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Cause of death in MS: Long-term follow-up of a randomised cohort, 21-years after the start of the pivotal IFNB-1b study

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ABSTRACT

Objective: Compared to controls, multiple sclerosis (MS) patients die, on average, 7–14 years prematurely. Nevertheless, there is incomplete knowledge about the causes of death (COD) and/or their MS relationship, especially in contemporary MS populations. We analysed COD in three patient cohorts followed for 21 years after their participation in the pivotal randomised, controlled trial (RCT) of interferon beta-1b.

Methods: Using multiple information sources, we attempted to establish COD and its relationship to MS in deceased patients. An independent adjudication committee, masked to treatment assignment, determined likely COD and its MS relationship using pre-specified criteria.

Results: After 21.1 years (median) from RCT enrolment, 98.4% (366/372) of patients in the original RCT-cohort were identified and 81 deaths recorded. Mean age at death was 51.7 (±8.7) years. COD, MS relationship, or both were determined for 88% of deaths (71/81). Patients were assigned to one of 9 COD categories: cardiovascular disease/stroke; cancer; pulmonary infections; sepsis; accidents; suicide; death due to MS; other known CODs; and unknown COD. Of the 69 patients for whom information on the relationship of death to MS was available, 78.3% (54/69) were adjudicated to be MS-related. Patients randomised to receive placebo during the RCT (compared with patients receiving active treatment) experienced an excessive number of MS-related deaths.

Conclusions: In this long-term, randomised, cohort study, MS patients receiving placebo during the RCT experienced greater all-cause mortality compared to those on active treatment. The excessive mortality in the original placebo group was largely from MS-related causes, especially, MS-related pulmonary infections.

ARTICLE SUMMARY

In the long-term followup study 21-years after the pivotal Interferon beta-1b trial, there were 46-47% fewer deaths in patients randomized to active treatment during the clinical trial compare to those who were randomized to receive placebo. All of these excess deaths were due to MS-related causes .

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. Typically, MS occurs mostly in women, has a peak onset in the mid 20s, and has a mean clinical onset at the beginning of the fourth decade. It pursues a life-long – but variable – disease course. Nevertheless, by 15 to 25 years after its clinical onset, many (if not, most) MS patients will experience notable physical and cognitive difficulties as manifested, for example, by their requiring aids for mobility (eg, canes, walkers, and wheelchairs) or by their being unable to sustain a full-time job. In addition, MS has also been consistently associated with a significant increase in the risk of death compared to an age- and sex-matched control population.[1-8]

To estimate this increased mortality risk, one metric commonly used in survival studies is the so-called standardised mortality ratio (SMR). This measure assesses the ratio of the mortality in patients with a condition (over the entire period of observation) divided by the mortality in an age- and sex-matched cohort (over the same interval) without the condition.[9,10] In MS, the SMR is generally in the range of 2–3, indicating that, in MS patients, death is 2–3 times more likely over the observation period than in age and gender-matched controls.[1,2,9-13] An alternative metric of effect on longevity in MS patients is the average time from clinical onset to death. This time is approximately 35 years (ranging from a low of 24.5 years in a Scottish cohort to a high of 45 years in a New Zealand cohort). Thus, compared to unaffected age- and sex-matched controls, MS patients die, on average, 7–14 years prematurely.[1,2,12,14,15]

Importantly, long-term outcomes such as the avoidance of unambiguous physical impairment, the ability to remain employed, and survival are of far greater importance to patients and families than are the short-term clinical and magnetic resonance imaging (MRI) outcomes measured during randomised controlled trials (RCTs). For this reason, long-term

follow-up (LTF) studies are essential to assess the true impact of MS therapies on the disease. Nevertheless, such studies are difficult to execute successfully. The study of mortality in MS has been infrequent and, even then, only as part of natural history studies.[1,11,12] Moreover, and particularly in the past 20 years, the potential impact of therapy on mortality has been largely ignored.

Recently, we reported our experience at 21 years (the 21Y-LTF) in the cohort of relapsing-remitting (RR) MS patients who had previously participated in the pivotal RCT of interferon beta (IFNβ)-1b for MS.[16-19] After a median of 21.1 years from RCT enrolment, we identified 98.4% (366/372) of the original patient cohort. In this group, 81 deaths were recorded (22.1%; 81/366). Patients originally randomised to receive IFNβ-1b (either 250 µg or 50 µg; every other day subcutaneously) had a significant reduction in "all-cause" mortality over the 21-year period compared to patients originally randomised to receive placebo. The marked reduction in "all-cause" mortality was reflected by hazard ratios (HRs) of 0.532 (P=0.0173) in the 250-µg group and 0.540 (P=0.0202) in the 50-µg group; representing reductions in the hazard rate by 46.8% and 46.0% respectively.

Although these findings clearly imply a mortality benefit of therapy, it is, nevertheless, important to determine both the causes of the observed deaths in these cohorts and the relationship between these deaths and the underlying MS. Thus, it is only through such an undertaking that one can connect the mortality benefit to an impact of therapy on MS. Nevertheless, this task can be problematic because the recorded cause-of-death (COD) may be unreliable due to multiple factors. These include the infrequency of autopsies in MS patients, the recording physician's lack of knowledge of the patient's medical history, and the absence of uniform diagnostic criteria.[4,13] Similarly, establishing the MS relationship is often difficult because MS may be only an indirect contributor to death. For example, MS-related disability (either physical or cognitive) can predispose patients to a variety of other

illnesses or conditions that, by themselves, can be fatal (eg, aspiration pneumonia, sepsis from pressure sores or urinary tract infections, deep-vein thromboses with subsequent pulmonary emboli, suicide, etc.).

In the present study we aimed to develop a reliable method to determine the COD for the patients who died and to assess the relationship of these deaths to MS. We also aimed to establish whether the excessive 21-year mortality, which was observed in patients originally randomised to placebo, was due either to MS-related or non–MS-related causes.

METHODS

Patients

All patients enrolled in the pivotal RCT of IFNβ-1b in RRMS were eligible to participate in the 21Y-LTF. The inclusion criteria, design, and methods for the original RCT have been published.[16] Briefly, treatment-naive RRMS patients (aged 18–50 years) with an Expanded Disability Status Scale (EDSS) score ≤5.5 [20] and with two or more clinical exacerbations within the prior 2 years, were randomised to receive IFNβ-1b 50 µg (n=125), IFNβ-1b 250 µg (n=124), or placebo (n=123) every other day. During the RCT, patients were treated and prospectively followed for a period of up to 5.1 years on their assigned treatment regimen (mean: 3.3±1.4 years; median: 3.8 years; range: 0.1–5.1 years). At the end of the RCT in 1993, subsequent use of disease-modifying treatment (DMT) was at the discretion of patients and their physicians. IFNβ-1b was the only DMT available until 1996 when the use of alternative DMTs became possible.[21] Post-RCT treatment information was available for 67% (249/372) of the original RCT population at the time of the 16-year (16Y)-LTF study [21]. Of these, 55% (138/249) received only IFNβ-1b and, in the remainder, there were no systematic differences in treatment or care observed across the three RCT-defined cohorts. [21] Treatment information for the final 5 years of follow-up was largely unavailable.

Study design and determination of vital status

Between 1 October 2009 to 15 December 2010 (approximately 21 years after RCT enrolment), investigators at each study site attempted to identify each of the 372 randomised patients who took part in the IFNβ-1b RCT.[16,17,19] They also attempted to determine the vital status for each of their study participants and to collect COD information for those who had died during the 21-year follow-up period. For patients whose vital status could not be determined by the investigators, further searches, using both public domain and private sources, were undertaken. For US sites, these included both death certificates, the US National Death Index (NDI), medical records, 'notes to file' by investigators, data from the RCT and the 16Y-LTF,[16,17,19,21,22] and (when possible) the 'in-person' information from relatives. For Canadian sites, the same data sources were utilised except for the NDI, which was not available.

The treatment cohorts at the time of the original randomised treatment assignment were maintained for the entire 21-year period of follow-up and a strict intention-to-treat (ITT) analysis was undertaken. The different treatment-allocation cohorts (from the RCT) were well-balanced for all baseline demographic variables.[16,17,19] This study was conducted in accordance with Good Clinical Practice guidelines. Appropriate written informed consent was obtained. The protocol was approved by the institutional review board or independent ethics committee at each study site.

Establishing cause of death

An adjudication committee, established to assess both the underlying COD and the relationship of death to MS in each of patients who died during the 21Y-LTF, consisted of five members, three of whom voted. The voting members included two neurologists (SC, GE)

and a critical care specialist (TO). Two of these three members (SC and TO) were completely independent from the 21Y-LTF. In addition, two non-voting members also served on the committee – a neurologist representative from Bayer (VK) and an academic biostatistician (GC). Committee members were blinded to the treatment allocation of the deceased patients. All COD categorisations and MS relationships required unanimous agreement of the voting members.

Predefined rules were used to classify the underlying COD and each case was assigned to one of the following nine COD-categories:

1. Cardiovascular disease and stroke
2. All cancers
3. Pulmonary infectious diseases
4. Sepsis
5. Accidental death
6. Suicide
7. Death due to MS
8. Other known causes
9. Unknown or indeterminate cause

The relationship of death to MS was determined using a pre-defined decision algorithm (table 1) using a variety of information sources. Three possible relationships of CODs to MS were considered: 1) CODs always related to MS; 2) CODs probably related to MS; and 3) CODs probably not related to MS.

Table 1. Decision algorithm for determining the relationship of death to MS

Always MS-Related	Probably MS-Related	Probably not MS-Related

1. Suicide	1. Brainstem dysfunction	1. CV disease and stroke
2. EDSS ≥7.0 prior to death	2. Pulmonary infections	2. All cancers
3. MS the only listed COD	3. Aspiration pneumonia	3. Other infections
4. Death due to MS	4. Respiratory insufficiency	4. Single organ failure
5. Death from MS treatment	5. Pulmonary embolism	
	6. Sepsis (esp. uro-sepsis)	
	7. Death due to trauma	

COD = Cause-of-death; CV = Cardiovascular; MS = multiple sclerosis;

EDSS = Extended Disability Status Scale

For the first of these possible MS relationships, it was agreed *a priori* that all suicides would be considered MS-related. This rule was invoked in eight patients. Also, if MS was listed as the first (or only) COD on the death certificate, then the death was classified as 'death due to MS', which was, by definition, MS-related. This rule was applied to 21 patients. Finally, if the patient had reached an EDSS ≥7 at any time prior to their demise, the death was always considered to be MS-related, regardless of the recorded COD. This rule was invoked to determine the MS relationship in six patients. In three of these, the COD was indeterminate but advanced disability was known to be present. In only three instances was this rule applied to patients in whom a COD other than MS was recorded – in two with a suspected cardiovascular COD and in one with a multi-system organ failure.

For the second of these possible MS relationships, it was agreed *a priori* that deaths due to brainstem dysfunction, aspiration pneumonia, respiratory insufficiency, sepsis, pulmonary embolism, trauma, or side effects of treatment were likely to be MS-related. In these cases, however, determination of the MS relationship was judged by the context in which the death occurred and required some ancillary information. For example, death from a

pulmonary embolism would be considered MS-related if the patient were known have had marked lower extremity weakness and/or was confined to wheelchair or bed and, especially, if the embolus was from a deep-vein thrombosis thought secondary to the patient's immobility. By contrast, the embolus would not be considered to be MS-related if it occurred spontaneously in a fully ambulatory individual.

For the third of these possible MS relationships, it was agreed *a priori* that deaths due to cancer, cardiovascular disease, infections (other than pulmonary or urinary tract), and single organ failures were unlikely to be related to MS unless they were either judged to be complications of treatment or the patient had an EDSS ≥7 prior to death. In this study, two deaths from cardiovascular disease and one death from bladder cancer (believed secondary to treatment with cyclophosphamide) were judged to be MS-related (based on the EDSS or other criteria of our decision-algorithm – see table 1).

Statistical analyses

No specific statistical analyses other than descriptive statistics were undertaken on these data as part of this study. Frequency tables were created to display our results and the means and standard deviations (SD) were computed for several of our parameter-estimates.

RESULTS

Disposition of patients

Of the 372 patients originally enrolled in the RCT, 366 (98.4%) were identified in the 21Y-LTF (figure 1). Of the six patients lost to follow-up, two were in each of the three randomised treatment groups (figure 1). These patients were in the study for periods of less than the length of the original trial and three of six withdrew from the RCT within 3 months of its start. Survival in these patients was very unlikely to have been influenced by their

treatment assignment. The remaining three patients terminated their participation in the RCT after 1.2, 2.9, and 4.2 years.

In the cohort of 366 identified patients, 81 (22.1%) were dead after a median interval of 21.1 years from RCT enrolment (figure 1). Among these, the average age at death (±SD) was 51.7 (±8.7) years. The COD could be assigned in 82.7% (67/81) and in all but two of these patients (65/81), the relationship between death and MS could be established (table 2). The MS relationship to death could be determined in four additional patients (table 1) despite the inability to assign a COD (table 2). Thus, the relationship between death and MS could be established in 85.2% (69/81) of the deaths (tables 2 and 3), and the COD, the MS relationship, or both could be determined in 88% (71/81) of the deaths.

Table 2. Number of patients in each COD category and the MS relationship for the 81 deaths in the different randomized treatment-allocation groups (numbers in parentheses represent MS-related deaths)

	Placebo	**IFNβ-1b**		**Total**
		50 µg	**250 µg**	
Number of Deaths	37	22	22	81
Category of Death				
1. Cardiovascular disease and stroke	4 (1)	1 (0)	5 (1)	10 (2)
2. All cancers	1 (0)	3 (0)	2 (1)	6 (1)
3. Pulmonary infectious diseases	12 (11)	2 (2)	3 (3)	17 (16)
4. Sepsis*	0	0	0	0
5. Accidental death	2 (1)	0 (0)	1 (1)	3 (2)
6. Suicide	3 (3)	2 (2)	3 (3)	8 (8)

7. Death due to MS	9 (9)	6 (6)	6 (6)	21 (21)
8. Other known COD	1 (0)	1 (1)	0 (0)	2 (1)
Total: COD known	32 (25)	15 (11)	20 (15)	67 (51)
Other MS Relationships				
COD known; MS relation unknown	1	0	1	2
MS relation known; COD unknown	1 (1)	2 (1)	1 (1)	4 (3)
COD unknown; MS relation unknown	4	5	1	10
Total: MS relationship known	32	17	20	69

COD = Cause-of-death; IFNβ-1b = interferon beta-1b; MS = multiple sclerosis.

* NB: The NDI death-certificate data does not include 'sepsis' as a separate COD category. Therefore these entries are all zero.

Table 3. Adjudicated MS relationship for the 81 observed deaths in the different randomised treatment-allocation groups.

	Placebo	**IFNβ-1b**		**Total**
		50µg	**250µg**	
Total Number of Deaths*	37 (45.7%)	22 (27.2%)	22 (27.2%)	81 (100%)
MS relationship Indeterminate	5 (6.2%)	5 (6.2%)	2 (2.5%)	12 (14.8%)
Total MS Relationship Known[†]	32 (46.4%)	17 (24.6%)	20 (29.0%)	69 (100%)
MS-related	26 (37.7%)	12 (17.4%)	16 (23.2%)	54 (78.3%)
Not MS-related	6 (8.7%)	5 (7.2%)	4 (5.8%)	15 (21.7%)
Expected in Null Condition[††]	33 (33.3%)	33 (33.3%)	33 (33.3%)	69 (100%)

MS-related	18 (26.1%)	18 (26.1%)	18 (26.1%)	54 (78.3%)
Not MS-related	5 (7.2%)	5 (7.2%)	5 (7.2%)	15 (21.7%)

IFNβ-1b = interferon beta-1b; MS = multiple sclerosis.

* Numbers represent the number of patients in each category. Numbers in parentheses represent the percentage of the total deaths (81) in each category for each treatment group separately. Total represents the combined numbers for all treatment arms

† Numbers represent the number of patients in each category. Numbers in parentheses represent the percentage of the total deaths where MS relationship known (69) in each category for each treatment group separately. Total represents the combined numbers for all treatment arms

†† The null condition represents the number of deaths expected in each of the three treatment groups if the 69 observed deaths (54 MS-related; 15 not MS-related) had been distributed evenly between groups. In the circumstances of the present study, there were 9 more deaths than expected in the placebo-treated group (8 MS-related; 1 not MS-related) and, similarly, and 9 fewer deaths than expected in the two treated groups combined.

Cause of death (COD)

CODs for the deceased patients are shown in table 2 and, of the 67 patients in whom a COD could be assigned, 'death due to MS' was the principal underlying COD in 31.3% (21/67). Two patients were assigned to the category of death due to 'other known causes' – one placebo-patient from a GI bleed and one patient in the IFNβ-1b 50-µg group who died from multi-system organ failure. The MS relationship to the death was determined in both patients – the adjudication committee judged the multi-system organ failure to be, and the GI bleed not to be, MS-related (table 2). In one patient in the IFNβ-1b 250-µg group the MS

relationship could not be determined despite the death being in the COD category of 'cardiovascular disease and stroke'. Following application of the decision algorithm for MS-relatedness (table 1), 54 of the deaths were adjudicated to be MS-related (tables 2 and 3). This represents 78.3% (54/69) of the adjudicated deaths and 67% (54/81) of the total observed deaths in the 21Y-LTF.

Almost all of the excess in deaths observed in patients originally assigned to the placebo group were adjudicated to be MS-related (table 3). Indeed, the percentage of deaths due to MS in each of the two treatment arms was about half that observed in the placebo group (table 3). Moreover, these deaths were accounted for, almost entirely, by an excess in the number of fatal pulmonary infections (table 2). By contrast, non–MS-related deaths are evenly distributed among the different treatment-groups (table 3).

DISCUSSION

This study provides considerable insight to the relationships between the early mortality in an MS cohort, the accrual of MS-related disability, and the impact of therapy on outcome in RRMS patients. In our earlier 21Y-LTF report,[18] we observed that the HR for death was significantly reduced by 46.8% in the IFNβ-1b 250-µg group and by 46.0% in the IFNβ-1b 50-µg group compared to placebo. This nearly identical effect size in the two independently randomised groups provided strong supportive evidence that the observed survival benefit was not due to chance (ie, from a type I error). Although it was still possible that the observed benefit reflected an unusually high mortality rate in the placebo arm, this too seemed unlikely given the virtual overlap of placebo-group mortality with natural history studies.[18] (Reference 14, supplementary Figure e-1) Thus, the survival rate for 29 years after disease onset (~70%) observed by others[2] was much like that in our placebo group (70.4%). In addition, the fact that after completion of the RCT, some patients chose to receive

alternative therapies[21], does not detract from the findings. The 21Y-LTF analysis was done on a strict intent-to-treat basis. Moreover, the use of alternative therapies after randomization will make any differences between the cohorts less (not more) conspicuous and, thus, should favor the null-hypothesis. Therefore, taken together, these findings of the 21Y-LTF strongly support the notion that there is a survival advantage following either earlier (or greater) exposure to IFNβ-1b.[18]

The patient population included in this cohort study is relatively young in the context of mortality and, indeed, our cohort exhibits many of the expected trends from such a circumstance. Thus, the average age (±SD) at the time of the 21Y-LTF was 56.3 (±7.1) years, with an average age at death even younger (51.7±8.7 years) – a feature characteristic of young and active cohorts.[2,3,11] Also typical of younger MS populations, the observed suicide rate was quite high (11.9%; 8/67). Moreover, the large majority of the deaths observed over the course of 21 years were due to MS-related causes. This finding is anticipated in a younger cohort, where diseases of the elderly (eg, cardiovascular disease, stroke, and cancer) have yet to overtake MS as the principal COD.[1,13,23] Thus, in the 21Y-LTF, 'death due to MS' accounted for a 31.3% (21/67) of the assignable CODs and 'MS-related death' accounted for 78.3% (54/69) of the assignable relationships and 67% of all deaths; these were more frequent compared with the combined category of cardiovascular disease, stroke and cancer, which accounted for only 23.9% (16/67) of the assignable CODs (tables 2 and 3). In reports on more complete survival-cohorts,[1,13,23] MS-related mortality ranges between 50 and 65%.

In addition to the fact that most of the observed deaths in this cohort were MS-related, three other observations support the notion that the observed intergroup differences in death are likely due to the MS disease state. First, the excess in 'all-cause' mortality in the placebo-assigned group is due, almost entirely, to an excess in MS-related deaths and not to other

CODs (table 3). Second, the excess in MS-related deaths is largely attributable to an excess in fatal pulmonary infections, a complication known to occur in end-stage MS (table 2). And, third, both of these observations were highly consistent in the two groups of patients who received active treatment during the RCT compared to those who received placebo (table 3). Taken together, these observations support the notion that the mortality benefit provided by IFNβ-1b therapy is related to a reduction in MS-related disability and, secondarily, from those complications, which are known to occur in the setting of advanced MS.

These findings underscore the importance of conducting LTF studies after completion of the RCTs that lead to product approval. Although LTF studies are not 'clinical trials' *per se*, when they have high ascertainment rates and measure unambiguously objective endpoints, they represent the primary analysis of independent data, unobtainable during the RCT and collected long after RCT completion. They also have several key advantages over other non-randomised cohort studies. For example, LTFs assess the association between treatment allocation during the RCT and those unambiguous outcomes such as ambulation status, employment status, or mortality, which are of far greater importance than the short-term MRI and clinical outcomes measured during the course of an RCT. Also, LTFs use strict intent-to-treat paradigms, which are statistically and methodologically conservative and, thus, any bias during the open-label treatment period will tend to favour the null hypothesis unless there has been a differential loss to follow-up between groups. In addition, because the study cohorts in these LTFs are randomised at their formation, all measured and unmeasured covariates will, on average, be balanced between groups. In fact, the pivotal trial cohorts were well-balanced on all measured baseline variables.[16,17,19] Consequently, even though LTF analyses are typically not pre-planned, there is still no need to match the cohorts for co-morbid conditions at baseline. Indeed, many methodological experts feel that such matching or adjustment (after randomisation) is unnecessary or even misleading. Even those who advocate adjustment after

randomisation, prefer the *a priori* identification of covariates or limiting these adjustments to variables that are known to be highly correlated with the outcome.[24,25]. As an example, hypertension among 30-year-olds, which has a low correlation with early mortality, would not fit this criterion nor be used for adjustment. The reason to limit the use of covariate adjustment in a randomised cohort is that matching can only be performed on known covariates. Nevertheless, balancing the analysis for known variables may unbalance the groups on unknown factors, which may have a greater (or equal) impact on the outcome than known variables. Such adjustment could potentially negate the principal advantage for bias reduction that randomisation provides (ie, achieving, on average, a balance on the unknown variables). Moreover, consideration of pre-morbid risk factors in an LTF setting becomes superfluous when the actual CODs in the cohort are known.

In sum, LTF studies following RCTs have several important (and often unique) design advantages that distinguish them from other long-term cohort studies in the literature in their ability to establish causation according to currently used methods.[26,27] These include the use of randomisation at baseline, the use of an intent-to-treat analysis, the collection of data independently from the data recorded during the RCT data, and the use of unquestionably objective outcome measures.[27]

An important feature of this study is its near complete ascertainment rate for survival data of the cohort (98.4%). This stands in stark contrast to previous LTF studies of MS patients,[28-30] in which ascertainment rates were substantially less (39.8–68.2%). Low ascertainment rates substantially increase the likelihood of bias, because patients who are lost to follow-up are more likely to be deceased than those who are actually located.[31]

In addition, the rules used for classifying the different CODs and establishing their MS relationship in this study were pre-defined and each assignment required the unanimous agreement of the three voting members on the adjudication committee (two of whom were

completely independent of the 21Y-LTF). The fact that the observed COD in our cohort was usually MS-related is, in general, consistent with previous reports,[1-4] however, the actual percentage of MS-related deaths (78.3%, 54/69) was somewhat higher than the 50–70% reported by others.[2-4,13,32,33] The reason for this is uncertain but probably reflects the younger age, the relatively early analysis compared to epidemiological studies with more complete mortality observations, and the selection of more active patients in this RCT-derived cohort compared to these other populations.

In summary, the large majority of deaths observed in this young RCT-derived cohort were adjudicated to be MS-related (78.3%). Moreover, the excess in deaths observed in the placebo randomised group were accounted for entirely by an excess in MS-related deaths and, in particular, by deaths due to pulmonary infections. Whether the impact of therapy on mortality is the consequence of early treatment or a larger cumulative exposure to IFNβ-1b cannot be resolved. Regardless, however, these data support the notion that the mortality benefit from IFNβ-1b is due to a treatment-related impact on the MS disease process itself.

Competing Interests

Douglas S Goodin has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Bayer-Schering Pharma, Merck-Serono, Teva Pharmaceuticals, and Novartis.

Anthony T Reder has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Abbott Laboratories, American Medical Association, Astra Merck, Athena Neurosciences, Aventis Pharma, Bayer Schering Pharma, Berlex Laboratories, Biogen and Biogen Idec, BioMS Medical Corp., Blue Cross, Blue Shield, Boehringer Ingelheim Pharmaceuticals Inc., Caremark Rx, Centocor, Inc., Cephalon, Inc., Connectics/Connective Therapeutics, CroMedica Global Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Genzyme Corporation, GlaxoSmithKline, Hoechst Marion Roussel Canada Research, Inc., Hoffman-LaRoche, Idec, Immunex, Institute for Health Care Quality, Johnson & Johnson Pharmaceutical Research & Development, LLC, Kalobios, S NARCOMS, Yale University, Barrow Neurological Institute, National Multiple Sclerosis Society & Paralyzed Veterans of America, “Pain Panel,” Neurocrine Biosciences, Novartis Corporation, Parke-Davis, Pfizer Inc, Pharmacia & Upjohn, Protein Design Labs, Inc, Quantum Biotechnologies, Inc., Questcor Pharmaceuticals Inc., Quintiles, Inc., Serono Sandoz (now Novartis) & Novartis, Sention, Inc., Serono, Shering AG, Smith Kline-Beecham, Berlipharm, Inc., Takeda Pharmaceuticals, Teva-Marion, and Triton Biosciences.

George C Ebers has received consulting fees from Roche, Biopartners, EISAI, MVM Life Science Partners, and Bayer HealthCare Pharmaceuticals; honoraria as an Executive

Committee member of the MS Forum from Bayer HealthCare Pharmaceuticals; and travel support from Bayer HealthCare Pharmaceuticals.

Gary Cutter has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Antisense Therapeutics Limited, Sanofi-Aventis, Bayhill Pharmaceuticals, BioMS Pharmaceuticals, Daichi-Sankyo, Genmab Biopharmaceuticals, Glaxo Smith Klein, PTC Therapeutics, Medivation, Eli Lilly, Teva, Vivus, University of Pennsylvania, NHLBI, NINDS, NMSS, Ono Pharmaceuticals, Alexion Inc., Accentia, Bayer, Bayhill, Barofold, CibaVision, Novartis, Diagenix, Consortium of MS Centers, Klein-Buendel Incorporated, Enzo Pharmaceuticals, Peptimmune, Somnus Pharmaceuticals, Teva pharmaceuticals, UTSouthwestern, Visioneering Technologies, Sandoz, and Nuron Biotech, Inc.

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Boards for Bayer HealthCare, Merck Serono, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec.

Mark Rametta and **Karola Beckmann** are salaried employees of Bayer HealthCare Pharmaceuticals

Volker Knappertz was a salaried employee of Bayer HealthCare Pharmaceuticals at the time of manuscript preparation.

Contributions

Douglas S Goodin has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Anthony T Reder has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

George C Ebers has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Gary Cutter has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Marcelo Kremenchutzky has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Joel Oger has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Mark Rametta has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Timothy O'Donnell has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Stuart Cook has contributed to the conceptualisation of study, data acquisition and development and has reviewed the manuscript.

Karola Beckmann has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Volker Knappertz has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

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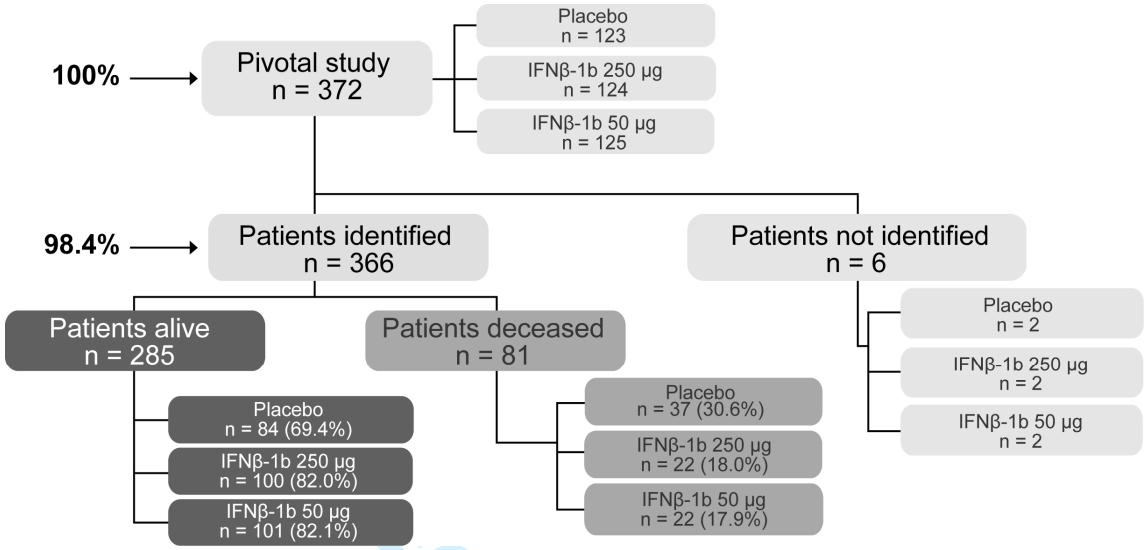
Data Sharing Statement

There are no unpublished data .

Figure 1. Patient Identification and Vital Status at the 21Y-LTF.



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Response to Reviewers:

Reviewer 1

I do not see enough novel in it to publish in JNNP. The Neurology paper covers most of this, including the headline result in the abstract (78.3% of deaths MS related, most due to pulmonary infections), leaving this paper only to explain how this figure was reached by outlining the adjudication process. This feels like an appendix to the main paper and, in an attempt to form a standalone paper, needs to repeat much of what is now in the public domain. I am surprised the method of determining COD was not required by publishers of the original paper, but this omission in itself does not warrant publication in another journal. If the objective, as stated, was genuinely to explore COD in contemporary MS cohorts, I would have thought a larger sample from a population based cohort would have been a more logical choice.

The detailed methods by which the causes of death were determined and adjudicated and the specific results of our analyses were too extensive for inclusion in *Neurology*, which had already asked us to trim our manuscript to arrive at a publishable length. The stated purpose of the present study was "to establish whether the excessive 21-year mortality, which was observed in patients originally randomised to placebo, was due either to MS-related or non–MS-related causes" (p. 5). It was not "to explore COD in contemporary cohorts".

The data in the Neurology paper is hard to accept, and, mostly by repeating the data and rehearsing the apologetics, this paper does not further the MS community's ability to understand the somewhat unexpected results.

The data is the data and it comes from ascertaining the vital status of virtually the entire RCT cohort after 21 years. Moreover, the authors believe that the finding that the excess mortality experienced by the placebo group was due to MS-related causes is important for a broader understanding of the original result.

Reviewer 2

The results might have pathogenetic and therapeutic implications in MS, although it is surprising that MR-related deaths were significantly less in patients allocated to 50 micrograms of IFNb-1b (one fifth of the ordinary treatment dose) in the RCT as well.

As we discussed in the original pivotal paper, the 50 mcg group did experience clinical benefit during the RCT (1). Moreover, a recent trial (2) has cast doubt on the importance of IFNβ dose (rather than frequency) in the treatment of MS. Finally, it is worth noting that 50 mcg every other day is actually a greater dose of IFNβ than that of Rebif which is 40 mcg three times a week.

The authors carefully avoided to mention a direct relationship between IFNb-1b treatment and the survival in the present study, but the major concern in this long-term

follow-up is that the details of treatments the three groups of patients received after the RCT were unknown (which DMT ?, and compliance ?). Those information have direct and significant impacts on the outcomes of this survey. The authors need to provide any relevant information or clearly state that such data were not available in Abstract and the text.

Information about the use of other DMTs treatments is now presented and discussed (pp. 5 & 13-14).

The following points should also be addressed.

1) Mention the doses (250 and 50 micrograms) ofIFNb-1b and the duration of RCT (median 3.8 years, range 1 – 5.1years) in Abstract.

We didn't do this, in part, because the information made the Abstract too long. Also this material is already presented in our description of the patients (p. 5). Nevertheless, we would be happy to add this to the Abstract. We leave this to editorial discretion.

2) In Abstract, "COD, MS relationship or both were determined in 88% of deaths (71/81)." How was 88% (71/81) obtained ? This was not stated in the text.

We have now clarified this calculation (p. 10).

3) The authors classified suicide as "Always MS-related", but I think suicide is "Probably MS-related" at best.

This was a decision made by the adjudication committee *a priori* and, moreover, the non-committee member authors believe that this was a reasonable approach. Nevertheless, either way, it doesn't impact the results because the suicides were evenly balanced between the groups (Table 2).

4) Are there any data to suggest a greater disability in the placebo group at the last follow-up ?

The primary endpoint of the 21Y LTF study was to ascertain the vital status of patients from the original pivotal study of IFNβ-1b. The study investigators did not perform clinical examinations of the patients in the cohorts at the 21year assessment.

Reviewer 3

The results of this work have been partially reported in a previous paper. Much of the discussion and conclusions are based on the results of that previous paper. The new data in this paper are not enough relevant and could have been described in the previous one.

Reviewer #1 made similar comments. See our response above.

This work has other criticisms.

1 - The main criticism is related to the pre-defined and arbitrary algorithm of causes of death (COD). The independent committee was blinded to the treatment of patients who died, however, it is known that in the placebo group there were more deaths than in the treatment arms. These results have been reported in previous meetings and there is a forthcoming publication. Therefore, the committee knew that there were more deaths in the placebo group.

The authors do not believe this knowledge lead to biased COD determinations. The members of the adjudication committee did not know which patients were in each treatment group and did not know in advance that the excess mortality in the placebo group was due to MS-related causes.

2 - The classification of COD, arbitrary, includes causes of death that may be debatable as related to MS. This reviewer does not understand why if EDSS > 7 the cause of death must be related to MS. Obviously, other causes not-M related can exist in patients with an EDSS >7. On the other hand, when MS is the only listed COD, it is likely that in this group there are missing data, and the same applies when the cause is "death due to MS."

These rules were decided upon by the adjudication committee *a priori*. The reviewer points out some of the difficulties in dealing with death certificate data. We acknowledge these problems and we discuss both the cases in which these rules were invoked (p. 8) and some the difficulties of this undertaking (p. 4).

3 - On the other hand, the authors say in methods section that a statistical analysis was not carried out because the study is purely descriptive; however, the results show that there is a greater proportion of patients with MS-related deaths in the placebo group. This reviewer has not noted any significant p value in the text. Moreover, table 3 shows that 26/32 deaths in the placebo group were associated with MS, while there are 28/37 in the treated group. These differences do not seem relevant.

It turns out that he calculations that this reviewer provides are actually not germane. Nevertheless, we agree that we could presented this much more clearly in the text. We have, therefore, added the expected outcomes under the null hypothesis to Table 3 (p. 12).

4 - Finally, it is difficult to understand that a therapy used 3 years during RCT have produced an influence on the outcome of death in a subsequent period of 21 years. Obviously without taking into account previous medical history data, and treatments prior to inclusion in the study and mainly subsequent treatments after the study; the data and findings of this study are difficult to interpret.

This same point was made by Reviewer #1. See our response above.

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Cause of death in MS: Long-term follow-up of a randomised cohort, 21-years after the start of the pivotal IFNB-1b study

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Cause of death in MS: Long-term follow-up of a randomised cohort, 21-years after the start of the pivotal IFNB-1b study

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Key Words: Multiple Sclerosis; Survival; Mortality; Long-term follow-up; Interferon beta; cause of death.

Word count: 3467

ABSTRACT

Objective: Compared to controls, multiple sclerosis (MS) patients die, on average, 7–14 years prematurely. Nevertheless, there is incomplete knowledge about the causes of death (COD) and/or their MS relationship, especially in contemporary MS populations. We analysed COD in three patient cohorts followed for 21 years after their participation in the pivotal randomised, controlled trial (RCT) of interferon beta-1b.

Methods: Using multiple information sources, we attempted to establish COD and its relationship to MS in deceased patients. An independent adjudication committee, masked to treatment assignment, determined likely COD and its MS relationship using pre-specified criteria.

Results: After 21.1 years (median) from RCT enrolment, 98.4% (366/372) of patients in the original RCT-cohort were identified and 81 deaths recorded. Mean age at death was 51.7 (±8.7) years. COD, MS relationship, or both were determined for 88% of deaths (71/81). Patients were assigned to one of 9 COD categories: cardiovascular disease/stroke; cancer; pulmonary infections; sepsis; accidents; suicide; death due to MS; other known CODs; and unknown COD. Of the 69 patients for whom information on the relationship of death to MS was available, 78.3% (54/69) were adjudicated to be MS-related. Patients randomised to receive placebo during the RCT (compared with patients receiving active treatment) experienced an excessive number of MS-related deaths.

Conclusions: In this long-term, randomised, cohort study, MS patients receiving placebo during the RCT experienced greater all-cause mortality compared to those on active treatment. The excessive mortality in the original placebo group was largely from MS-related causes, especially, MS-related pulmonary infections.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, which has been consistently associated with a significant increase in the risk of death compared to an age- and sex-matched control population.[1-8] To estimate this increased mortality risk, one metric commonly used in survival studies is the so-called standardised mortality ratio (SMR). This measure assesses the ratio of the mortality in patients with a condition (over the entire period of observation) divided by the mortality in an age- and sex-matched cohort (over the same interval) without the condition.[9,10] In MS, the SMR is generally in the range of 2–3, indicating that, in MS patients, death is 2–3 times more likely over the observation period than in age and gender-matched controls.[1,2,9-13] An alternative metric of effect on longevity in MS patients is the average time from clinical onset to death. This time is approximately 35 years (ranging from a low of 24.5 years in a Scottish cohort to a high of 45 years in a New Zealand cohort). Thus, compared to unaffected age- and sex-matched controls, MS patients die, on average, 7–14 years prematurely.[1,2,12,14,15]

Importantly, long-term outcomes such as the avoidance of unambiguous physical impairment, the ability to remain employed, and survival are of far greater importance to patients and families than are the short-term clinical and magnetic resonance imaging (MRI) outcomes measured during randomised controlled trials (RCTs). For this reason, long-term follow-up (LTF) studies are essential to assess the true impact of MS therapies on the disease. Nevertheless, such studies are difficult to execute successfully. The study of mortality in MS has been infrequent and, even then, only as part of natural history studies.[1,11,12] Moreover, and particularly in the past 20 years, the potential impact of therapy on mortality has been largely ignored.

Recently, we reported our experience at 21 years (the 21Y-LTF) in the cohort of relapsing-remitting (RR) MS patients who had previously participated in the pivotal RCT of

interferon beta (IFNβ)-1b for MS.[16-19] After a median of 21.1 years from RCT enrolment, we identified 98.4% (366/372) of the original patient cohort. In this group, 81 deaths were recorded (22.1%; 81/366). Patients originally randomised to receive IFNβ-1b (either 250 μg or 50 μg; every other day subcutaneously) had a significant reduction in the hazard rate for "all-cause" mortality (46.8% and 46.0% respectively) over the 21-year period compared to patients originally randomised to receive placebo.

Although these findings clearly imply a mortality benefit of therapy, it is, nevertheless, important to determine both the causes of the observed deaths in these cohorts and the relationship between these deaths and the underlying MS. Thus, it is only through such an undertaking that one can connect the mortality benefit to an impact of therapy on MS. Nevertheless, this task can be problematic because the recorded cause-of-death (COD) may be unreliable due to multiple factors. These include the infrequency of autopsies in MS patients, the recording physician's lack of knowledge of the patient's medical history, and the absence of uniform diagnostic criteria.[4,13] Similarly, establishing the MS relationship is often difficult because MS may be only an indirect contributor to death. For example, MS-related disability (either physical or cognitive) can predispose patients to a variety of other illnesses or conditions that, by themselves, can be fatal (eg, aspiration pneumonia, sepsis from pressure sores or urinary tract infections, deep-vein thromboses with subsequent pulmonary emboli, suicide, etc.).

In the present study we aimed to develop a reliable method to determine the COD for the patients who died and to assess the relationship of these deaths to MS. We also aimed to establish whether the excessive 21-year mortality, which was observed in patients originally randomised to placebo, was due either to MS-related or non–MS-related causes.

METHODS

Patients

All patients enrolled in the pivotal RCT of IFNβ-1b in RRMS were eligible to participate in the 21Y-LTF. The inclusion criteria, design, and methods for the original RCT have been published.[16] Briefly, treatment-naive RRMS patients (aged 18–50 years) with an Expanded Disability Status Scale (EDSS) score ≤5.5 [20] and with two or more clinical exacerbations within the prior 2 years, were randomised to receive IFNβ-1b 50 µg (n=125), IFNβ-1b 250 µg (n=124), or placebo (n=123) every other day. During the RCT, patients were treated and prospectively followed for a period of up to 5.1 years on their assigned treatment regimen (mean: 3.3±1.4 years; median: 3.8 years; range: 0.1–5.1 years). At the end of the RCT in 1993, subsequent use of disease-modifying treatment (DMT) was at the discretion of patients and their physicians. IFNβ-1b was the only DMT available until 1996 when the use of alternative DMTs became possible.[21] Post-RCT treatment information was available for 67% (249/372) of the original RCT population at the time of the 16-year (16Y)-LTF study [21]. Of these, 55% (138/249) received only IFNβ-1b and, in the remainder, there were no systematic differences in treatment or care observed across the three RCT-defined cohorts. [21] Treatment information for the final 5 years of follow-up was largely unavailable.

Study design and determination of vital status

Between 1 October 2009 to 15 December 2010 (approximately 21 years after RCT enrolment), investigators at each study site attempted to identify each of the 372 randomised patients who took part in the IFNβ-1b RCT.[16,17,19] They also attempted to determine the vital status for each of their study participants and to collect COD information for those who had died during the 21-year follow-up period. For patients whose vital status could not be determined by the investigators, further searches, using both public domain and private sources, were undertaken. For US sites, these included both death certificates, the US

National Death Index (NDI), medical records, 'notes to file' by investigators, data from the RCT and the 16Y-LTF,[16,17,19,21,22] and (when possible) the 'in-person' information from relatives. For Canadian sites, the same data sources were utilised except for the NDI, which was not available.

The treatment cohorts at the time of the original randomised treatment assignment were maintained for the entire 21-year period of follow-up and a strict intention-to-treat (ITT) analysis was undertaken. The different treatment-allocation cohorts (from the RCT) were well-balanced for all baseline demographic variables.[16,17,19] This study was conducted in accordance with Good Clinical Practice guidelines. Appropriate written informed consent was obtained. The protocol was approved by the institutional review board or independent ethics committee at each study site.

Establishing cause of death

An adjudication committee, established to assess both the underlying COD and the relationship of death to MS in each of patients who died during the 21Y-LTF, consisted of five members, three of whom voted. The voting members included two neurologists (SC, GE) and a critical care specialist (TO). Two of these three members (SC and TO) did not participate in the 21Y-LTF (i.e., they were completely independent). In addition, two non-voting members also served on the committee – a neurologist representative from Bayer (VK) – who oversaw the deliberations - and an academic biostatistician (GC). Committee members were blinded to the treatment allocation of the deceased patients. All COD categorisations and MS relationships required unanimous agreement of the voting members.

Predefined rules were used to classify the underlying COD and each case was assigned to one of the following nine COD-categories:

1. Cardiovascular disease and stroke
2. All cancers
3. Pulmonary infectious diseases
4. Sepsis
5. Accidental death
6. Suicide
7. Death due to MS
8. Other known causes
9. Unknown or indeterminate cause

The relationship of death to MS was determined using a pre-defined decision algorithm (table 1) using a variety of information sources. Three possible relationships of CODs to MS were considered: 1) CODs always related to MS; 2) CODs probably related to MS; and 3) CODs probably not related to MS.

Table 1. Decision algorithm for determining the relationship of death to MS

Always MS-Related	**Probably MS-Related**	**Probably not MS-Related**
1. Suicide	1. Brainstem dysfunction	1. CV disease and stroke
2. EDSS ≥7.0 prior to death	2. Pulmonary infections	2. All cancers
3. MS the only listed COD	3. Aspiration pneumonia	3. Other infections
4. Death due to MS	4. Respiratory insufficiency	4. Single organ failure
5. Death from MS treatment	5. Pulmonary embolism	
	6. Sepsis (esp. uro-sepsis)	
	7. Death due to trauma	

COD = Cause-of-death; CV = Cardiovascular; MS = multiple sclerosis;

EDSS = Extended Disability Status Scale

For the first of these possible MS relationships, it was agreed *a priori* that all suicides would be considered MS-related. This rule was invoked in eight patients (evenly divided among the treatment arms). Also, if MS was listed as the first (or only) COD on the death certificate, then the death was classified as 'death due to MS', which was, by definition, MS-related. This rule was applied to 21 patients. Finally, if the patient had reached an EDSS ≥7 at any time prior to their demise, the death was always considered to be MS-related, regardless of the recorded COD. This rule was invoked to determine the MS relationship in six patients. In three of these, the COD was indeterminate but advanced disability was known to be present. In only three instances was this rule applied to patients in whom a COD other than MS was recorded – in two with a suspected cardiovascular COD and in one with a multi-system organ failure. These three patients were evenly divided among the treatment arms and excluding didn't alter the analysis.

For the second of these possible MS relationships, it was agreed *a priori* that deaths due to brainstem dysfunction, aspiration pneumonia, respiratory insufficiency, sepsis, pulmonary embolism, trauma, or side effects of treatment were likely to be MS-related. In these cases, however, determination of the MS relationship was judged by the context in which the death occurred and required some ancillary information. For example, death from a pulmonary embolism would be considered MS-related if the patient were known have had marked lower extremity weakness and/or was confined to wheelchair or bed and, especially, if the embolus was from a deep-vein thrombosis thought secondary to the patient's immobility. By contrast, the embolus would not be considered to be MS-related if it occurred spontaneously in a fully ambulatory individual.

For the third of these possible MS relationships, it was agreed *a priori* that deaths due to cancer, cardiovascular disease, infections (other than pulmonary or urinary tract), and single organ failures were unlikely to be related to MS unless they were either judged to be complications of treatment or the patient had an EDSS ≥7 prior to death. In this study, two deaths from cardiovascular disease and one death from bladder cancer (believed secondary to treatment with cyclophosphamide) were judged to be MS-related (based on the EDSS or other criteria of our decision-algorithm – see table 1).

Statistical analyses

Only descriptive statistics were undertaken. Frequency tables were created to display our results and the means and standard deviations (SD) were computed for several of our parameter-estimates.

RESULTS

Disposition of patients

Of the 372 patients originally enrolled in the RCT, 366 (98.4%) were identified in the 21Y-LTF (figure 1). Of the six patients lost to follow-up, two were in each of the three randomised treatment groups (figure 1). These patients were in the study for periods of less than the length of the original trial and three of six withdrew from the RCT within 3 months of its start. Survival in these patients was very unlikely to have been influenced by their treatment assignment. The remaining three patients terminated their participation in the RCT after 1.2, 2.9, and 4.2 years.

In the cohort of 366 identified patients, 81 (22.1%) were dead after a median interval of 21.1 years from RCT enrolment (figure 1). Among these, the average age at death (±SD) was 51.7 (±8.7) years. The COD could be assigned in 82.7% (67/81) and in all but two of

these patients (65/81), the relationship between death and MS could be established (table 2). The MS relationship to death could be determined in four additional patients (table 1) despite the inability to assign a COD (table 2). Thus, the relationship between death and MS could be established in 85.2% (69/81) of the deaths (tables 2 and 3), and the COD, the MS relationship, or both could be determined in 88% (71/81) of the deaths.

Table 2. Number of patients in each COD category and the MS relationship for the 81 deaths in the different randomized treatment-allocation groups (numbers in parentheses represent MS-related deaths)

	Placebo	**IFNβ-1b**		**Total**
		50 µg	**250 µg**	
Number of Deaths	37	22	22	81
Category of Death				
1. Cardiovascular disease and stroke	4 (1)	1 (0)	5 (1)	10 (2)
2. All cancers	1 (0)	3 (0)	2 (1)	6 (1)
3. Pulmonary infectious diseases	12 (11)	2 (2)	3 (3)	17 (16)
4. Sepsis*	0	0	0	0
5. Accidental death	2 (1)	0 (0)	1 (1)	3 (2)
6. Suicide	3 (3)	2 (2)	3 (3)	8 (8)
7. Death due to MS	9 (9)	6 (6)	6 (6)	21 (21)
8. Other known COD	1 (0)	1 (1)	0 (0)	2 (1)
Total: COD known	32 (25)	15 (11)	20 (15)	67 (51)
Other MS Relationships				
COD known; MS relation unknown	1	0	1	2

MS relation known; COD unknown	1 (1)	2 (1)	1 (1)	4 (3)
COD unknown; MS relation unknown	4	5	1	10
Total: MS relationship known	32	17	20	69

COD = Cause-of-death; IFNβ-1b = interferon beta-1b; MS = multiple sclerosis.

* NB: The NDI death-certificate data does not include 'sepsis' as a separate COD category. Therefore these entries are all zero.

Table 3. Adjudicated MS relationship for the 81 observed deaths in the different randomised treatment-allocation groups.

	Placebo	**IFNβ-1b**		**Total**
		50µg	**250µg**	
Total Number of Deaths*	37 (45.7%)	22 (27.2%)	22 (27.2%)	81 (100%)
MS relationship Indeterminate	5 (6.2%)	5 (6.2%)	2 (2.5%)	12 (14.8%)
Total MS Relationship Known†	32 (46.4%)	17 (24.6%)	20 (29.0%)	69 (100%)
MS-related	26 (37.7%)	12 (17.4%)	16 (23.2%)	54 (78.3%)
Not MS-related	6 (8.7%)	5 (7.2%)	4 (5.8%)	15 (21.7%)
Expected in Null Condition††	33 (33.3%)	33 (33.3%)	33 (33.3%)	69 (100%)
MS-related	18 (26.1%)	18 (26.1%)	18 (26.1%)	54 (78.3%)
Not MS-related	5 (7.2%)	5 (7.2%)	5 (7.2%)	15 (21.7%)

IFNβ-1b = interferon beta-1b; MS = multiple sclerosis.

* Numbers represent the number of patients in each category. Numbers in parentheses represent the percentage of the total deaths (81) in each category for each treatment group separately. Total represents the combined numbers for all treatment arms

† Numbers represent the number of patients in each category. Numbers in parentheses represent the percentage of the total deaths where MS relationship known (69) in each category for each treatment group separately. Total represents the combined numbers for all treatment arms

†† The null condition represents the number of deaths expected in each of the three treatment groups if the 69 observed deaths (54 MS-related; 15 not MS-related) had been distributed evenly between groups. In the circumstances of the present study, there were 9 more deaths than expected in the placebo-treated group (8 MS-related; 1 not MS-related) and, similarly, and 9 fewer deaths than expected in the two treated groups combined.

Cause of death (COD)

CODs for the deceased patients are shown in table 2 and, of the 67 patients in whom a COD could be assigned, 'death due to MS' was the principal underlying COD in 31.3% (21/67). Two patients were assigned to the category of death due to 'other known causes' – one placebo-patient from a GI bleed and one patient in the IFNβ-1b 50-µg group who died from multi-system organ failure. The MS relationship to the death was determined in both patients – the adjudication committee judged the multi-system organ failure to be, and the GI bleed not to be, MS-related (table 2). In one patient in the IFNβ-1b 250-µg group the MS relationship could not be determined despite the death being in the COD category of 'cardiovascular disease and stroke'. Following application of the decision algorithm for MS-relatedness (table 1), 54 of the deaths were adjudicated to be MS-related (tables 2 and 3).

This represents 78.3% (54/69) of the adjudicated deaths and 67% (54/81) of the total observed deaths in the 21Y-LTF.

Almost all of the excess in deaths observed in patients originally assigned to the placebo group were adjudicated to be MS-related (table 3). Indeed, the percentage of deaths due to MS in each of the two treatment arms was about half that observed in the placebo group (table 3). Moreover, these deaths were accounted for, almost entirely, by an excess in the number of fatal pulmonary infections (table 2). By contrast, non–MS-related deaths are evenly distributed among the different treatment-groups (table 3).

DISCUSSION

This study provides considerable insight to the relationships between the early mortality in an MS cohort, the accrual of MS-related disability, and the impact of therapy on outcome in RRMS patients. In our earlier 21Y-LTF report,[18] we observed that the HR for death was significantly reduced by 46.8% in the IFNβ-1b 250-µg group and by 46.0% in the IFNβ-1b 50-µg group compared to placebo. This nearly identical effect size in the two independently randomised groups provided strong supportive evidence that the observed survival benefit was not due to chance (ie, from a type I error). Although it was still possible that the observed benefit reflected an unusually high mortality rate in the placebo arm, this too seemed unlikely given the virtual overlap of placebo-group mortality with natural history studies.[18] (Reference 14, supplementary Figure e-1) Thus, the survival rate for 29 years after disease onset (~70%) observed by others[2] was much like that in our placebo group (70.4%). In addition, the fact that after completion of the RCT, some patients chose to receive alternative therapies[21], does not detract from the findings. The 21Y-LTF analysis was done on a strict intent-to-treat basis. Moreover, the use of alternative therapies after randomization will make any differences between the cohorts less (not more) conspicuous and, thus, should

favor the null-hypothesis. Therefore, taken together, these findings of the 21Y-LTF strongly support the notion that there is a survival advantage following either earlier (or greater) exposure to IFNβ-1b.[18]

The patient population included in this cohort study is relatively young in the context of mortality and, indeed, our cohort exhibits many of the expected trends from such a circumstance. Thus, the average age (±SD) at the time of the 21Y-LTF was 56.3 (±7.1) years, with an average age at death even younger (51.7±8.7 years) – a feature characteristic of young and active cohorts.[2,3,11] Also typical of younger MS populations, the observed suicide rate was quite high (11.9%; 8/67). Moreover, the large majority of the deaths observed over the course of 21 years were due to MS-related causes. This finding is anticipated in a younger cohort, where diseases of the elderly (eg, cardiovascular disease, stroke, and cancer) have yet to overtake MS as the principal COD.[1,13,23] Thus, in the 21Y-LTF, 'death due to MS' accounted for a 31.3% (21/67) of the assignable CODs and 'MS-related death' accounted for 78.3% (54/69) of the assignable relationships and 67% of all deaths; these were more frequent compared with the combined category of cardiovascular disease, stroke and cancer, which accounted for only 23.9% (16/67) of the assignable CODs (tables 2 and 3). In reports on more complete survival-cohorts,[1,13,23] MS-related mortality ranges between 50 and 65%.

In addition to the fact that most of the observed deaths in this cohort were MS-related, three other observations support the notion that the observed intergroup differences in death are likely due to the MS disease state. First, the excess in 'all-cause' mortality in the placebo-assigned group is due, almost entirely, to an excess in MS-related deaths and not to other CODs (table 3). Second, the excess in MS-related deaths is largely attributable to an excess in fatal pulmonary infections, a complication known to occur in end-stage MS (table 2). And, third, both of these observations were highly consistent in the two groups of patients who

received active treatment during the RCT compared to those who received placebo (table 3). Taken together, these observations support the notion that the mortality benefit provided by IFNβ-1b therapy is related to a reduction in MS-related disability and, secondarily, from those complications, which are known to occur in the setting of advanced MS.

These findings underscore the importance of conducting LTF studies after completion of the RCTs that lead to product approval, particularly when they use (as ours did) a strict intention-to-treat analysis, have very high ascertainment rates, and measure unambiguously objective endpoints. Although, there has been some surprising controversy about the need to perform group-matching procedures in these randomised LTF populations, several methodologists have pointed out that such procedures (in randomised trials) can actually introduce bias where none existed prior [24-27].

A very important feature of our study is its near complete ascertainment rate for survival data of the cohort (98.4%). This stands in stark contrast to previous LTF studies of MS patients,[28-30] in which ascertainment rates were substantially less (39.8–68.2%). Low ascertainment rates substantially increase the likelihood of bias, because patients who are lost to follow-up are more likely to be deceased than those who are actually located.[31] In addition, the rules used for classifying the different CODs and establishing their MS relationship in this study were pre-defined and each assignment required the unanimous agreement of the three voting members on the adjudication committee (two of whom were completely independent of the 21Y-LTF). The fact that the observed COD in our cohort was usually MS-related is, in general, consistent with previous reports,[1-4] however, the actual percentage of MS-related deaths (78.3%, 54/69) was somewhat higher than the 50–70% reported by others.[2-4,13,32,33] The reason for this is uncertain but probably reflects the younger age, the relatively early analysis compared to epidemiological studies with more

complete mortality observations, and the selection of more active patients in this RCT-derived cohort compared to these other populations.

In summary, the large majority of deaths observed in this young RCT-derived cohort were adjudicated to be MS-related (78.3%). Moreover, the excess in deaths observed in the placebo randomised group were accounted for entirely by an excess in MS-related deaths and, in particular, by deaths due to pulmonary infections. Whether the impact of therapy on mortality is the consequence of early treatment or a larger cumulative exposure to IFNβ-1b cannot be resolved. Regardless, however, these data support the notion that the mortality benefit from IFNβ-1b is due to a treatment-related impact on the MS disease process itself.

Competing Interests

Douglas S Goodin has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Bayer-Schering Pharma, Merck-Serono, Teva Pharmaceuticals, and Novartis.

Anthony T Reder has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Abbott Laboratories, American Medical Association, Astra Merck, Athena Neurosciences, Aventis Pharma, Bayer Schering Pharma, Berlex Laboratories, Biogen and Biogen Idec, BioMS Medical Corp., Blue Cross, Blue Shield, Boehringer Ingelheim Pharmaceuticals Inc., Caremark Rx, Centocor, Inc., Cephalon, Inc., Connectics/Connective Therapeutics, CroMedica Global Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Genzyme Corporation, GlaxoSmithKline, Hoechst Marion Roussel Canada Research, Inc., Hoffman-LaRoche, Idec, Immunex, Institute for Health Care Quality, Johnson & Johnson Pharmaceutical Research & Development, LLC, Kalobios, S NARCOMS, Yale University, Barrow Neurological Institute, National Multiple Sclerosis Society & Paralyzed Veterans of America, "Pain Panel," Neurocrine Biosciences, Novartis Corporation, Parke-Davis, Pfizer Inc, Pharmacia & Upjohn, Protein Design Labs, Inc, Quantum Biotechnologies, Inc., Questcor Pharmaceuticals Inc., Quintiles, Inc., Serono Sandoz (now Novartis) & Novartis, Sention, Inc., Serono, Shering AG, Smith Kline-Beecham, Berlipharm, Inc., Takeda Pharmaceuticals, Teva-Marion, and Triton Biosciences.

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Boards for Bayer HealthCare, Merck Serono, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec.

Mark Rametta and **Karola Beckmann** are salaried employees of Bayer HealthCare Pharmaceuticals

Volker Knappertz was a salaried employee of Bayer HealthCare Pharmaceuticals at the time of manuscript preparation.

Contributions

Douglas S Goodin has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Anthony T Reder has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

George C Ebers has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Gary Cutter has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Marcelo Kremenchutzky has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Joel Oger has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Mark Rametta has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Timothy O'Donnell has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Stuart Cook has contributed to the conceptualisation of study, data acquisition and development and has reviewed the manuscript.

Karola Beckmann has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Volker Knappertz has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

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Data Sharing

There are no unpublished data.

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Cause of death in MS: Long-term follow-up of a randomised cohort, 21-years after the start of the pivotal IFNB-1b study

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ABSTRACT

Objective: Compared to controls, multiple sclerosis (MS) patients die, on average, 7–14 years prematurely. Nevertheless, there is incomplete knowledge about the causes of death (COD) and/or their MS relationship, especially in contemporary MS populations. We analysed COD in three patient cohorts followed for 21 years after their participation in the pivotal randomised, controlled trial (RCT) of interferon beta-1b.

Methods: Using multiple information sources, we attempted to establish COD and its relationship to MS in deceased patients. An independent adjudication committee, masked to treatment assignment, determined likely COD and its MS relationship using pre-specified criteria.

Results: After 21.1 years (median) from RCT enrolment, 98.4% (366/372) of patients in the original RCT-cohort were identified and 81 deaths recorded. Mean age at death was 51.7 (±8.7) years. COD, MS relationship, or both were determined for 88% of deaths (71/81). Patients were assigned to one of 9 COD categories: cardiovascular disease/stroke; cancer; pulmonary infections; sepsis; accidents; suicide; death due to MS; other known CODs; and unknown COD. Of the 69 patients for whom information on the relationship of death to MS was available, 78.3% (54/69) were adjudicated to be MS-related. Patients randomised to receive placebo during the RCT (compared with patients receiving active treatment) experienced an excessive number of MS-related deaths.

Conclusions: In this long-term, randomised, cohort study, MS patients receiving placebo during the RCT experienced greater all-cause mortality compared to those on active treatment. The excessive mortality in the original placebo group was largely from MS-related causes, especially, MS-related pulmonary infections.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system~~,~~ ~~which~~. Typically, MS occurs mostly in women, has a peak onset in the mid 20s, and has a mean clinical onset at the beginning of the fourth decade. It pursues a life-long – but variable – disease course. Nevertheless, by 15 to 25 years after its clinical onset, many (if not, most) MS patients will experience notable physical and cognitive difficulties as manifested, for example, by their requiring aids for mobility (eg, canes, walkers, and wheelchairs) or by their being unable to sustain a full-time job. In addition, MS has also been consistently associated with a significant increase in the risk of death compared to an age- and sex-matched control population.[1-8]

To estimate this increased mortality risk, one metric commonly used in survival studies is the so-called standardised mortality ratio (SMR). This measure assesses the ratio of the mortality in patients with a condition (over the entire period of observation) divided by the mortality in an age- and sex-matched cohort (over the same interval) without the condition.[9,10] In MS, the SMR is generally in the range of 2–3, indicating that, in MS patients, death is 2–3 times more likely over the observation period than in age and gender-matched controls.[1,2,9-13] An alternative metric of effect on longevity in MS patients is the average time from clinical onset to death. This time is approximately 35 years (ranging from a low of 24.5 years in a Scottish cohort to a high of 45 years in a New Zealand cohort). Thus, compared to unaffected age- and sex-matched controls, MS patients die, on average, 7–14 years prematurely.[1,2,12,14,15]

Importantly, long-term outcomes such as the avoidance of unambiguous physical impairment, the ability to remain employed, and survival are of far greater importance to patients and families than are the short-term clinical and magnetic resonance imaging (MRI) outcomes measured during randomised controlled trials (RCTs). For this reason, long-term

follow-up (LTF) studies are essential to assess the true impact of MS therapies on the disease. Nevertheless, such studies are difficult to execute successfully. The study of mortality in MS has been infrequent and, even then, only as part of natural history studies.[1,11,12] Moreover, and particularly in the past 20 years, the potential impact of therapy on mortality has been largely ignored.

Recently, we reported our experience at 21 years (the 21Y-LTF) in the cohort of relapsing-remitting (RR) MS patients who had previously participated in the pivotal RCT of interferon beta (IFNβ)-1b for MS.[16-19] After a median of 21.1 years from RCT enrolment, we identified 98.4% (366/372) of the original patient cohort. In this group, 81 deaths were recorded (22.1%; 81/366). Patients originally randomised to receive IFNβ-1b (either 250 µg or 50 µg; every other day subcutaneously) had a significant reduction in ~~the hazard rate for~~ "all-cause" mortality ~~(46.8% and 46.0% respectively)~~ over the 21-year period compared to patients originally randomised to receive placebo. The marked reduction in "all-cause" mortality was reflected by hazard ratios (HRs) of 0.532 (*P*=0.0173) in the 250-µg group and 0.540 (*P*=0.0202) in the 50-µg group; representing reductions in the hazard rate by 46.8% and 46.0% respectively.

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Although these findings clearly imply a mortality benefit of therapy, it is, nevertheless, important to determine both the causes of the observed deaths in these cohorts and the relationship between these deaths and the underlying MS. Thus, it is only through such an undertaking that one can connect the mortality benefit to an impact of therapy on MS. Nevertheless, this task can be problematic because the recorded cause-of-death (COD) may be unreliable due to multiple factors. These include the infrequency of autopsies in MS patients, the recording physician's lack of knowledge of the patient's medical history, and the absence of uniform diagnostic criteria.[4,13] Similarly, establishing the MS relationship is often difficult because MS may be only an indirect contributor to death. For example, MS-

related disability (either physical or cognitive) can predispose patients to a variety of other illnesses or conditions that, by themselves, can be fatal (eg, aspiration pneumonia, sepsis from pressure sores or urinary tract infections, deep-vein thromboses with subsequent pulmonary emboli, suicide, etc.).

In the present study we aimed to develop a reliable method to determine the COD for the patients who died and to assess the relationship of these deaths to MS. We also aimed to establish whether the excessive 21-year mortality, which was observed in patients originally randomised to placebo, was due either to MS-related or non–MS-related causes.

METHODS

Patients

All patients enrolled in the pivotal RCT of IFNβ-1b in RRMS were eligible to participate in the 21Y-LTF. The inclusion criteria, design, and methods for the original RCT have been published.[16] Briefly, treatment-naive RRMS patients (aged 18–50 years) with an Expanded Disability Status Scale (EDSS) score ≤5.5 [20] and with two or more clinical exacerbations within the prior 2 years, were randomised to receive IFNβ-1b 50 µg (n=125), IFNβ-1b 250 µg (n=124), or placebo (n=123) every other day. During the RCT, patients were treated and prospectively followed for a period of up to 5.1 years on their assigned treatment regimen (mean: 3.3±1.4 years; median: 3.8 years; range: 0.1–5.1 years). At the end of the RCT in 1993, subsequent use of disease-modifying treatment (DMT) was at the discretion of patients and their physicians. IFNβ-1b was the only DMT available until 1996 when the use of alternative DMTs became possible.[21] Post-RCT treatment information was available for 67% (249/372) of the original RCT population at the time of the 16-year (16Y)-LTF study [21]. Of these, 55% (138/249) received only IFNβ-1b and, in the remainder, there were no

systematic differences in treatment or care observed across the three RCT-defined cohorts. [21] Treatment information for the final 5 years of follow-up was largely unavailable.

Study design and determination of vital status

Between 1 October 2009 to 15 December 2010 (approximately 21 years after RCT enrolment), investigators at each study site attempted to identify each of the 372 randomised patients who took part in the IFNβ-1b RCT.[16,17,19] They also attempted to determine the vital status for each of their study participants and to collect COD information for those who had died during the 21-year follow-up period. For patients whose vital status could not be determined by the investigators, further searches, using both public domain and private sources, were undertaken. For US sites, these included both death certificates, the US National Death Index (NDI), medical records, 'notes to file' by investigators, data from the RCT and the 16Y-LTF,[16,17,19,21,22] and (when possible) the 'in-person' information from relatives. For Canadian sites, the same data sources were utilised except for the NDI, which was not available.

The treatment cohorts at the time of the original randomised treatment assignment were maintained for the entire 21-year period of follow-up and a strict intention-to-treat (ITT) analysis was undertaken. The different treatment-allocation cohorts (from the RCT) were well-balanced for all baseline demographic variables.[16,17,19] This study was conducted in accordance with Good Clinical Practice guidelines. Appropriate written informed consent was obtained. The protocol was approved by the institutional review board or independent ethics committee at each study site.

Establishing cause of death

An adjudication committee, established to assess both the underlying COD and the relationship of death to MS in each of patients who died during the 21Y-LTF, consisted of five members, three of whom voted. The voting members included two neurologists (SC, GE) and a critical care specialist (TO). Two of these three members (SC and TO) ~~did not participate in the 21Y-LTF (i.e., they~~ were completely independent~~).~~ from the 21Y-LTF. In addition, two non-voting members also served on the committee – a neurologist representative from Bayer (VK) ~~– who oversaw the deliberations –~~ and an academic biostatistician (GC). Committee members were blinded to the treatment allocation of the deceased patients. All COD categorisations and MS relationships required unanimous agreement of the voting members.

Predefined rules were used to classify the underlying COD and each case was assigned to one of the following nine COD-categories:

1. Cardiovascular disease and stroke
2. All cancers
3. Pulmonary infectious diseases
4. Sepsis
5. Accidental death
6. Suicide
7. Death due to MS
8. Other known causes
9. Unknown or indeterminate cause

The relationship of death to MS was determined using a pre-defined decision algorithm (table 1) using a variety of information sources. Three possible relationships of

CODs to MS were considered: 1) CODs always related to MS; 2) CODs probably related to MS; and 3) CODs probably not related to MS.

Table 1. Decision algorithm for determining the relationship of death to MS

Always MS-Related	Probably MS-Related	Probably not MS-Related
1. Suicide	1. Brainstem dysfunction	1. CV disease and stroke
2. EDSS ≥7.0 prior to death	2. Pulmonary infections	2. All cancers
3. MS the only listed COD	3. Aspiration pneumonia	3. Other infections
4. Death due to MS	4. Respiratory insufficiency	4. Single organ failure
5. Death from MS treatment	5. Pulmonary embolism	
	6. Sepsis (esp. uro-sepsis)	
	7. Death due to trauma	

COD = Cause-of-death; CV = Cardiovascular; MS = multiple sclerosis;
EDSS = Extended Disability Status Scale

For the first of these possible MS relationships, it was agreed *a priori* that all suicides would be considered MS-related. This rule was invoked in eight patients ~~(evenly divided among the treatment arms).~~ Also, if MS was listed as the first (or only) COD on the death certificate, then the death was classified as 'death due to MS', which was, by definition, MS-related. This rule was applied to 21 patients. Finally, if the patient had reached an EDSS ≥7 at any time prior to their demise, the death was always considered to be MS-related, regardless of the recorded COD. This rule was invoked to determine the MS relationship in six patients. In three of these, the COD was indeterminate but advanced disability was known to be present. In only three instances was this rule applied to patients in whom a COD other than

MS was recorded – in two with a suspected cardiovascular COD and in one with a multi-system organ failure. ~~These three patients were evenly divided among the treatment arms and excluding didn't alter the analysis.~~

For the second of these possible MS relationships, it was agreed *a priori* that deaths due to brainstem dysfunction, aspiration pneumonia, respiratory insufficiency, sepsis, pulmonary embolism, trauma, or side effects of treatment were likely to be MS-related. In these cases, however, determination of the MS relationship was judged by the context in which the death occurred and required some ancillary information. For example, death from a pulmonary embolism would be considered MS-related if the patient were known have had marked lower extremity weakness and/or was confined to wheelchair or bed and, especially, if the embolus was from a deep-vein thrombosis thought secondary to the patient's immobility. By contrast, the embolus would not be considered to be MS-related if it occurred spontaneously in a fully ambulatory individual.

For the third of these possible MS relationships, it was agreed *a priori* that deaths due to cancer, cardiovascular disease, infections (other than pulmonary or urinary tract), and single organ failures were unlikely to be related to MS unless they were either judged to be complications of treatment or the patient had an EDSS ≥7 prior to death. In this study, two deaths from cardiovascular disease and one death from bladder cancer (believed secondary to treatment with cyclophosphamide) were judged to be MS-related (based on the EDSS or other criteria of our decision-algorithm – see table 1).

Statistical analyses

~~Only~~No specific statistical analyses other than descriptive statistics were undertaken~~.~~ on these data as part of this study. Frequency tables were created to display our results and

the means and standard deviations (SD) were computed for several of our parameter-estimates.

RESULTS

Disposition of patients

Of the 372 patients originally enrolled in the RCT, 366 (98.4%) were identified in the 21Y-LTF (figure 1). Of the six patients lost to follow-up, two were in each of the three randomised treatment groups (figure 1). These patients were in the study for periods of less than the length of the original trial and three of six withdrew from the RCT within 3 months of its start. Survival in these patients was very unlikely to have been influenced by their treatment assignment. The remaining three patients terminated their participation in the RCT after 1.2, 2.9, and 4.2 years.

In the cohort of 366 identified patients, 81 (22.1%) were dead after a median interval of 21.1 years from RCT enrolment (figure 1). Among these, the average age at death (±SD) was 51.7 (±8.7) years. The COD could be assigned in 82.7% (67/81) and in all but two of these patients (65/81), the relationship between death and MS could be established (table 2). The MS relationship to death could be determined in four additional patients (table 1) despite the inability to assign a COD (table 2). Thus, the relationship between death and MS could be established in 85.2% (69/81) of the deaths (tables 2 and 3), and the COD, the MS relationship, or both could be determined in 88% (71/81) of the deaths.

Table 2. Number of patients in each COD category and the MS relationship for the 81 deaths in the different randomized treatment-allocation groups (numbers in parentheses represent MS-related deaths)

	Placebo	IFNβ-1b	Total

		50 µg	250 µg	
Number of Deaths	37	22	22	81
Category of Death				
1. Cardiovascular disease and stroke	4 (1)	1 (0)	5 (1)	10 (2)
2. All cancers	1 (0)	3 (0)	2 (1)	6 (1)
3. Pulmonary infectious diseases	12 (11)	2 (2)	3 (3)	17 (16)
4. Sepsis*	0	0	0	0
5. Accidental death	2 (1)	0 (0)	1 (1)	3 (2)
6. Suicide	3 (3)	2 (2)	3 (3)	8 (8)
7. Death due to MS	9 (9)	6 (6)	6 (6)	21 (21)
8. Other known COD	1 (0)	1 (1)	0 (0)	2 (1)
Total: COD known	32 (25)	15 (11)	20 (15)	67 (51)
Other MS Relationships				
COD known; MS relation unknown	1	0	1	2
MS relation known; COD unknown	1 (1)	2 (1)	1 (1)	4 (3)
COD unknown; MS relation unknown	4	5	1	10
Total: MS relationship known	32	17	20	69

COD = Cause-of-death; IFNβ-1b = interferon beta-1b; MS = multiple sclerosis.

* NB: The NDI death-certificate data does not include 'sepsis' as a separate COD category. Therefore these entries are all zero.

Table 3. Adjudicated MS relationship for the 81 observed deaths in the different randomised treatment-allocation groups.

	Placebo	IFNβ-1b		Total
		50µg	250µg	
Total Number of Deaths*	37 (45.7%)	22 (27.2%)	22 (27.2%)	81 (100%)
MS relationship Indeterminate	5 (6.2%)	5 (6.2%)	2 (2.5%)	12 (14.8%)
Total MS Relationship Known†	32 (46.4%)	17 (24.6%)	20 (29.0%)	69 (100%)
MS-related	26 (37.7%)	12 (17.4%)	16 (23.2%)	54 (78.3%)
Not MS-related	6 (8.7%)	5 (7.2%)	4 (5.8%)	15 (21.7%)
Expected in Null Condition††	33 (33.3%)	33 (33.3%)	33 (33.3%)	69 (100%)
MS-related	18 (26.1%)	18 (26.1%)	18 (26.1%)	54 (78.3%)
Not MS-related	5 (7.2%)	5 (7.2%)	5 (7.2%)	15 (21.7%)

IFNβ-1b = interferon beta-1b; MS = multiple sclerosis.

* Numbers represent the number of patients in each category. Numbers in parentheses represent the percentage of the total deaths (81) in each category for each treatment group separately. Total represents the combined numbers for all treatment arms

† Numbers represent the number of patients in each category. Numbers in parentheses represent the percentage of the total deaths where MS relationship known (69) in each category for each treatment group separately. Total represents the combined numbers for all treatment arms

†† The null condition represents the number of deaths expected in each of the three treatment groups if the 69 observed deaths (54 MS-related; 15 not MS-related) had been distributed evenly between groups. In the circumstances of the present study, there were 9 more

deaths than expected in the placebo-treated group (8 MS-related; 1 not MS-related) and, similarly, and 9 fewer deaths than expected in the two treated groups combined.

Cause of death (COD)

CODs for the deceased patients are shown in table 2 and, of the 67 patients in whom a COD could be assigned, 'death due to MS' was the principal underlying COD in 31.3% (21/67). Two patients were assigned to the category of death due to 'other known causes' – one placebo-patient from a GI bleed and one patient in the IFNβ-1b 50-µg group who died from multi-system organ failure. The MS relationship to the death was determined in both patients – the adjudication committee judged the multi-system organ failure to be, and the GI bleed not to be, MS-related (table 2). In one patient in the IFNβ-1b 250-µg group the MS relationship could not be determined despite the death being in the COD category of 'cardiovascular disease and stroke'. Following application of the decision algorithm for MS-relatedness (table 1), 54 of the deaths were adjudicated to be MS-related (tables 2 and 3). This represents 78.3% (54/69) of the adjudicated deaths and 67% (54/81) of the total observed deaths in the 21Y-LTF.

Almost all of the excess in deaths observed in patients originally assigned to the placebo group were adjudicated to be MS-related (table 3). Indeed, the percentage of deaths due to MS in each of the two treatment arms was about half that observed in the placebo group (table 3). Moreover, these deaths were accounted for, almost entirely, by an excess in the number of fatal pulmonary infections (table 2). By contrast, non–MS-related deaths are evenly distributed among the different treatment-groups (table 3).

DISCUSSION

This study provides considerable insight to the relationships between the early mortality in an MS cohort, the accrual of MS-related disability, and the impact of therapy on outcome in RRMS patients. In our earlier 21Y-LTF report,[18] we observed that the HR for death was significantly reduced by 46.8% in the IFNβ-1b 250-µg group and by 46.0% in the IFNβ-1b 50-µg group compared to placebo. This nearly identical effect size in the two independently randomised groups provided strong supportive evidence that the observed survival benefit was not due to chance (ie, from a type I error). Although it was still possible that the observed benefit reflected an unusually high mortality rate in the placebo arm, this too seemed unlikely given the virtual overlap of placebo-group mortality with natural history studies.[18] (Reference 14, supplementary Figure e-1) Thus, the survival rate for 29 years after disease onset (~70%) observed by others[2] was much like that in our placebo group (70.4%). In addition, the fact that after completion of the RCT, some patients chose to receive alternative therapies[21], does not detract from the findings. The 21Y-LTF analysis was done on a strict intent-to-treat basis. Moreover, the use of alternative therapies after randomization will make any differences between the cohorts less (not more) conspicuous and, thus, should favor the null-hypothesis. Therefore, taken together, these findings of the 21Y-LTF strongly support the notion that there is a survival advantage following either earlier (or greater) exposure to IFNβ-1b.[18]

The patient population included in this cohort study is relatively young in the context of mortality and, indeed, our cohort exhibits many of the expected trends from such a circumstance. Thus, the average age (±SD) at the time of the 21Y-LTF was 56.3 (±7.1) years, with an average age at death even younger (51.7±8.7 years) – a feature characteristic of young and active cohorts.[2,3,11] Also typical of younger MS populations, the observed suicide rate was quite high (11.9%; 8/67). Moreover, the large majority of the deaths observed over the course of 21 years were due to MS-related causes. This finding is

anticipated in a younger cohort, where diseases of the elderly (eg, cardiovascular disease, stroke, and cancer) have yet to overtake MS as the principal COD.[1,13,23] Thus, in the 21Y-LTF, 'death due to MS' accounted for a 31.3% (21/67) of the assignable CODs and 'MS-related death' accounted for 78.3% (54/69) of the assignable relationships and 67% of all deaths; these were more frequent compared with the combined category of cardiovascular disease, stroke and cancer, which accounted for only 23.9% (16/67) of the assignable CODs (tables 2 and 3). In reports on more complete survival-cohorts,[1,13,23] MS-related mortality ranges between 50 and 65%.

In addition to the fact that most of the observed deaths in this cohort were MS-related, three other observations support the notion that the observed intergroup differences in death are likely due to the MS disease state. First, the excess in 'all-cause' mortality in the placebo-assigned group is due, almost entirely, to an excess in MS-related deaths and not to other CODs (table 3). Second, the excess in MS-related deaths is largely attributable to an excess in fatal pulmonary infections, a complication known to occur in end-stage MS (table 2). And, third, both of these observations were highly consistent in the two groups of patients who received active treatment during the RCT compared to those who received placebo (table 3). Taken together, these observations support the notion that the mortality benefit provided by IFNβ-1b therapy is related to a reduction in MS-related disability and, secondarily, from those complications, which are known to occur in the setting of advanced MS.

These findings underscore the importance of conducting LTF studies after completion of the RCTs that lead to product approval~~, particularly~~. Although LTF studies are not 'clinical trials' *per se*, when they ~~use (as ours did) a strict intention-to-treat analysis,~~ have ~~very~~ high ascertainment rates~~,~~ and measure unambiguously objective endpoints~~. Although, there has been some surprising controversy about~~, they represent the ~~need to perform group-matching procedures in these randomised LTF populations, several methodologists have pointed out~~

~~that such procedures (in randomised trials) can actually introduce bias where none existed prior~~ primary analysis of independent data, unobtainable during the RCT and collected long after RCT completion. They also have several key advantages over other non-randomised cohort studies. For example, LTFs assess the association between treatment allocation during the RCT and those unambiguous outcomes such as ambulation status, employment status, or mortality, which are of far greater importance than the short-term MRI and clinical outcomes measured during the course of an RCT. Also, LTFs use strict intent-to-treat paradigms, which are statistically and methodologically conservative and, thus, any bias during the open-label treatment period will tend to favour the null hypothesis unless there has been a differential loss to follow-up between groups. In addition, because the study cohorts in these LTFs are randomised at their formation, all measured and unmeasured covariates will, on average, be balanced between groups. In fact, the pivotal trial cohorts were well-balanced on all measured baseline variables.~~[24-27]~~[16,17,19].~~ Consequently, even though LTF analyses are typically not pre-planned, there is still no need to match the cohorts for co-morbid conditions at baseline. Indeed, many methodological experts feel that such matching or adjustment (after randomisation) is unnecessary or even misleading. Even those who advocate adjustment after randomisation, prefer the *a priori* identification of covariates or limiting these adjustments to variables that are known to be highly correlated with the outcome.[24,25]. As an example, hypertension among 30-year-olds, which has a low correlation with early mortality, would not fit this criterion nor be used for adjustment. The reason to limit the use of covariate adjustment in a randomised cohort is that matching can only be performed on known covariates. Nevertheless, balancing the analysis for known variables may unbalance the groups on unknown factors, which may have a greater (or equal) impact on the outcome than known variables. Such adjustment could potentially negate the principal advantage for bias reduction that randomisation provides (ie, achieving, on average, a balance on the unknown

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variables). Moreover, consideration of pre-morbid risk factors in an LTF setting becomes superfluous when the actual CODs in the cohort are known.

~~A very~~ In sum, LTF studies following RCTs have several important (and often unique) design advantages that distinguish them from other long-term cohort studies in the literature in their ability to establish causation according to currently used methods.[26,27] These include the use of randomisation at baseline, the use of an intent-to-treat analysis, the collection of data independently from the data recorded during the RCT data, and the use of unquestionably objective outcome measures.[27]

An important feature of ~~our~~this study is its near complete ascertainment rate for survival data of the cohort (98.4%). This stands in stark contrast to previous LTF studies of MS patients,[28-30] in which ascertainment rates were substantially less (39.8–68.2%). Low ascertainment rates substantially increase the likelihood of bias, because patients who are lost to follow-up are more likely to be deceased than those who are actually located.[31]

In addition, the rules used for classifying the different CODs and establishing their MS relationship in this study were pre-defined and each assignment required the unanimous agreement of the three voting members on the adjudication committee (two of whom were completely independent of the 21Y-LTF). The fact that the observed COD in our cohort was usually MS-related is, in general, consistent with previous reports,[1-4] however, the actual percentage of MS-related deaths (78.3%, 54/69) was somewhat higher than the 50–70% reported by others.[2-4,13,32,33] The reason for this is uncertain but probably reflects the younger age, the relatively early analysis compared to epidemiological studies with more complete mortality observations, and the selection of more active patients in this RCT-derived cohort compared to these other populations.

In summary, the large majority of deaths observed in this young RCT-derived cohort were adjudicated to be MS-related (78.3%). Moreover, the excess in deaths observed in the

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placebo randomised group were accounted for entirely by an excess in MS-related deaths and, in particular, by deaths due to pulmonary infections. Whether the impact of therapy on mortality is the consequence of early treatment or a larger cumulative exposure to IFNβ-1b cannot be resolved. Regardless, however, these data support the notion that the mortality benefit from IFNβ-1b is due to a treatment-related impact on the MS disease process itself.

Competing Interests

Douglas S Goodin has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Bayer-Schering Pharma, Merck-Serono, Teva Pharmaceuticals, and Novartis.

Anthony T Reder has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Abbott Laboratories, American Medical Association, Astra Merck, Athena Neurosciences, Aventis Pharma, Bayer Schering Pharma, Berlex Laboratories, Biogen and Biogen Idec, BioMS Medical Corp., Blue Cross, Blue Shield, Boehringer Ingelheim Pharmaceuticals Inc., Caremark Rx, Centocor, Inc., Cephalon, Inc., Connectics/Connective Therapeutics, CroMedica Global Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Genzyme Corporation, GlaxoSmithKline, Hoechst Marion Roussel Canada Research, Inc., Hoffman-LaRoche, Idec, Immunex, Institute for Health Care Quality, Johnson & Johnson Pharmaceutical Research & Development, LLC, Kalobios, S NARCOMS, Yale University, Barrow Neurological Institute, National Multiple Sclerosis Society & Paralyzed Veterans of America, "Pain Panel," Neurocrine Biosciences, Novartis Corporation, Parke-Davis, Pfizer Inc, Pharmacia & Upjohn, Protein Design Labs, Inc, Quantum Biotechnologies, Inc., Questcor Pharmaceuticals Inc., Quintiles, Inc., Serono Sandoz (now Novartis) & Novartis, Sention, Inc., Serono, Shering AG, Smith Kline-Beecham, Berlipharm, Inc., Takeda Pharmaceuticals, Teva-Marion, and Triton Biosciences.

George C Ebers has received consulting fees from Roche, Biopartners, EISAI, MVM Life Science Partners, and Bayer HealthCare Pharmaceuticals; honoraria as an Executive

Committee member of the MS Forum from Bayer HealthCare Pharmaceuticals; and travel support from Bayer HealthCare Pharmaceuticals.

Gary Cutter has received either personal compensation (for consulting, serving on a scientific advisory board, or speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Antisense Therapeutics Limited, Sanofi-Aventis, Bayhill Pharmaceuticals, BioMS Pharmaceuticals, Daichi-Sankyo, Genmab Biopharmaceuticals, Glaxo Smith Klein, PTC Therapeutics, Medivation, Eli Lilly, Teva, Vivus, University of Pennsylvania, NHLBI, NINDS, NMSS, Ono Pharmaceuticals, Alexion Inc., Accentia, Bayer, Bayhill, Barofold, CibaVision, Novartis, Diagenix, Consortium of MS Centers, Klein-Buendel Incorporated, Enzo Pharmaceuticals, Peptimmune, Somnus Pharmaceuticals, Teva pharmaceuticals, UTSouthwestern, Visioneering Technologies, Sandoz, and Nuron Biotech, Inc.

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Timothy O'Donnell has received compensation from Bayer for sitting on the adjudication committee for this study and has participated as an investigator for open label, and safety and efficacy trials with Otsuka, Schering, and Bristol-Myers Squibb pharmaceutical companies.

Stuart Cook has received personal compensation for consultations or lectures from Merck Serono, Bayer HealthCare, Sanofi Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, Genmab and Actinobac Biomed Inc. He has served on Scientific Advisory

Boards for Bayer HealthCare, Merck Serono, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec.

Mark Rametta and **Karola Beckmann** are salaried employees of Bayer HealthCare Pharmaceuticals

Volker Knappertz was a salaried employee of Bayer HealthCare Pharmaceuticals at the time of manuscript preparation.

Contributions

Douglas S Goodin has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Anthony T Reder has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

George C Ebers has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Gary Cutter has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Marcelo Kremenchutzky has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Joel Oger has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Mark Rametta has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Timothy O'Donnell has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content.

Stuart Cook has contributed to the conceptualisation of study, data acquisition and development and has reviewed the manuscript.

Karola Beckmann has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

Volker Knappertz has contributed to the design/conceptualisation of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content.

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Figure 1. Patient Identification and Vital Status at the 21Y-LTF.

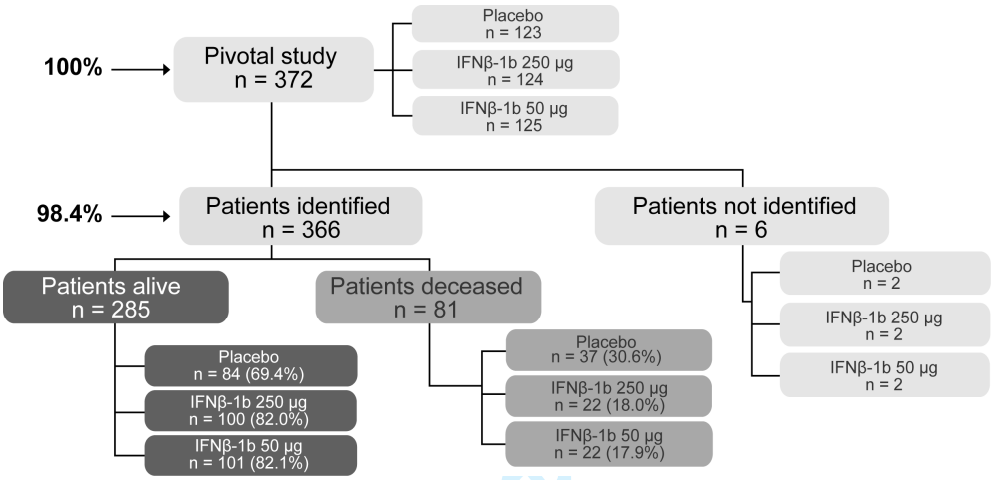

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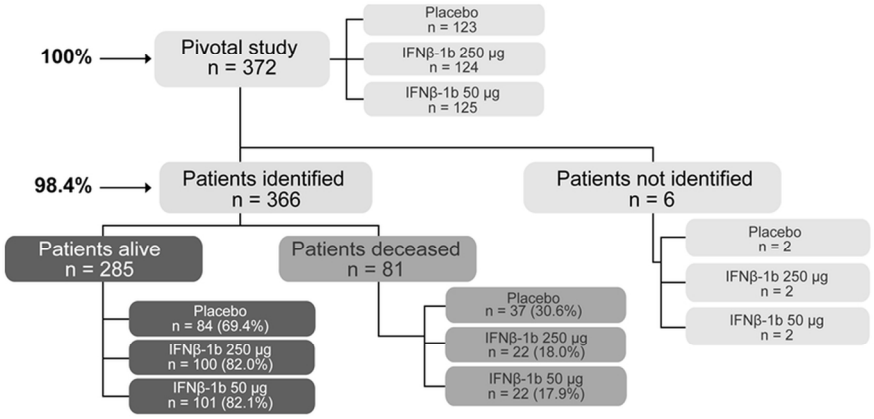
Figure 1. Patient Identification and Vital Status at the 21Y-LTF.



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