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REVIEW

Approved Beta Interferons in Relapsing-Remitting Multiple Sclerosis: Is There an Odd One Out?

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Abstract: Three interferons are marketed for the treatment of relapsing-remitting multiple sclerosis. In its pivotal trial, one of them demonstrated impressive efficacy as a once-weekly regimen, but later head-to-head studies and reviews questioned its superiority. Analysis of this pivotal trial in publications and health authority reviews has shown that its early termination might have caused attrition bias. Censored patients were different from those completing the study on magnetic resonance imaging parameters and benefited from placebo in terms of relapse rate. Early progression of disability and differences in follow-up duration could have favored the benefit observed for the progression of disability outcome. Only the raw data could be of help to confirm or refute doubts about this trial. Raw data should be made available to the scientific community.

Keywords: interferons, relapsing-remitting multiple sclerosis, efficacy

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Background

Since 1995, three interferons have been marketed in Europe for the treatment of relapsing-remitting multiple sclerosis. These therapies include one interferon β-1b (IFNβ-1b) administered subcutaneously on alternate days (Betaferon®/Betaseron®/Extavia®) and two interferon β-1a products, ie, Avonex® (IFNβ-1a IM) administered once weekly by the intramuscular route and Rebif® (IFNβ-1a SC) administered three times weekly subcutaneously. Each of the three interferons was approved for the treatment of relapsing-remitting multiple sclerosis on the basis of one main, randomized, placebo-controlled clinical trial, ie, the pivotal IFN β-1b Trial,[1–3] the MSCRG (Multiple Sclerosis Collaborative Research Group) trial,[4–6] and the PRISMS (Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis) trial,[7,8] respectively.

IFNβ-1a IM quickly became the worldwide leader of the multiple sclerosis market in turnover in 1999, and kept this leadership, either in terms of number of patients treated or turnover until 2008.[9] IFNβ-1a IM was still the leader of the beta interferon market in 2011.[9] The summary of product characteristics for IFNβ-1a IM claimed that this product had similar efficacy in preventing relapses than the other interferons and superior efficacy in terms of preventing progression of disability. A once-weekly injection regimen was considered more patient-friendly. Since then, head-to-head studies[10,11] and reviews of the initial trials[12–15] have questioned the superiority of IFNβ-1a IM over the other interferons as well as the magnitude of its benefit.

This review analyzes the data from the initial trials to assess whether such a conclusion is warranted on the basis of the results of the three pivotal trials. Most of the data for the IFNβ-1a IM trial were extracted from the Food and Drug Administration (FDA) summary used for regulatory approval,[16] the FDA clinical review,[17] and the FDA statistical review.[18]

Description of the Trials

All three trials were randomized, multicenter, double-blind, placebo-controlled in design. The planned duration of the trials was 2 years for the PRISMS and MSCRG studies and 3 years for the IFNβ-1b Trial. Over 90% of patients in the IFNβ-1b Trial[1] and PRISMS[7] were followed up for 2 years. In the IFNβ-1b Trial, 23 patients in the placebo group and 24 patients in the IFNβ-1b 250 μg group discontinued treatment during the first 2 years; however, the 2-year data includes 112/123 patients on placebo and 115/124 patients on IFNβ-1b 250 μg. The MSCRG study was stopped earlier than planned, and 57% of its patients were followed up for 2 years.

The primary outcome of the IFNβ-1b Trial[1] and PRISMS[7] was relapse rate during follow-up. The primary outcome of MSCRG[4] was progression of disability, measured as time to onset of a sustained worsening of Extended Disability Status Scale (EDSS) score defined as deterioration from baseline by at least one point on the EDSS persisting for at least 6 months. Worsening on the EDSS could begin on a scheduled or unscheduled visit but had to persist for at least two scheduled visits 6 months apart. Progression of disability was a secondary outcome in the IFN β-1b Trial and PRISMS, and was defined as progression sustained for 3 months. The three pivotal trials and their main clinical outcomes are summarized in Table 1.

Magnetic resonance imaging (MRI) outcomes differed between the three trials. In the IFNβ-1b Trial,[2] the MRI attack rate as measured by median number of scans with activity (–80%; $P < 0.009$) and the median volume of MRI T2 disease burden (–17.3%; $P < 0.001$) were reduced in the IFNβ-1b arm compared with placebo-treated patients.

In the MSCRG study,[4] the MRI attack rate, as measured by the median number of gadolinium-enhancing lesions, was reduced in the IFNb-1a IM arm compared with the placebo-treated arm(–33%; $P = 0.05$),[13] but the reduction in total volume of T2 disease burden was not significant (–6.7%; $P = 0.36$).[13]

In PRISMS,[8] the MRI attack rate, as measured by the median number of T2 active lesions (22 μg × 3/week, –67%, $P < 0.0001$; 44 μg × 3/week, –78%, $P < 0.0001$) and T2-weighted volume of white matter disease (22 μg × 3/week, –12.1%, $P < 0.0001$; 44 μg × 3/week –14.7%, $P < 0.0001$) were significantly reduced in both treatment arms compared with the placebo arm.

All three trials led to the approval of interferon in relapsing-remitting multiple sclerosis.

Table 1. Patients, baseline characteristics and main results of the three pivotal trials.

	MSCRG[4,16] 30 µg × 1/week		PRISMS[7,19] 22 µg × 3/week		IFN β-1b[1,3] 250 µg eod		PRISMS[7,19] 44 µg × 3/week	
Interferon	β-1a		β-1a		β-1b		β-1a	
Total weekly dose (µg) and route of administration	30 (im)		66 (sc)		875 (sc)		132 (sc)	
EDSS range	1–3.5		0–5		0–5.5		0–5	
	IFN	**Placebo**	**IFN**	**Placebo**	**IFN**	**Placebo**	**IFN**	**Placebo**
Prestudy exacerbation rate	1.2	1.2	1.5	1.5	1.7	1.8	1.5	1.5
EDSS at baseline	2.4	2.3	2.5	2.4	3.0	2.8	2.5	2.4
Patients included (n)	158	143	189	187	124	123	184	187
Patients followed up at end of year 2 for analysis (n)	85	87	177	177	115	112	179	177
Year 2 patients for analysis/included (%)	53.8%	60.8%	93.7%	94.7%	92.7%	91.1%	97.3%	94.7%
Relapse rate reduction ITT all patients (2 years)	–18%*,‡		–29%		–34%		–32%	
Relapse rate reduction during year 2	–31%		–22%		–28%		–25%	
Relapse rate reduction during year 1 (all patients)	–10%*		–33%		–33%		–37%	
Confirmed progressions (% decrease)	–37%		–22%*,#		–29%†,*		–30%	

Notes: †Three-year data; *not significant; ‡–17.4%, $P = 0.063$ according to US Food and Drug Administration Center for Biologics Evaluation and Research analysis;[17] –18%, $P = 0.04$ according to the sponsor analysis;[4] #Not significant according to US Food and Drug Administration analysis,[19] significant according to sponsor analysis.[7]
Abbreviations: EDSS, Extended Disability Status Scale; MSCRG, Multiple Sclerosis Collaborative Research Group; PRISMS, Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis study; IFN, interferon; ITT, intent-to-treat; eod, every other day.

Analysis of Clinical Outcome Measures and MRI Data; Digging Deeper into the Data

Relapses

In PRISMS and the IFN β-1b Trial, the relapse rate reduction was slightly lower in year 2 than in year 1 (Table 1). In the MSCRG study,[4,16] the relapse rate reduction was markedly higher for patients followed up for 2 years than for those followed up for one year (–32.2% versus –9.6%). According to the IFNβ-1a IM FDA summary used as the basis for regulatory approval,[16] the sponsor suggested a lag time between initiation of treatment and onset of clinical benefit. This suggestion is not confirmed on more thorough analysis of the relapse rate (Table 2).

For analysis of MSCRG,[4] three different cohorts of patients are considered: patients followed up for

Table 2. Data on relapse rate in Multiple Sclerosis Collaborative Research Group.[16,17]

	Patients (n)		Annualized relapse rate		%
	Placebo	**IFNβ-1a IM**	**Placebo**	**IFNβ-1a IM**	
First year completers year 1 data	132	150	0.94	0.85	–9.6%*
Patients followed-up at year 1 only	45	65	0.80	1.03	+28.8%
Patient followed up at 2 years: first year data	87	85	1.01	0.72	–28.7%
Patient followed up at 2 years: second year data	87	85	0.78	0.54	–30.8%
Patients followed up 2 years: two-year data	87	85	0.90	0.61	–32.2%
Intend to treat analysis	143	158	0.815	0.673	–17.4%*,†

Notes: *Not statistically significant; †$P = 0.063$ according to US Food and Drug Administration Center for Biologics Evaluation and Research analysis;[17] –18%, $P = 0.04$ according to the sponsor's analysis.

at least one year (ie, a year 1 patient cohort); patients followed up for 2 years (ie, a year 2 patient cohort, ie, a subset of the year 1 patient cohort); and patients followed up for only one year (ie, a year 1 only patient cohort). Comparative analysis of the relapse rate (Table 2) for patients followed up for only one year and those followed up for 2 years during their first and second year on study shows that:

- patients followed up for 2 years had the same benefit (approximately −30%) during year 1 and year 2
- patients followed up for only one year had a benefit from placebo (with a +29% increase in relapse rate for the IFNβ-1a IM group).

This evaluation indicates that there is no lag time between initiation of treatment and onset of clinical benefit in terms of relapse rate for patients followed up for 2 years, but does show a surprising difference between the year 2 cohort and the year 1 only cohort with regard to the efficacy of IFNβ-1a IM. The year 2 cohort is thus a subset of the randomized cohort favoring IFNβ-1a IM efficacy regarding relapse rate. Unfortunately, the baseline characteristics of the year 2 cohort are not well described.

It cannot be reasonably assumed that changes in outcome of −32.2% and +29% truly reflect the efficacy of IFNβ-1a IM in patients treated for 2 years or only one year, respectively. Considering this difference between the two cohorts, can we assume that intent-to-treat analysis is giving us a correct result for the randomized cohort? Calculation of exacerbation rate was based on the number of exacerbations per patient-year in each treatment group, ie, total number of exacerbations per treatment group in the follow-up period divided by the total number of patient-years.[17]

Intent-to-treat analysis of the whole cohort during the entire follow-up period increases the benefit of treatment with IFNβ-1a IM in terms of relapse rate, in that year 2 patients experiencing better efficacy from IFNβ-1a IM are given twice as much time (2 years instead of one year) in the calculation of mean intent-to-treat annualized relapse rate than year 1 only patients who are benefiting from placebo. They will weigh twice as much as those followed for one year only in the calculation. However, we can evaluate what could have been the benefit of IFNβ-1a IM if all patients had been followed up 2 years.

Let us consider the annualized relapse rate of year 1 patients that would have evolved in the same proportion as did the one from year 1 to year 2 for patients followed up 2 years. The annualized relapse rates would be 0.83 for placebo: $=[(45 \times 0.8) + (45 \times 0.8 \times 0.78/1.01) + (87 \times 1.01) + (87 \times 0.78)]/(132 \times 2)$ and 0.75 for IFNβ-1a IM $= [(65 \times 1.03) + (65 \times 1.03 \times 0.54/0.72) + (85 \times 0.72) + (85 \times 0.54)]/(150 \times 2)$. The benefit on relapse would be −10.1%, corresponding logically to the results obtained for all patients during the first year of the study (−9.6%).

The impact of the difference in follow-up duration between the different subsets of patients and treatment groups on the efficacy of IFNβ-1a IM in the prevention of relapse can also be evaluated using data from the FDA clinical review.[17] These data comprise:

- a histogram of percentage of non-zero time at risk for patients progressing as per EDSS score and treatment group
- a histogram of percentage per year of non-zero time at risk for patients progressing as per EDSS score and treatment group
- a table of exacerbation rate and number of patients with non-zero time at risk as per EDSS score and treatment group.

The time at risk as per EDSS and treatment arm can be evaluated from the histogram bar measurements (Table 3).[17] The benefit of IFNβ-1a IM on relapse rate increases from −11.5% to −17.2% when time at risk for each EDSS group is taken into account in the calculation showing the impact of follow-up duration on the outcome of relapse rate. Therefore, the time at risk is not equal to the duration on study, but this information is not available for each EDSS and treatment group in reviews by health authorities or in the published literature. The efficacy of IFNβ-1a IM in the prevention of relapse is thus probably nearer to −10%. Other figures: −32.2%, −18% and fortunately +29% do not correctly reflect the efficacy of IFNβ-1a IM in the randomized cohort.

Progression of disability

The IFNβ-1b Trial did not demonstrate a significant beneficial effect on sustained progression of disability and, according to the FDA analysis, the results of PRISMS[19] were considered to be not significant for the 22 μg × 3/week regimen and significant for

Table 3. Data according to EDSS and treatment group.[17,18]

	EDSS 1	EDSS 1.5	EDSS 2	EDSS 2.5	EDSS 3	EDSS 3.5	Total	Mean/patients	% change
Number of patients with non-zero time at risk*									
Placebo	10	33	21	21	17	30	132		
IFNβ-1a IM	12	26	34	26	17	34	149		
Progressors (%)†									
Placebo	20	21.2	28.6	33.3	29.4	30			
IFNβ-1a IM	16.7	19.2	20.6	15.4	5.9	14.7			
Progressors per year at risk (%)†									
Placebo	13.4	13.1	20.1	25.4	24.6	16.5			
IFNβ-1a IM	11.9	12.0	13.2	11.4	4.3	11.5			
Patients with EDSS increase (≥1 point) from week 0 to week 26* (n)									
Placebo	3	7	6	5	4	6	31		
IFNβ-1a IM	2	4	7	4	0	9	26		
Δ	1	3	–1	1	4	–3	5		
Number of final progressors									
Placebo	2	7	6	7	5	9	36		
IFNβ-1a IM	2	5	7	4	1	5	24		
Δ	0	2	–1	3	4	4	12		
Mean time at risk (months)									
Placebo	17.9	19.4	17.1	15.7	14.3	21.9		18.2	
IFNβ-1a IM	16.9	19.3	18.7	16.2	16.6	15.4		17.2	
Mean annualized relapse rate*									
Placebo	0.397	0.638	0.834	0.717	0.992	0.98		0.76	
IFNβ-1a IM	0.412	0.716	0.62	0.584	0.727	0.93		0.66	–12.50%
Mean annualized relapse rate × number of patients per group									
Placebo	4.0	21.1	17.5	15.1	16.9	29.4		0.79	
IFNβ-1a IM	4.9	18.6	21.1	15.2	12.4	31.6		0.70	–11.5%
Mean annualized relapse rate × number of patients per group × mean time at risk (in years)									
Placebo	5.9	34.0	24.9	19.7	20.1	53.6		1.20	
IFNβ-1a IM	7.0	29.9	32.8	20.6	17.1	40.5		0.99	–17.2%

Notes: *Figures obtained from the reference; †figures obtained from histogram bar measurements; other figures are calculated.
Abbreviations: EDSS, Extended Disability Status Scale; IFN, interferon; IM, intramuscularly.

the 44 μg × 3/week. None of the three subcutaneous interferon arms could match the −37% benefit seen for IFNβ-1a IM in terms of reducing sustained progression of disability.

In the MSCRG study, 12 patients account for the difference in number of patients progressing in the placebo and IFNβ-1a IM arms. Eleven of these patients were in the year 2 cohort, favoring IFNβ-1a IM for reducing the risk of relapse and eight of these 11 patients started to progress during their first year on study. In the cohort of patients followed up for less than 2 years, seven patients on placebo and six patients on IFNβ-1a IM showed sustained progression. Five of seven patients on placebo and all patients on IFNβ-1a IM started to progress during year 1 (Table 4). The difference in increased benefit of IFNβ-1a IM on the outcome of relapse rate between the two cohorts seems to have also impacted the outcome of progression of disability. In the context of a trial of short duration with a 6-month delay in validation, early evolution of EDSS and follow-up duration are important parameters for validation of sustained progression.

Comparison of the numbers of patients progressing by at least one point at week 26 and the final numbers of patients who progressed as per EDSS in the different treatment arms indicates that most of the initial EDSS progression might have occurred during the first semester (Table 3). The numbers of patients who progressed in each EDSS and treatment group at week 26 and at the end of the study are often similar, except for the EDSS 3.5 group, suggesting an immediate difference between the two treatment arms which occurred during the first semester.

Table 4. Number of patients who progressed according to treatment group, cohort, and year on study.[4,16]

	First 52 weeks	Second 52 weeks	Total 104 weeks
All patients using all data[16]			
Placebo	24	12	36
IFNβ-1a IM	17	7	24
Patients in study for ≥104 weeks:[4] year 2 cohort			
Placebo	19	10	29
IFNβ-1a IM	11	7	18
Δ calculated: patients in study for <104 weeks			
Placebo	5	2	7
IFNβ-1a IM	6	0	6

Abbreviation: IFN, interferon.

In the EDSS 3.5 group, more patients on IFNβ-1a IM had progressed by week 26 (nine versus six), but at the end of the study, more patients on placebo had experienced sustained progression (five versus nine). The difference between the placebo and IFNβ-1a IM arms with regard to patients who progressed between week 26 and the final evaluation therefore changed from −3 to +4. All nine patients on placebo who progressed were from the year 2 cohort.[18] EDSS 3.5 placebo group is the one with the longest time at risk, the EDSS 3.5 IFNβ-1a IM group, the one with the smallest.

Early EDSS evolution and differences in time at risk might account for the apparent efficacy of IFNβ-1a IM with regard to the outcome of disability progression. Unfortunately, without raw data, we cannot confirm that patients who started to progress between week 0 and week 26 are those with sustained progression at the end of the study or that the difference in time at risk favored the IFNβ-1a IM arm in terms of the disability outcome.

MRI data

MRI outcomes demonstrated a significant benefit from interferon in the IFNβ-1b Trial and PRISMS, but were less impressive in the MSCRG trial, especially for T2-weighted lesion volume. In the MSCRG study, analysis of MRI characteristics at baseline shows differences between the year 1, year 2, and year 1 only cohorts. Mean gadolinium and T2 lesion volumes for patients who were on study for only one year can be calculated from the available baseline data for year 1 and year 2 patients as per treatment group, mean gadolinium lesion volume, mean T2 lesion volume, and number of patients with MRI results (Table 5).

For the subsets of patients, those on placebo had a higher mean T2 lesion volume than patients on IFNβ-1a IM (+25%, +26%, and +23% for patients followed up at one year, 2 years, and one year only, respectively). Compared with the IFNβ-1a IM group, the median T2 lesion volume in the placebo group was 1.29 higher for the year 1 cohort and 1.54 higher for the year 2 cohort.[16] Patients followed up for 2 years had a higher mean T2 lesion volume than patients followed up for one year only (+34% for IFNβ-1a IM and +32% for placebo).

Patients on IFNβ-1a IM and those on placebo followed up for 2 years had a similar gadolinium lesion volume (253 mm^3 versus 252 mm^3), but patients on

Table 5. Baseline magnetic resonance imaging data for the Multiple Sclerosis Collaborative Research Group study.[5]

	Mean Gd lesion volume (mm^3)		Δ	Mean T2 lesion volume (mm^3)		Δ	Patients (n)	
	Placebo	IFN*		Placebo	IFN*		Placebo	IFN*
Year 1 cohort	249	220	29	15703	12454	3249	113	120
Year 2 cohort	252	253	–1	16963	13617	3346	80	78
Year 1 only (calculated)	242	159	83	12648	10298	2350	33	42
Δ Year 2–year 1 only	10	94		4315	3319			

Abbreviation: Gd, gadolinium.
Note: *IFN = interferon β-1a IM.

IFNβ-1a IM followed up for only one year had a lower mean gadolinium lesion volume compared with either IFNβ-1a IM patients followed up for 2 years (159 mm^3 versus 253 mm^3) or placebo patients followed up for year 1 only (159 mm^3 versus 242 mm^3).

The baseline MRI data confirm that patients followed up for one year only are different from those followed for 2 years. The baseline MRI data also suggest that the placebo and IFNβ-1a IM arms in the year 2 and year 1 only cohorts might have different profiles, but the small patient numbers limit the power of statistical testing of such a possibility.

Discussion

Of the three registration trials, the MSCRG seems to be the odd one out. The significant benefits of IFNβ-1a IM reported for relapse rate (–32%) and progression of disability (–37%) have been drawn from two different cohorts, ie, a year 2 cohort for relapse rate and an all-patient cohort for progression of disability. Neither figure is significant when drawn from the opposing cohort, even if a 5% threshold is used.[18,20]

The MSCRG does not provide us with an accurate evaluation of the benefit of IFNβ-1a IM on relapse rate except during year 1, ie, –10% calculated from the randomized cohort. Other figures for the efficacy of IFNβ-1a IM in reducing the relapse rate, such as –32.2% for patients who complete 2 years of treatment and –18%[4] (–17.4% $P = 0.063$)[17] for intend-to-treat analysis and fortunately +29% for patients followed up for one year only, should be interpreted with caution.

The difference in outcome for relapse rate between the year 1 cohort and the year 2 cohort is not linked to a lag time between initiation of treatment and onset of clinical benefit, and is more probably linked to differences between the two subsets of patients, ie, the year 1 and year 2 patient cohorts and/or between the treatment groups in these different cohorts.

The published comparisons of baseline characteristics for the placebo and IFNβ-1a IM arms per accrual period (4 of 6.5 months each)[4] do not exclude the possibility of a difference between the year 1 only patients and those followed up for 2 years. Patients followed up for one year only might be the last patients included or early dropouts among the patients recruited, and none of the four periods analyzed would include just the year 1 only patients.

The difference between the two cohorts and the absence of information on their baseline characteristics beg the question of whether the 172 (87 placebo and 85 IFNβ-1a IM) patients in the year 2 cohort are actually the first 172 patients enrolled in this trial. This point is crucial to analysis of the trial.[21]

There was a considerable imbalance in treatment assignment between the two treatment arms, leading to inclusion of 143 patients on placebo and 158 patients on IFNβ-1a IM. This imbalance was even greater for patients included in the analysis of the primary endpoint, ie, 132 patients on placebo and 151 patients on IFNβ-1a IM.[18] This imbalance is not apparent for the 172 patients followed up for 2 years, (87 on placebo and 85 on IFNβ-1a IM). Between weeks 78 and 104, 24 patients on placebo and 38 patients on IFNβ-1a IM attending the week 78 visit did not attend the week 104 visit.[4] This implies that either the imbalance in treatment assignment occurred almost exclusively during this 6-month period or that censoring linked to study termination does not correspond to the recruitment schedule, with the consequence that the year 2 cohort is not representative of the first 172 patients included. If such an imbalance in assignment did actually occur during this 6-month period, it remains to be explained how randomization provided two cohorts

with such different responses to the study treatment, ie, the year 2 cohort benefiting from IFNβ-1a IM and the year 1 only cohort benefiting from placebo.

If the year 2 cohort is not a direct consequence of the recruitment schedule, evaluation on any cohort, randomized or year 2 cohort is doubtful. The absence of a significant difference in baseline characteristics between the placebo and IFNβ-1a IM patients resulting from the small study population would not allow consideration of any of the cohorts as valid for statistical purposes. Only raw data could provide us with the answer to this question.

Furthermore, baseline comparison of randomized patients in a truncated trial does not give any information on whether follow-up of patients is similar in the two treatment groups with regard to any prognostic factor or disease categorization. For example, staying time at each EDSS score decreases from EDSS 1 to EDSS 5.[22] A difference in follow-up duration between the two treatment groups in the upper range of EDSS would increase the likelihood of more patients progressing than in the lower range of EDSS. In the MSCRG study, patients on placebo in the year 2 cohort had the highest mean and median T2 lesion volumes and were probably in the upper part of the EDSS range, with their EDSS at entry to the study being weakly but significantly correlated with T2 lesion volume.[5] The extra time at risk for the placebo group with EDSS 3.5 thus predisposes to bias, and this cannot be seen in the published baseline patient characteristics for the MSCRG study. Once again, only raw data could be of help to confirm or refute the possible impact of a difference in follow-up duration on the outcome for disability.

Early differences between disease evolution in the placebo and treatment arms can be seen in the survival curves, which diverge during the first months of the study. This early gap is seen in the disability progression survival curves for the MSCRG study. Unintentional unblinding is suspected,[14] and possibly linked to the flu-like syndrome which can occur during the 48 hours after IFNβ-1a IM injection, a side effect known to patients via the patient information sheet required as part of the informed consent procedure.

Early divergence of the survival curves was also seen in CHAMPS (the Controlled High Risk Avonex Multiple Sclerosis Study)[23] especially in the subgroup with spinal cord syndrome.[24] In CHAMPS,[23] almost 60% of the difference in the number of patients developing clinically definite multiple sclerosis between the two arms occurred during the first 4 months of the study and one third during the first month. This disability outcome is thus very sensitive to the evolution of a few patients and progression or non-progression, sustained or not, for each single patient will depend on early evolution possibly linked to unintentional unblinding and time on study linked to censoring.

The above hypotheses are based on calculations of mean time at risk and characteristics for the different subsets of patients. These confirm differences between the year 1 only and the year 2 cohorts which differences induced a better "mean" condition for a positive trial through attrition bias. Unfortunately, time on study, ranking of enrollment, evolution of EDSS, and date of censoring cannot be deduced on a patient basis from the published literature or the reviews available from health authorities.

These results on the MSCRG study, if confirmed by analysis of the raw data, imply that the efficacy of IFNβ-1a IM is not similar to that of the other interferons. They imply that analysis of responders to interferon or the efficacy of interferon should probably separate IFNβ-1a IM data from those obtained with the approved regimens for IFNβ-1a SC and IFNβ-1b. Further, we may need to consider products compared with IFNβ-1a IM and other interferons differently. However, these results do not imply that IFNβ-1a IM might not benefit some patients.

IFNβ-1a IM biosimilars might not be able to demonstrate a significant clinical effect. Manufacturers of biosimilars will prefer copying the more effective products to lower the costs of a placebo-controlled clinical trial, with the consequence that less efficient biologic products will more often remain "biosimilar-free", be more heavily promoted, and thus probably more widely prescribed.

Further analysis should be done on the MSCRG and on raw data, as already requested by Filippini et al,[25] to confirm or refute doubts and uncertainties concerning the outcomes. Gathering raw data from clinical trials and analyzing patient characteristics and evolution could also help to understand better the evolution of the disease, the impact of treatments, and enable comparison of trials and more comprehensive meta-analysis.

Unfortunately, raw data from clinical trials are not often available. Good and less good reasons, such as confidentiality, ownership of data, lack of permission of patients, and commercial interests continue to restrict their publication, but solutions to some obstacles reasons have been proposed.[26] Advantages of publication of raw data are numerous,[27] and evaluation of interferons in relapsing-remitting multiple sclerosis provides us with a good example of its potential benefit.

The European Medicine Agency was unable to retrieve the IFNβ-1a IM marketing authorization file from its archives upon request. A complaint has been lodged with the European ombudsman, but 18 months after the initial request made, raw data are still unavailable.

Conclusion

Evaluation of agents used to treat in multiple sclerosis is challenging. This evaluation points out some problems in the evaluation of IFNβ-1a IM in multiple sclerosis. The efficacy of IFNβ-1a IM in multiple sclerosis could have been overestimated by an attrition bias linked to early trial termination. However, this possibility warrants further analysis using raw data. Unfortunately, raw data from clinical trials are still very difficult to obtain from the pharmaceutical industry and health authorities. Availability of raw data would not only help, as in the present case, in the reanalysis of clinical trials, but would also provide the scientific community with a huge amount of information on pathology, patient characteristics, and evolution of disease, as well as enabling comprehensive meta-analysis.

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Author Contributions

Conceived and designed the experiments: AC. Analysed the data: AC. Wrote the first draft of the manuscript: AC. Contributed to the writing of the manuscript: AC. Agree with manuscript results and conclusions: AC. Jointly developed the structure and arguments for the paper: AC. Made critical revisions and approved final version: AC. All authors reviewed and approved of the final manuscript.

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Competing Interests

AC worked for Serono from 1994 to 2000. AC invited to two dinners and one lunch by Serono in Dusseldorf during ECTRIMS 2009 (participation, hotel and travel paid by AC).

Disclosures and Ethics

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Supplementary Data

1. US Food and Drug Administration. Clinical review of PLA-95-0979 Biogen-Inc Interferon Beta-1a.
2. US Food and Drug Administration. Statistical Review PLA-95-0979 Biogen-Inc Interferon Beta-1a.