.5)	595 (66.3)
Age, years	36.92 ± 9.34	36.53 ± 10.12	36.82 ± 9.86
MS disease duration, years	7.31 ± 7.00	7.30 ± 8.48	7.31 ± 7.61
sc IFN-β1a dose, *n* (%)			
44 μg tiw	2343 (66.7)	NA	471 (52.5)
sc IFN-β1a treatment duration, *n* (%)			
< 2 years	1991 (56.6)	NA	493 (55.0)
≥ 2 years	1524 (43.4)	NA	404 (45.0)
Placebo treatment duration, *n* (%)			
< 2 years	NA	107 (67.7)	445 (49.6)
≥ 2 years	NA	51 (32.3)	452 (50.4)
Baseline comorbidities, *n* (%)			
Hypertension	188 (5.3)	6 (3.8)	30 (3.3)
Diabetes mellitus	21 (0.6)	1 (0.6)	5 (0.6)
Cardiovascular disorder	1 (0.0)	0	0
Obesity	62 (1.8)	2 (1.3)	7 (0.8)
Atrial fibrillation	2 (0.1)	0	0
Carotid artery disease	0	0	0
Peripheral artery disease	22 (0.6)	0	6 (0.7)
Myocardial ischemia	2 (0.1)	0	1 (0.1)
Cardiac failure	0	1 (0.6)	1 (0.1)
Cardiac and vascular disorders congenital	15 (0.4)	0	2 (0.2)
Cardiac valve disorders	32 (0.9)	0	2 (0.2)
Prior stroke	42 (1.2)	3 (1.9)	20 (2.2)

Data are number (%) or mean (SD)
MS multiple sclerosis, *NA* not applicable, *sc* subcutaneous, *SD* standard deviation, *tiw* three times weekly

location, and sequelae associated with cerebrovascular accidents.

The incidence rates (IR) of stroke per 100 PY, and associated 95% confidence intervals (CIs), were estimated in patients who received sc IFN-β1a and patients who received placebo using a Poisson regression model adjusted for treatment, age, sex, any comorbidities, and MS duration. The sc IFN-β1a group was then compared with placebo through the incidence rate ratios (IRR) and 95% CIs. The adjusted IRR were modeled estimates based on the ratio of adjusted IR of treatment divided by adjusted IR for placebo. Hazard ratios (HR) with 95% CI were

calculated using a Cox regression model for stroke in patients with MS treated with sc IFN-β1a compared to those treated with placebo. The association of stroke with dose was also assessed using a Cox regression model and the results expressed with the HR with 95% CI. IR, IRR, and HR were all adjusted by age, sex, any comorbidity, and MS duration (< 2 years and ≥ 2 years). A sensitivity analysis was performed excluding those patients with any history of prior stroke at baseline.

Data From the Merck Safety Database in the Post-Marketing Setting

The Merck KGaA Global Safety Database receives all individual case safety reports (ICSRs) reported in the post-marketing setting. ICSRs are gathered from various sources including healthcare professionals, competent authorities, patients, published case reports, and clinical trial reports. The database also records all ICSRs from clinical trials that have been classified as serious events. This corresponds to 1.7% of all events reported in the database.

This analysis comprised all ICSRs recorded cumulatively between 3 May 1998 (corresponding to the International Birth Date of sc IFN-β1a) and the data lock point of 22 May 2017. ICSRs from patients exposed to sc IFN-β1a at any dose in the indication of multiple sclerosis were included from the analysis while those recorded from patients receiving placebo in clinical trials were excluded. ICSRs were included regardless of being serious or non-serious reports with event ranking and causality assessment conducted by either the reporter or Merck KGaA. The included ICSRs were categorized into two groups according to their origin: (1) medically confirmed reports received from a healthcare professional, health authority, literature case report, or clinical trial; (2) non-medically confirmed reports received from a patient or relative, either spontaneously or when solicited (i.e., provided from the company support network).

The same 93 preferred terms corresponding to the medical concept of stroke used for the analysis of pooled data from sc IFN-β1a clinical trials were used for the analysis of data from the safety database. The exposure of patients to sc IFN-β1a in the post-marketing setting was obtained from sales volume. The rate of stroke, overall and by preferred term, was calculated for patients using sc IFN-β1a in the post-marketing setting by dividing the number of cumulative events per 10,000 PY by exposure to sc IFN-β1a.

RESULTS

Phase II–IV Merck KGaA-Sponsored Trials

The baseline characteristics of 4570 patients with MS (regardless of subtype) included in the analysis of clinical trial data showed that patient demographics were similar among cohorts A, B, and C. The majority of patients were female (approximately 66.5%) and the mean age in years was comparable among cohorts (approximately 36.5 years) (Table 2). A total of 4412 patients were treated with sc IFN-β1a and 1055 were treated with placebo (897 were treated with both, i.e., placebo followed by sc IFN-β1a), for a total of 10,622 and 2005 PY (Table 3).

The adjusted IR/100 PY (95% CI) of stroke was 0.025 (0.004, 0.150) for sc IFN-β1a-treated patients (n = 4412), and 0.051 (0.008, 0.349) for placebo-treated patients (n = 1055), with 25 and 11 patients reporting events in each treatment group, respectively. Compared with placebo, the adjusted IRR (95% CI) for sc IFN-β1a was 0.486 (0.238, 0.995) for any treatment duration. The adjusted IRR (95% CI) for sc IFN-β1a compared to placebo was 0.602 (0.159, 2.277) for treatment duration < 2 years and 0.469 (0.196, 1.124) for ≥ 2 years. In patients receiving sc IFN-β1a 44 μg dosed three times weekly (tiw) versus placebo the IRR (95% CI) was 0.436 (0.190, 0.998) (Table 3). By treatment duration, the adjusted IR (per 100 PY) of stroke in patients exposed to sc IFN-β1a for < 2 years was 0.076 (0.005, 1.222) and for those ≥ 2 years it was 0.010 (0.001, 0.104).

The adjusted HR (95% CI) for time to stroke-related event for sc IFN-β1a treatment at any dose compared with placebo was 0.496 (0.235, 1.043). For sc IFN-β1a 44 μg tiw, the adjusted HR

Table 3 Incidence rate and incidence rate ratio with 95% confidence interval for sc IFN-β1a relative to placebo for stroke-related event in phase II–IV Merck KGaA-sponsored trials

	Total exposure to treatment (PY)	Number of patients with events	Adjusted IR per 100 PY (95% CI)	Adjusted IRR (95% CI)
Overall				
Any placebo	2005	11	0.051 (0.008, 0.349)	0.486 (0.238, 0.995)
Any sc IFN-β1a	10621.9	25	0.025 (0.004, 0.150)	
< 2 years				
Any placebo	686.8	3	0.127 (0.008, 2.088)	0.602 (0.159, 2.277)
Any sc IFN-β1a	2849.6	9	0.076 (0.005, 1.222)	
≥ 2 years				
Any placebo	1318.1	8	0.020 (0.002, 0.278)	0.469 (0.196, 1.124)
Any sc IFN-β1a	7772.3	16	0.010 (0.001, 0.104)	
44 μg tiw	5693.3	12	0.024 (0.004, 0.151)	0.436 (0.190, 0.998)

Any placebo includes only time and events while on placebo for patients in cohort B and/or C (i.e., before switching to sc IFN-β1a); any sc IFN-β1a includes time and events while on sc IFN-β1a for patients in cohort A and/or C (i.e., after switching to sc IFN-β1a)

CI confidence interval, *IR* incidence rate, *IRR* incidence rate ratio, *PY* patient-years, *sc* subcutaneous, *tiw* three times weekly

(95% CI) for time to stroke-related event compared with placebo was 0.454 (0.194, 1.061) (Fig. 1).

Merck Safety Database

The customized SMQ for stroke retrieved 2039 adverse events (AE) from the Merck KGaA database of which 421 (21%) were medically confirmed. Furthermore, of the 2039 AEs retrieved, 1345 (66%) were serious AEs (SAE), of which 375 were medically confirmed (28%). The estimated cumulative patient exposure to sc IFN-β1a in the post-marketing setting from launch until 3 May 2017 amounted to 1534,655 PY. The reporting rate by preferred term is shown in Table 4. The 2039 stroke AEs corresponded to a reporting rate of 13.286 per 10,000 PY and, the most frequently reported event corresponding to the medical concept of stroke, in patients receiving sc IFN-β1a, was hemiparesis ($n = 893$). Of these 893 AEs, 230 were classed as SAEs and 54 of these were medically confirmed (23.5%). The remaining 663 AEs were non-serious, of which 46 were medically confirmed (7%).

DISCUSSION

This study assesses the risk of stroke in MS patients treated with sc IFN-β1a and the association between stroke and treatment duration. This is a topic of relevance as the impact of comorbidities in MS patients is becoming increasingly of interest and stroke is one of the comorbidities with the highest incidence [3]. Results from these analyses show a trend towards decreased risk of stroke for sc IFN-β1a compared to placebo for 4570 MS patients with 12,627 PY of follow-up clinical trial data. Further analysis was planned to estimate the impact of prior history of stroke on risk of stroke with treatment.

An increased risk of stroke with sc IFN-β1a was not observed during this study which was in contrast to a recent nested case–control analysis which used real-world data from a population-based health administrative

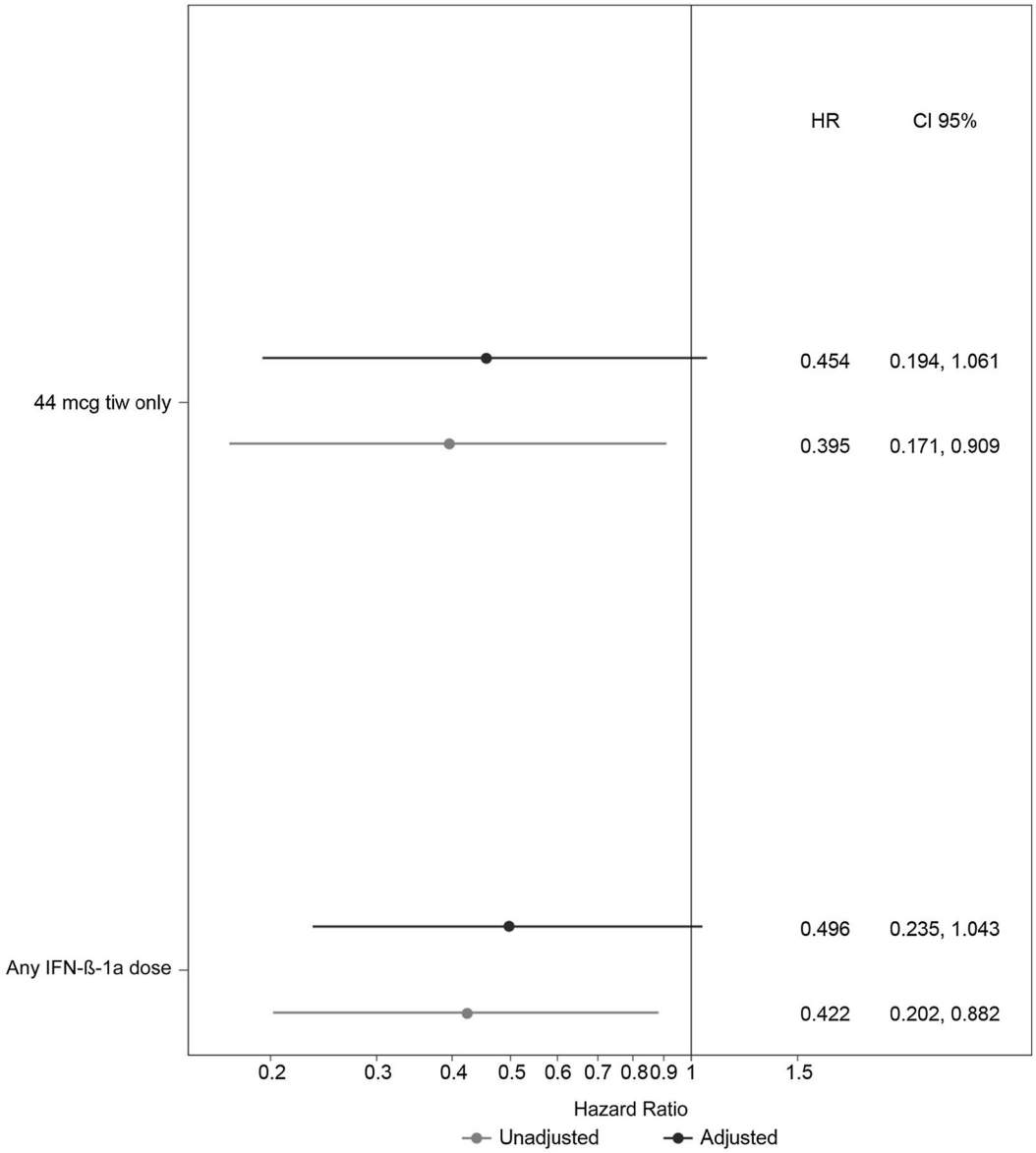

Fig. 1 Hazard ratio with 95% confidence interval for time to stroke-related event in phase II–IV Merck KGaA-sponsored trials for sc IFN-β1a treatment at any dose and at 44 µg tiw compared with placebo. CI confidence interval, HR hazard ratio, tiw three times weekly. The HR with 95% CIs of stroke in patients with MS are for 44 µg tiw only and for any sc IFN dose with time on placebo as the reference. HR and 95% CIs were calculated using Cox regression models and adjusted for age, sex, any comorbidities, and MS duration

database to show that IFN-β was associated with a 1.8-fold increase in the risk of stroke [22]. The study found that, of 2485 eligible RRMS patients, 1031 received IFN-β (all formulations; dose and trade name not specified) and patients with incident stroke were more likely to have previous exposure to IFN-β when compared with matched controls, with an adjusted odds ratio of 1.83 (95% CI 1.16, 2.89) [22]. The mean age of the 2485 patients was 41.3 years and 77% were female; the mean follow-up was 8 years. The nested case–control analysis included all potential adverse events (selected a priori after a comprehensive literature search and defined

Table 4 Reporting rate for most frequent serious and non-serious preferred term for stroke in patients exposed to sc IFN-β1a

Preferred term	Serious			Non-serious			Total	Reporting rate[a]
	Medically confirmed		Total	Medically confirmed		Total		
	Yes	No		Yes	No			
Total	375	970	1345	46	648	694	2039	13.286
Hemiparesis	54	176	230	46	617	663	893	5.819
Cerebrovascular accident	133	436	569	0	0	0	569	3.708
Transient ischemic attack	28	127	155	0	1	1	156	1.017
Hemiplegia	13	48	61	0	30	30	91	0.593
Cerebral hemorrhage	33	52	85	0	0	0	85	0.554

[a] Reporting rate calculated as number of cumulative events of stroke per 10,000 PY

with International Classification of Diseases-9/-10 diagnosis codes from physician and hospital claims) in the treated patients involving at least 30 incident cases. For each case, up to 20 controls, matched by age, sex, and cohort entry year, were randomly selected from the population of patients at risk for the condition of interest [22]. The contrasting results between the nested case–control analysis and the present study may be explained in part by potential selection bias in controlled trials towards "healthier" patients through the use of prespecified criteria to exclude patients with certain comorbidities or receiving certain co-medications. However, it is important to note that the present study includes patients with different severities of MS. The nested case–control study is based on data from a claims database and it should be noted that this type of analysis is subject to limitations when compared with data from randomized controlled trials. The absolute number of individual events may have been overestimated as only one claim was used to define a possible adverse event and this could potentially have included false positives. Furthermore, potential confounders such as treatment adherence and family history of stroke were not considered. It is also important to note the differences in patient populations and sample sizes between the nested case–control analysis and the present study. The present study combines "real-world" data from the global Merck safety database with extensive data from clinical trials and includes patients regardless of MS type. The nested case–control study analyzed data from a single region and only included patients with RRMS.

The observed absence of increased stroke risk reported in the clinical trials was also reflected in the post-marketing surveillance database in which there was an overall rate of 13.286 per 10,000 PY for stroke in patients exposed to sc IFN-β1a. The analysis found that the majority of stroke events occurred in women, which is in line with the population for MS [23].

There were no apparent trends in time to onset analysis. In most cases stroke was reported in patients also reporting underlying diseases and risk factors for development of stroke including hypertension, smoking, diabetes mellitus, and hypercholesterolemia. Importantly, in the majority of cases, treatment with IFN-β was reported to have continued after the stroke event.

The duration of sc IFN-β1a treatment did not appear to impact the risk of stroke. Previous studies have shown contradictory results about the risk of stroke in patients treated with sc IFN-β1a over time. While one study reported an increased risk of stroke in patients with > 2 years IFN-β exposure [22], a population-based cohort study found an increased risk of overall stroke within the first year of MS diagnosis and attributed it to surveillance bias

(e.g., an increased frequency of neuroimaging during the initial period after multiple sclerosis diagnosis) [16]. Two studies have reported a slight and persisting risk of overall stroke over the long term [6, 17].

In this study, the combination of both "real-world" clinical practice data from the Merck safety database and extensive data from randomized, control trials provides a broad and robust assessment of the risk of stroke in patients treated with sc IFN-β1a. It included a large number of trials, long follow-up, and a high number of patient years. However, clinical trial data was limited by a short follow-up of most of the placebo-controlled phases and a relatively small sample size. All data is presented "per patient years" which accounts for different exposures. Furthermore, the analysis of time to event and differentiation between less than or more than 2 years of exposure shows no increased risk. This indicates that further exposure to IFN-β over time does not increase the risk of a stroke. Information was lacking about relevant risk factors of stroke such as smoking, dyspepsia, the use of over-the-counter medicines, or presence of restricted mobility [24]. Regarding post-marketing data, some limitations should be mentioned [25]. Passive surveillance suffers from underreporting of AE which might affect the accuracy of the reporting rates. Furthermore, in the surveillance system, data about patients with the same underlying condition but unexposed to sc IFN-β1a are lacking. Information concerning the total number of doses of sc IFN-β1a actually administered to patients is not provided. Furthermore, it was not always possible to differentiate between causal and coincidental conditions using the Merck Safety Database and therefore the risk of stroke is likely being overreported.

CONCLUSION

The analyses of clinical trial data showed a trend towards decreased risk of stroke for sc IFN-β1a when compared with placebo. Furthermore, there was no significant increase in risk of stroke observed in patients with short-term (< 2 years) or long-term (≥ 2 years) exposure to sc IFN-β1a, or by dose level. Safety data from both clinical trial and post-marketing settings suggest that treatment with sc IFN-β1a does not increase the risk of stroke in patients with MS.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain data collected by any of the authors.

Data Availability. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All data

generated or analyzed during this study are included in this published article.

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