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Subcutaneous interferon β-1a three times weekly and the natural evolution of gadolinium-enhancing lesions into chronic black holes in relapsing and progressive multiple sclerosis: Analysis of PRISMS and SPECTRIMS trials

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Abstract

Background: Evolution of gadolinium-enhancing lesions into chronic black holes (CBH) may be reduced by interferon (IFN) therapy.

Objective: The objective of this paper is to assess the effect of IFN β-1a and placebo on CBH evolution and disability in patients with relapsing–remitting multiple sclerosis (RRMS), as well as CBH evolution in patients with secondary progressive multiple sclerosis (SPMS).

Methods: A post hoc, exploratory analysis of patients with RRMS and SPMS with monthly MRI scans (months –1 to 9) from two separate placebo-controlled clinical trials of IFN β-1a was conducted.

Results: In RRMS patients, the risk of ≥1 evolved CBH was lower for IFN β-1a versus placebo (odds ratio 0.42; $p = 0.024$); volume of newly evolved CBH was numerically reduced. A numerically higher proportion of patients with ≥1 evolving CBH vs no evolving CBH had confirmed three-month disability progression (four-year rate 55.8% vs 43.1%, respectively). Proportion of lesions evolving into CBH (patient level: 34.7% vs 12.6%, $p < 0.0001$; lesion level: 28.8% vs 11.0%, $p < 0.0001$) and evolved CBH volume (median 33.5 mm^3 (Quartile 1, 0.0; Quartile 3, 173.4) vs 0.0 mm^3 (0.0; 52.4); $p = 0.0008$) was higher for SPMS than RRMS patients treated with IFN β-1a.

Conclusion: In RRMS, IFN β-1a significantly decreased the proportion of new T1 Gd+ lesions evolving into CBH and the risk of developing a CBH. In patients with SPMS, more lesions develop to CBH, indicating reduced repair capacity, and the natural history of lesion development appears to be unaffected by IFN β-1a treatment.

Keywords: Chronic black holes, disability progression, disease progression, interferon beta-1a, magnetic resonance imaging, relapsing–remitting multiple sclerosis, secondary progressive multiple sclerosis, T1 hypointensity

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Introduction

Magnetic resonance imaging (MRI) is an important tool in the diagnosis and follow-up of multiple sclerosis (MS), and its routine use has improved our understanding of the disease.[1,2] MRI measures of inflammation (active lesions) include the count of new or enlarged T2 lesions and gadolinium-enhancing (Gd+) T1-weighted MRI lesions, with the latter being recommended for the clinical classification of MS disease types and recognized as reflecting contemporary relapses.[2] Gd+ T1-weighted MRI is a well-established marker of blood-brain barrier disruption and areas of acute inflammatory activity.[3]

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In T1-weighted images, the majority of Gd+ T1 lesions resolve radiologically, becoming isointense to surrounding white matter, but approximately 20%–40% of such active lesions will evolve over 6–12 months into areas of low signal.[4,5] These T1 hypointense lesions, or chronic "black holes" (CBH), correspond to areas of more severe tissue damage (demyelination, axonal loss, and matrix destruction).[4,6–9]

An increasing body of literature shows a strong correlation between MRI and MS clinical disease activity.[2] The evolution of CBH was significantly associated with poor recovery from an acute MS relapse,[10] while the rate of accumulation and load of CBH may correlate with clinical disability and disease progression better than the presence of other lesions.[11,12] Consequently, CBH represent an appealing measure of tissue damage and disease progression and an important treatment target.

There are few reports into the longitudinal changes in CBH during treatment of MS with interferon (IFN) β, as persistent black hole volume has not been a predefined outcome in most clinical trials, likely owing to difficulties measuring CBH and the need to perform monthly MRI over an extended period of time.[4] Those studies that have been reported have suggested that IFN β may reduce the number of CBH in patients with clinically isolated syndrome, relapsing–remitting MS (RRMS) and secondary progressive MS (SPMS).[13–15] However, these studies either did not address or did not show an effect of treatment on the rate of Gd+ lesions developing into CBH.

In a retrospective analysis of the frequent MRI cohorts of two placebo-controlled clinical trials (Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) and Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS)), we evaluate the effect of IFN β-1a treatment on CBH evolution and its relation with clinical outcomes, and characterize the evolution of black holes in patients with RRMS and SPMS treated with placebo or subcutaneous (sc) IFN β-1a.

Methods

Study design and patients

This was a post hoc, exploratory analysis of patients participating in the frequent MRI subcohorts of two separate placebo-controlled clinical trials of sc IFN β-1a: PRISMS[16] in RRMS and SPECTRIMS[17] in SPMS. These contemporaneous studies, which had parallel recruitment, were designed to assess the efficacy of sc IFN β-1a treatment on clinical and MRI measures of disease activity. The designs of these studies have been described in detail previously.[16,17] Briefly, these were multicenter, randomized, double-blind, placebo-controlled, Phase III trials in which patients received sc IFN β-1a (44 μg or 22 μg three times weekly) or matching placebo for two years (PRISMS) or three years (SPECTRIMS). At study entry, patients in PRISMS had RRMS, Expanded Disability Status Scale (EDSS) scores of 0–5, and active disease (≥2 relapses during the two years pre-study) that had been stable for four weeks at the pre-study evaluation; patients in SPECTRIMS had SPMS, EDSS score 3.0–6.5, pyramidal functional score ≥2, and active disease without exacerbation in the eight weeks prior to the study. Patients in PRISMS who received placebo were re-randomized to sc IFN β-1a after two years (delayed treatment (DT)) while those assigned sc IFN β-1a continued the same treatment. Patients in SPECTRIMS were not re-randomized.

Patients were included in this analysis if they took at least one dose of study drug, underwent monthly MRI assessments (from month –1 to month 9; the frequent MRI cohort), and had ≥1 newly enhancing T1 Gd+ lesion in the month –1 through month 3 scans. Patients without newly enhancing lesions were included in analyses of disability outcome only. MRI techniques in both PRISMS and SPECTRIMS are summarized in Supplementary Appendix 1.[18,19] Briefly, in both PRISMS and SPECTRIMS, scan data were read, converted, and stored on the University of British Columbia (UBC) MS/MRI Research Group's computer (the group had no knowledge of patients' treatment and outcomes). Enhancing lesions were identified and assigned T1-Gd identification numbers, which were recorded in a database. In this analysis, a CBH was defined as a newly enhancing T1 Gd+ lesion that evolved into a T1 hypointense lesion that was visible for ≥6 months. MRI scans were re-analyzed by the UBC MS/MRI Research Group to obtain data on the evolution of new T1 Gd+ lesions from months –1 to 3 (or months –1 to 2 for patients without a month 9 scan) to CBH at month 9 (or month 8 for those without a month 9 scan), ensuring a period of ≥6 months to evaluate whether newly enhancing lesions evolved into CBH.

Statistical analysis

Descriptive statistics were used to summarize baseline demographic variables. Data from treatment arms receiving sc IFN β-1a (44 µg or 22 µg) were pooled.

Percentage of newly enhancing T1 Gd+ lesions at months –1 to 2/3 that evolved into CBH at Month 8/9 was assessed at the patient and lesion level. Percentage of CBH per patient at month 8/9 was defined as the total number of CBH per patient at month 8/9 divided by the total number of newly enhancing lesions per patient from month –1 to 3, multiplied by 100. A nonparametric analysis of variance (ANOVA) model on ranks, adjusted for baseline T2 lesion load (measured as a total T2 lesion volume in mm^3), was used for pairwise comparisons for the percentage of evolved CBH. To assess the probability of a newly enhancing lesion evolving into a CBH an analysis on the lesion level was performed: A logistic regression model fitted by generalized estimating equations (GEE), which adjusted for correlations of newly enhancing T1 Gd+ lesions within the same patient, was used to compare the odds of a newly enhancing T1 Gd+ lesion evolving into a CBH between sc IFN β-1a and placebo groups (presented as odds ratios (OR) and 95% confidence interval (CI)). Logistic regression was performed to evaluate the risk of patients having ≥1 CBH between sc IFN β-1a and placebo groups. Volume of evolved CBH at month 8/9 was analyzed using ANOVA on ranks data, adjusted for baseline T2 lesion load, baseline Scripps Neurological Rating Scale, and MS duration.

Confirmed disability progression was defined as an increase in EDSS score of ≥1 point if baseline was ≤5.5, or increase of 0.5 point if baseline was ≥6 and confirmed three months later. The association between CBH presence and disability progression in the different treatment groups (IFN β-1a or placebo (DT group)) was assessed for up to four years of follow-up using logistic regression adjusted for baseline covariates (age, T2 lesion load, and EDSS).

Results

Patient population

Of all the eligible patients who received placebo or sc IFN β-1a and who had monthly MRI ($N = 462$), 253 patients had ≥1 newly enhancing T1 Gd+ lesion from months –1 to 2/3 and were included in this analysis. Of these, 122 patients were included from PRISMS ($n = 122/205$; placebo, $n = 49$; sc IFN β-1a 22 µg, $n = 39$; sc IFN β-1a 44 µg, $n = 34$) and 131 from SPECTRIMS ($n = 131/257$; placebo, $n = 52$; sc IFN β-1a 22 µg, $n = 40$; sc IFN β-1a 44 µg, $n = 39$). Patient demographics and baseline characteristics are shown in Table 1.

A total of 196 patients from PRISMS (including the 122 patients with newly enhancing lesions) were included in the analysis of disability progression (sc IFN β-1a, $n = 129$; DT group, $n = 67$). The patient demographics and baseline clinical characteristics of this group were similar to the PRISMS group above with the exception of a lower T2 lesion load (Supplementary Table 1).

Newly enhancing lesions and CBH (PRISMS IFN β-1a vs placebo)

In patients from PRISMS with ≥1 newly enhancing T1 Gd+ lesion in the month –1 to month 2/3 scans, the total numbers of newly enhancing T1 Gd+ lesions from months –1 to 2/3, those evolving to CBH at month 8/9, and the percentages of lesions evolving to CBH at month 8/9 were lower in patients receiving sc IFN β-1a vs placebo (Table 2). At the lesion level, the percentage of newly enhancing T1 Gd+ lesions evolving into a CBH at month 8/9 was similar with sc IFN β-1a (60/544 lesions; 11.0%), and placebo (49/424 lesions; 11.6%), also the probability of newly enhancing lesions evolving into a CBH (OR 0.95 (95% CI, 0.52, 1.73); $p = 0.86$). At the patient level, the percentage of newly enhancing T1 Gd+ lesions evolving into CBH at month 8/9 was reduced by 36% in patients who received sc IFN β-1a versus placebo ($p = 0.033$) (Table 2; Figure 1). Overall the percentage of patients with ≥1 lesion evolving to CBH at month 8/9 was also lower with sc IFN β-1a (34%) than with placebo (55%), resulting in a significantly lower risk of having ≥1 lesion evolving to CBH with sc IFN β-1a versus placebo (OR 0.42 (95% CI, 0.20, 0.89); $p = 0.024$) (Figure 2).

The volume of newly evolved CBH per patient at month 8/9 was reduced numerically by 44% for all patients who received sc IFN β-1a (median 0.0 mm^3 (Quartile 1, 0.0; Quartile 3, 52.4)) versus placebo (median 6.6 mm^3 (Quartile 1, 0.0; Quartile 3, 83.0); $p = 0.073$) (Supplementary Figure 1).

Predictive value of CBH on disability progression

In the 196 patients from PRISMS included in this analysis, new enhancing lesions were present in 73/129 (57%) patients who received continuous sc IFN β-1a versus 49/67 (73%) in the DT group; CBH

Table 1. Demographics and baseline characteristics of frequent MRI cohort patients with ≥ 1 T1 Gd+ lesion between month –1 and month 3 ($n = 253$).

	PRISMS		SPECTRIMS	
Variable	Placebo ($n = 49$)	sc IFN β-1a[a] ($n = 73$)	Placebo ($n = 52$)	sc IFN β-1a[a] ($n = 79$)
Age, mean (SD) years	34.7 (8.4)	34.7 (7.0)	41.4 (5.9)	42.2 (7.3)
Female, %	73.5	69.9	63.5	60.8
EDSS score				
Mean (SD)	2.5 (1.2)	2.4 (1.2)	5.7 (0.9)	5.5 (1.0)
Median (Q1, Q3)	2.5 (2.0, 3.5)	2.5 (1.5, 3.5)	6.0 (5.5, 6.5)	6.0 (5.0, 6.0)
Time since onset of MS, mean (SD) years	7.3 (5.4)	8.0 (6.1)	14.2 (6.7)	13.5 (7.0)
T2 lesion load, mm^2				
Mean (SD)	4344.4 (3706.0)	3868.6 (3583.7)	6365.4 (3906.9)	6112.9 (4126.9)
Median (Q1, Q3)	3509.0 (1754.0, 5486.0)	2725.0 (1148.0, 5706.0)	5785.0 (3386.0, 8572.0)	5381.0 (3167.0, 7441.0)

[a]44 µg and 22 µg dose groups combined.
EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; IFN: interferon; MRI: magnetic resonance imaging; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; Q: quartile; sc: subcutaneous; SD: standard deviation; SPECTRIMS: Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS.

Table 2. Total newly enhancing T1 Gd+ lesions, counts of evolved CBH, and percentage of evolved CBH at month 8/9.

	Total newly enhancing T1 Gd+ lesions from month –1 to 2/3		Counts of evolved CBH at month 8/9		Percentage of T1 Gd+ lesions that evolved CBH at month 8/9	
	Placebo	sc IFN β-1a[a]	Placebo	sc IFN β-1a[a]	Placebo	sc IFN β-1a[a]
PRISMS (RRMS)						
Patients (n)	49	73	27	25	27	25
Mean (SD)	8.7 (12.7)	7.5 (16.5)	1.0 (1.3)	0.8 (1.7)	19.8 (28.9)	12.6 (24.7)
Median (Q1, Q3)	4.0 (2.0, 11.0)	4.0 (1.0, 7.0)	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	6.3 (0.0, 28.6)[c]	0.0 (0.0, 12.5)[d]
					sc IFN β-1a vs placebo $p = 0.033$[b]	
SPECTRIMS (SPMS)						
Patients (n)	52	79	32	53	32	53
Mean (SD)	9.9 (15.4)	4.6 (5.4)	2.7 (5.5)	1.3 (1.7)	27.7 (31.9)	34.7 (35.8)
Median (Q1, Q3)	4.0 (2.0, 11.0)	3.0 (1.0, 6.0)	1.0 (0.0, 2.5)	1.0 (0.0, 2.0)	16.5 (0.0, 50.0)[c]	25.0 (0.0, 60.0)[d]
					sc IFN β-1a vs placebo $p = 0.311$[b]	

n refers to the number of patients with newly enhancing T1 Gd+ lesions or patients with T1 Gd+ lesions that evolved to CBH.
[a]44 µg and 22 µg dose groups combined. [b]Based on ANOVA on ranks data. [c]RRMS versus SPMS $p = 0.204$, based on ANOVA on ranks data. [d]RRMS versus SPMS $p < 0.0001$, based on ANOVA on ranks data.
ANOVA: analysis of variance; CBH: chronic black hole; Gd+: gadolinium-enhancing; IFN: interferon; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; Q: quartile; sc: subcutaneous; RRMS: relapsing–remitting multiple sclerosis; SD: standard deviation; SPECTRIMS: Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS; SPMS: secondary progressive multiple sclerosis.

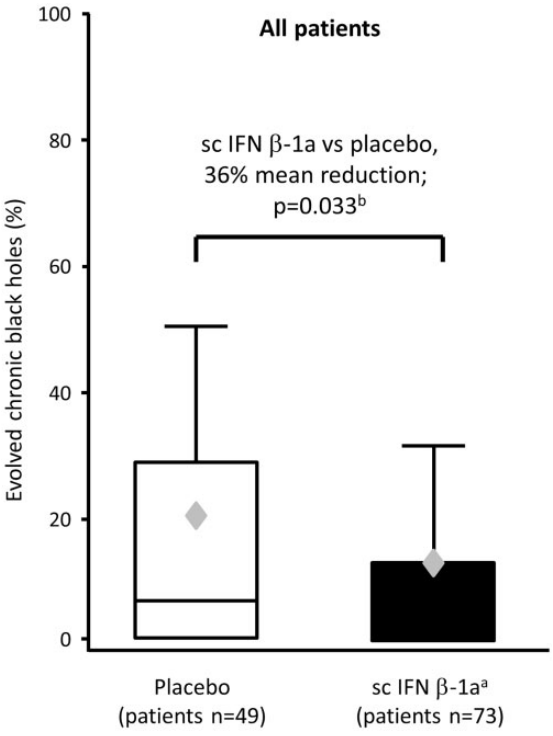

Figure 1. Percentage of new T1 Gd+ lesions that evolved into CBH at month 8/9 from PRISMS placebo versus sc IFN β-1a (patient level).
[a]44 μg and 22 μg dose groups combined. [b]Based on ANOVA on ranks data.
Bottom and top of box = first and third quartiles; band inside box = median; ends of whiskers = last observed value within 1.5 times the IQR; diamond = mean. For sc IFN β-1a, the first quartile and median values overlapped.
ANOVA: analysis of variance; CBH: chronic black holes; Gd+: gadolinium-enhancing; IFN: interferon; IQR: interquartile range; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; sc: subcutaneous.

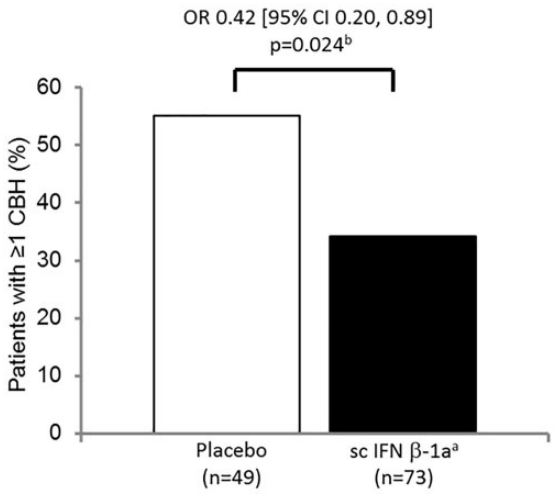

Figure 2. Percentage of patients with ≥1 CBH at month 8/9 from PRISMS placebo versus sc IFN β-1a.
[a]44 μg and 22 μg dose groups combined. [b]Based on logistic regression model.
CBH: chronic black hole; CI: confidence interval; IFN: interferon; OR: odds ratio; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; sc: subcutaneous.

occurred in 34% and 55% of patients, respectively, as described above.

Overall, a numerically higher proportion of patients who developed CBH had confirmed three-month disability progression compared with those with no CBH development. Confirmed disability progression occurred at a higher rate in all patients who had ≥1 CBH ($n = 52$) versus those without CBH ($n = 144$) in year 2 (40.4% vs 31.9%), year 3 (53.8% vs 38.9%), and at year 4 (55.8% vs 43.1%); however, the odds of confirmed disability progression for those with ≥1 and without any CBH were not statistically significant (Table 3).

Descriptive data analysis indicated a similar trend across the treatment groups. In the DT group, fewer patients with no CBH had disability progression after two years (37.5%) versus those with CBH (48.1%); respective values at four years were 45.0% and 59.3% (Table 3). For continued sc IFN β-1a, this trend became evident from year 3; rates at year 4 were 42.3% and 52.0% for no CBH versus CBH (Table 3; Figure 3(a)). At both year 2 and 4, fewer patients on sc IFN β-1a had disability progression compared with those on DT (Table 3).

The presence or absence of CBH was also related to the change in median EDSS score at each of these time points. In the DT group, the median EDSS score increased from 2.0 at month 8/9 to 2.5 at year 4 in patients with no CBH compared with an increase from 2.0 to 3.5 in those with ≥1 CBH (Figure 3(b)). In the sc IFN β-1a group, median EDSS score was also higher in those with ≥1 CBH, increasing from 2.5 at year 1 to 3.0 at years 2–4. In those with no CBH receiving sc IFN β-1a, median EDSS score was 2.0 at years 1, 2, and 4, and 2.5 at year 3 (Figure 3(b)).

The analyses of change in median EDSS scores were repeated by excluding patients who were not on treatment at the time of EDSS assessment, with similar results observed. In the DT group, median EDSS scores for those with ≥1 CBH versus no CBH were, 2.0 and 2.0 at month 9; 2.5 versus 2.0 at year 2; 3.0 versus 2.0 at year 3; 2.5 versus 2.5 at year 4.

Table 3. Confirmed three-month disability progression in patients with ≥1 CBH vs those with no CBH from analysis of PRISMS.

	Delayed treatment group ($n=67$)		Continued sc IFN β-1a ($n=129$)		All ($n=196$)	
Confirmed progression	≥1 CBH ($n=27$)	No CBH ($n=40$)	≥1 CBH ($n=25$)	No CBH ($n=104$)	≥1 CBH ($n=52$)	No CBH ($n=144$)
Two years	48.1%	37.5%	32.0%	29.8%	40.4%	31.9%
Odds ratio (95% CI);	1.36 (0.5, 4.1);		1.42 (0.5, 4.4);		1.54 (0.7, 3.2);	
p value	$p=0.579$		$p=0.536$		$p=0.254$	
Three years	55.6%	37.5%	52.0%	39.4%	53.8%	38.9%
Odds ratio (95% CI);	1.95 (0.7, 5.8)		1.80 (0.7, 4.9)		1.86 (0.9, 3.8)	
p value	$p=0.232$		$p=0.253$		$p=0.091$	
Four years	59.3%	45.0%	52.0%	42.3%	55.8%	43.1%
Odds ratio (95% CI);	1.63 (0.5, 4.9);		1.35 (0.5, 3.6);		1.54 (0.8, 3.2);	
p value	$p=0.383$		$p=0.557$		$p=0.238$	

Confirmed disability progression: an increase in EDSS score ≥1 point if baseline EDSS score is ≤5.5, or increase of 0.5 point if baseline ≥6 and confirmed three months later. Assessed using logistic regression adjusted for baseline covariates (age, burden of disease, and EDSS). *P* values are for ≥1 CBH vs no CBH.
CI: confidence interval; CBH: chronic black hole; EDSS: Expanded Disability Status Scale; IFN: interferon; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; sc: subcutaneous.

The respective scores for sc IFN β-1a were 2.5 versus 2.0; 3.0 versus 2.0; 3.0 versus 2.5; and 2.5 versus 2.0.

Analysis of CBH evolution in RRMS patients (PRISMS) versus SPMS patients (SPECTRIMS)

The proportion of newly enhancing Gd+ lesions that evolved into CBH at month 8/9 (patient level) was numerically lower in patients receiving placebo with RRMS compared with those with SPMS ($p=0.204$). The proportion was also lower in sc IFN β-1a-treated patients with RRMS than in patients with SPMS ($p<0.0001$) (Table 2).

In patients with RRMS, there was a significantly lower probability of newly enhancing T1 Gd+ lesions evolving into a CBH than in patients with SPMS, irrespective of treatment. The proportions of lesions evolving into CBH in the placebo group were 11.6% for RRMS and 27.2% for SPMS (OR, 0.35; $p=0.001$); in the sc IFN β-1a group the proportions were 11.0% and 28.8% (OR, 0.31; $p<0.0001$) (Figure 4). In patients treated with sc IFN β-1a, the volume of newly evolved CBH at month 8/9 was smaller for patients with RRMS (median 0.0 mm^3 (Quartile 1, 0.0; Quartile 3, 52.4)) compared with those with SPMS (median 33.5 mm^3 (Quartile 1, 0.0; Quartile 3, 173.4); $p=0.0008$). In those who received placebo, CBH volume was numerically smaller in patients with RRMS (median 6.6 mm^3 (Quartile 1, 0.0; Quartile 3, 83.0)) compared with SPMS (median 12.1 mm^3 (Quartile 1, 0.0; Quartile 3, 171.5); $p=0.321$) (Supplementary Figure 2).

Discussion

This post hoc analysis of the PRISMS frequent MRI cohort demonstrates that in patients with RRMS, at the patient level, treatment with sc IFN β-1a was associated with a significantly decreased proportion of newly enhancing T1 Gd+ lesions evolving into CBH versus placebo. In addition, the risk of having ≥1 evolved CBH was significantly lower with sc IFN β-1a versus placebo. The data reported here are consistent with the improved MRI outcomes reported in previous studies of patients who received IFN β.[13,18,20,21] In patients with clinically isolated syndromes suggestive of MS, sc IFN β-1a resulted in significantly lower numbers of new T1 hypointense and Gd+ lesions versus placebo,[21] and in patients with RRMS, sc IFN β-1a resulted in 69% fewer combined unique active lesions versus placebo,[20] with a dose-dependent beneficial effect of sc IFN β-1a on MRI outcomes observed. Our analysis does also contribute to a better understanding of the underlying mechanism for the significantly reduced risk of CBH with sc IFN β-1a versus placebo in RRMS patients. The overall reduction in the number of newly enhancing Gd+ lesions with sc IFN β-1a is certainly one plausible mechanism as it would be expected that the formation of fewer

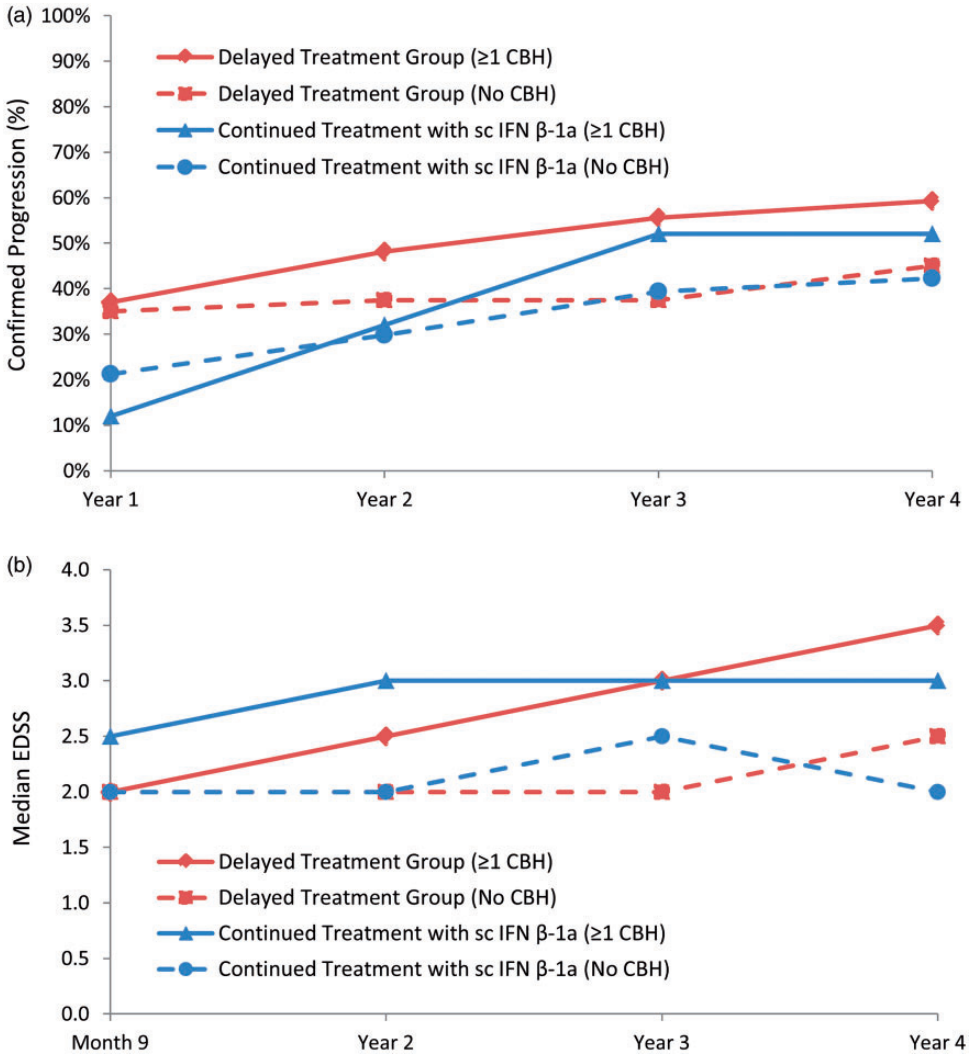

Figure 3. (a) Confirmed disability progression and (b) median EDSS score from Year 1 to 4 in patients with ≥1 CBH versus those with no CBH according to treatment (delayed treatment ($n = 67$) or continued treatment with sc IFN β-1a combined ($n = 129$)) from PRISMS placebo versus sc IFN β-1a.
Data are presented descriptively.
CBH: chronic black hole; EDSS, Expanded Disability Status Scale; IFN: interferon; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; sc: subcutaneous.

Gd+ lesions leads to lower absolute numbers of lesions evolving into CBH. But this assumption would not explain the relative reduction of the percentage of newly enhancing T1 Gd+ lesions evolving into CBH at month 8/9 observed at the patient level. Although it would be tempting to assume additional, directly protective or repair promoting effects, other explanations should also be considered. The anti-inflammatory effects of IFN β-1a may result not only in lower numbers of newly enhancing lesions but may also affect other features in those lesions occurring despite treatment, like size or actual tissue damage. Large enhancing lesions bear a higher risk of evolving to CBH.[14]

CBH volume measurement in our study did indicate only a trend toward lower values in the early sc IFN β-1a group. Black hole volume can be difficult to measure and is dependent on scan quality.[22] Other studies including higher numbers of patients have shown an effect of IFN β on T1 hypointense lesion volume: Intramuscular IFN β-1a significantly reduced lesion volume and slowed volume progression over three years,[13] and sc IFN β-1a treatment had a stabilizing effect on lesion volume following an increase in volume during a pretreatment phase.[23]

Others have reported a correlation between T1 hypointense lesions and EDSS score, which over two

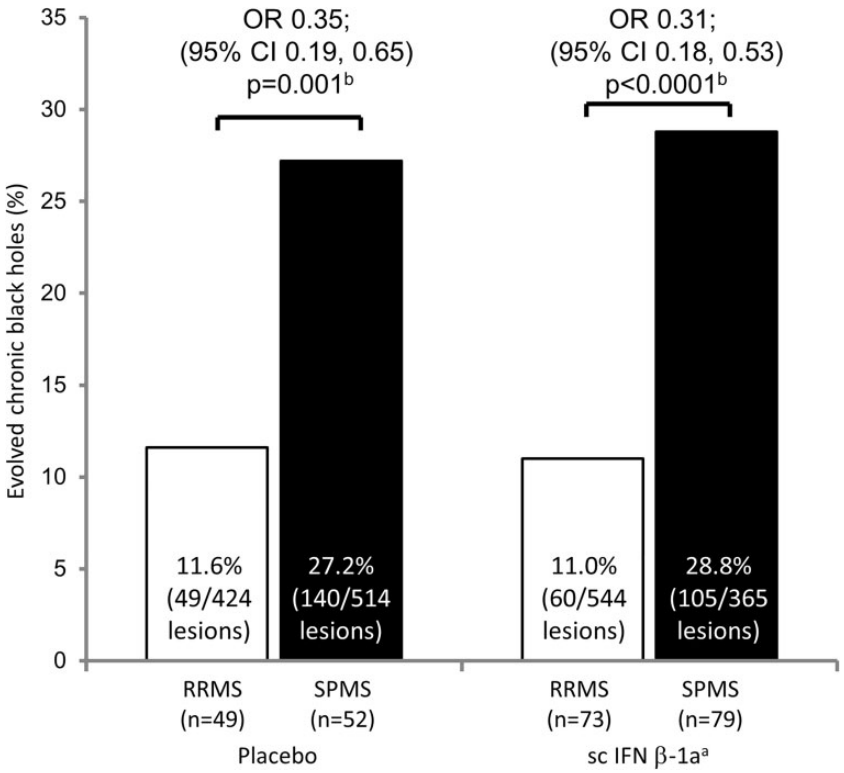

Figure 4. Probability of a newly enhancing T1 Gd+ lesion evolving into a CBH at month 8/9 (lesion level); RRMS (PRISMS) versus SPMS (SPECTRIMS).
[a]44 µg and 22 µg dose groups combined. [b]Based on logistic regression model fitted by generalized estimating equations.
CBH: chronic black hole; CI: confidence interval; Gd+: gadolinium-enhancing; IFN: interferon; OR: odds ratio; PRISMS: Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; sc: subcutaneous; RRMS: relapsing–remitting multiple sclerosis; sc: subcutaneous; SD: standard deviation; SPECTRIMS: Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS; SPMS: secondary progressive multiple sclerosis.

years exceeds the strength of correlation between T2 hyperintense lesions and EDSS score.[4,13,24] Nevertheless, the relationship between brain lesions and disability cannot fully explain most of the disability as expressed by the EDSS score;[13] clinical disability measures are known to be heavily influenced by ambulation status, and might be better measured by spinal cord involvement.[25] Furthermore, T1 hypointense lesions are widely distributed within the brain, including regions unlikely to cause disability.[13] The current study did not aim at evaluating the effect of continuous sc IFN β-1a versus DT on confirmed disability progression at four years. The respective data, presented descriptively, are in line with the overall PRISMS results. In the DT group only we observed a numerical trend for an association between $\geq$1 CBH and higher rates of disability progression versus no CBH, suggesting that CBH may be a prognostic factor; however, the utility of CBH for predicting future disability requires further investigation.

Although generally a decreased number of new lesions would be expected in patients with SPMS compared with RRMS, the number of newly enhancing Gd+ lesions was similar between RRMS and SPMS in patients who received placebo and lower only in patients with SPMS who received IFN β-1a, indicating a relatively active population and the anti-inflammatory effect of IFN β-1a in SPMS shown in the overall analysis of SPECTRIMS. Patients with SPMS tended to have higher evolved CBH volume than those with RRMS, consistent with previous findings.[12] The probability of a newly enhancing Gd+ lesion evolving into a CBH was significantly higher in patients with SPMS versus RRMS both for placebo and sc IFN β-1a. A placebo-controlled study of IFN β-1b in SPMS patients showed a significant effect in reducing the number of new enhancing lesions during the first months of treatment and reducing the numbers of hypointense T1 lesions that had developed; the treatment effect in reducing new lesion formation would be expected to result in

fewer new hypointense T1 lesions developing during subsequent months.[14] The longer, 18 months of follow-up in that study would have excluded lesions due to subacute pathology (edema and demyelination), which may resolve gradually.[14,26] In the current study in SPMS patients, the proportion of enhancing lesions that developed into hypointense T1 lesions was found to be unaffected by treatment when compared with placebo. Our findings support a hypothesis of a "reduced repair capacity" in patients with SPMS, with a higher risk of lesions that, once established and showing enhancement, progress irrespective of IFN β treatment.[14]

Study limitations include analyses of data from two separate trials with different patient populations and disease courses. However, the similarities in the methodology of the two trials together with the contemporaneous, parallel recruitment, enable such a comparison. Pooling the two sc IFN β-1a doses for these analyses was performed to overcome too few patient numbers in the individual dosing arms for valid statistical analyses. The logistic regression model investigating the association between CBH status and disability progression was adjusted for the baseline covariates age, T2 lesion load, and EDSS. However, the analysis did not adjust for parameters that might have confounded the analysis, such as sex, race, disease duration, and the baseline number of Gd+ lesions; for the latter, baseline values were not available and so T2 lesion load was adjusted for instead. In addition, the CBH analysis did not adjust for concomitant steroid use. Future analyses that investigate the evolution of Gd+ lesions and the impact of CBH on disability progression should consider these additional factors.

Potential additional analyses include an evaluation of Gd+ lesion persistence in the acute phase and whether later disease activity is greater in patients with Gd+ lesions that persist beyond current analyses. CBH duration may be influenced by enhancing lesion duration.[26,27] IFN β has been shown to reduce duration of enhancement of new lesions,[28] suggested to be due to an effect on the blood-brain barrier. A comparison over time would allow an examination of whether the lesion developed pre- or post-dosing, as well as the predictive impact of lesion volume.

The data from these analyses suggest that sc IFN β-1a treatment affects the course of the disease in patients with RRMS by changing the natural evolution of lesions, in terms of decreasing the risk of developing a CBH and the proportion of new T1 Gd+ lesions evolving into CBH. The association of this treatment effect on the evolution of lesions with long-term outcomes, such as disability progression, requires further investigation. In patients with SPMS, the natural history of lesion development appears to be unaffected by IFN β-1a treatment.

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Supplementary material

Supplementary material is available for this article online.

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