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Interferon beta-1b 16-Year Long-Term Follow-Up Study: MRI Outcomes

AUTHORS

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ABSTRACT

Background: The interferon beta-1b (IFNB-1b; Betaferon®) pivotal study demonstrated efficacy, safety and tolerability of IFNB-1b in patients with relapsing-remitting multiple sclerosis (RRMS), including a persistent beneficial effect on (MRI) lesion burden over 5 years. The 16-Year Long-Term Follow-Up (16-Year LTF) study is hypothesis generating, with the aim to assess the long-term treatment effects of IFNB-1b on clinical and MRI outcomes.

Design/Methods: The 16-Year LTF is a multicentre, open-label, observational study utilising cross-sectional data collected from patients from all 11 centres who participated in the original pivotal trial. MRI scans were analysed at a single centre and MRI outcome measures assessed included T2 burden of disease (BOD), normalised brain volume (NBV), gadolinium-enhancing lesions (Gd), T1 hypointense lesions 'black holes' (BH) and cervical cord area at C2 (CCA).

Results: 328 of the original 372 patients have been identified (i.e. 88.2%). 192 patients underwent MRI studies (BOD, NBV – 187 patients, Gd – 184 patients, BH – 180 and CCA – 81). A trend was observed between T2 BOD, NBV, BH, CCA in correlation with disability within the stratified groups. The continuous suppression of Gd-enhancing lesions in patients on IFNB-1b treatment within the last 60 days compared with patients who discontinued treatment at least 90 days ago suggest a sustained treatment effect even after 16 years of therapy.

Conclusions: Although significant differences in the intention-to-treat analyses were not observed, preliminary results indicate that the changes in the different MRI measures over time in the whole cohort are in line with expected clinical progression. Assessment of the CCA was done for a first time in a multicentre setting. Results are consistent with the brain measurements, even though this variable was only assessed in a smaller number of patients, mainly for technical reasons and availability at specific centres.

Introduction

- Interferon beta-1b (IFNB-1b; Betaferon®) is the first marketed immunomodulatory therapy for the treatment of relapsing forms of multiple sclerosis (MS). Its regulatory approval was based on a double-blind, placebo-controlled study performed in the USA and Canada from 1988–1993.[1–3]
- In this pivotal North American study[1–3] 372 patients were randomly assigned to receive treatment with either placebo, 50 µg IFNB-1b or 250 µg IFNB-1b administered subcutaneously (sc) every other day (eod) for up to 5 years. The study consisted of a 2-year double-blind, randomised period with the option to continue double-blind treatment and evaluation for an additional 3 years. The majority of patients chose this option, however the sample size decreased over the 5-year period. All patients were offered 250 µg IFNB-1b sc eod following regulatory approval of this dose in October 1993.
- Yearly magnetic resonance imaging (MRI) analyses were performed on 327 of the patients in this pivotal study. The MRI results supported the clinical results, demonstrating a significant reduction in disease activity as measured by numbers of active scans (median 80% reduction, P=0.0082) and appearance of new lesions. Furthermore, a similar significant reduction in MRI-detected burden of disease (BOD) was observed in treated patients compared with the placebo groups (mean group difference was 23%, P=0.001).[3]
- During the last two decades, MRI equipment and techniques have significantly improved. Advances include increased magnet strength (from 0.15 up to 3.0 Tesla), developments in software and pulse sequence programming resulting in shorter scanning time and improved brain coverage. In addition, gadolinium (Gd) enhancement, brain volume measures, as well as more advanced MRI techniques such as MR spectroscopy, magnetised transfer, diffusion and relaxation have since been developed, allowing different aspects of the MS pathology to be studied.
- It is, therefore, challenging to compare MRI scans performed using current equipment and methods with those taken in the 1980s.
- This report presents new MRI findings from patients who were in the original cohort of the pivotal IFNB-1b trial, and constitutes the longest follow-up for any disease-modifying therapy in MS.

Objectives of the 16-Year LTF Study: MRI

- To determine the long-term effect of IFNB-1b treatment on MRI measures.

Study Design

- Multicentre, open-label, observational study of patients with relapsing forms of MS who participated in the pivotal IFNB-1b trial. The cross-sectional analysis will evaluate the current MRI status of the patients and correlation with clinical disability.
- T2/PD (proton density) cranial MRI scans, using magnets with field strengths ranging from 0.15 Tesla to 1.5 Tesla (GE, Fonar, Philips, Picker, Siemens), were performed in the majority of the patients during the pivotal trial. Original data tapes were stored securely.
- Current MRI scans have been done at one single visit together with the clinical evaluations. To allow for proper scheduling the visit could be performed over a maximum of 3 days within a 21-day period.

Assessments

- The details of the clinical assessments have been published previously.[4,5]
- Patients underwent a single MRI scan using a pre-determined protocol developed by the UBC MS/MRI Research Group. Scanners were all at 1.5 Tesla (GE, Siemens, Philips).
- The following MRI variables were investigated:
  - Volume of hyperintense lesions on axial PD/T2-weighted images (T2 BOD)
  - Number of Gd-enhancing lesions on axial T1-weighted images
  - Number of patients with Gd-enhancing scans on axial T1-weighted images
  - Number and volume of hypointense lesions on pre-contrast axial T1-weighted images (black holes)
  - Normalised brain volume (NBV)
  - Cervical cord area at C2.
- All MRI scans were evaluated in a blinded fashion at the central analysis centre. Most rejected scans were repeated without delay and within the suggested 21-day study period.

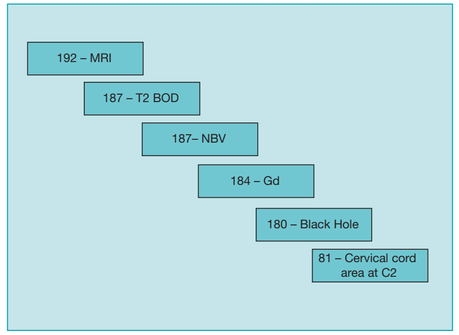
Statistical Analysis

- Due to the hypothesis-generating intent of this study, analyses were exploratory and descriptive in nature.[4]

Results

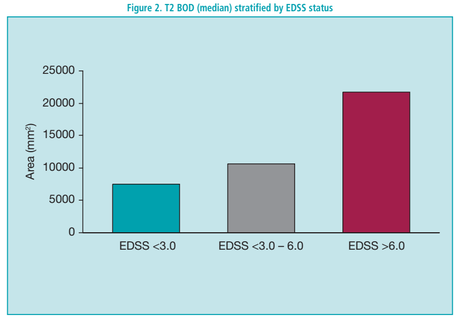
- At total of 328 of the original 372 patients (88.2%) have been identified from the 11 participating study centres and 293 are alive while 35 have been identified as deceased. Patient disposition in the 16-year follow up is shown in Poster P666. MRI scans were analysed from 192 patients. The number of patients from which the individual MRI parameters were obtained is shown in Figure 1.

Figure 1. Patient distribution according to MRI parameter



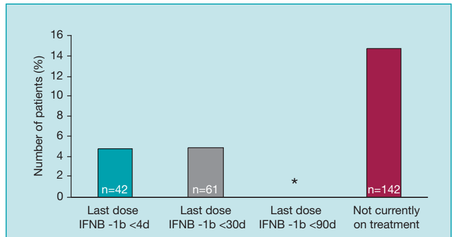
- There was an equal effect in all patient groups (placebo, 50 µg or 250 µg IFNB-1b) with respect to the MRI analyses presented.
- A correlation was observed between the T2 BOD and the EDSS status of the patients (Figure 2). Patients with higher EDSS and greater disability had higher T2 BOD.

Figure 2. T2 BOD (median) stratified by EDSS status



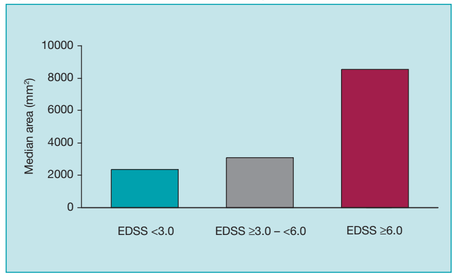
- Due to technical advances the original T2 BOD data cannot be directly compared to the current MRI results. However, the current clinical status seems to correlate with the MRI findings for the disability measures.
- Figure 3 shows the number of patients with Gd-enhancing lesions according to current IFNB-1b treatment. There is a paucity of data on the duration of treatment effects on suppression of Gd-enhancing lesions after discontinuation of therapy. A stratification of patients by current treatment or most recent discontinuation (<4 days, <30 days, <90 days or ≥90 days since discontinuation of IFNB-1b) reveals that if IFNB-1b 250 µg eod has been discontinued within the last 30 days, a treatment effect persists, even after up to 16 years of therapy. An analysis of lasting effects of up to 90 days since discontinuation was planned, but identified no patients in this group, therefore, this evaluation could not be performed.
- The area of T1 hypointense lesions (black holes) according to the patients' EDSS status in the total cohort is summarised in Figure 4. Patients with greater disability had higher T1 black hole volumes. This finding correlates well with the T2 BOD results.

Figure 3. Patients in the total cohort with Gd-enhancing lesions stratified according to treatment



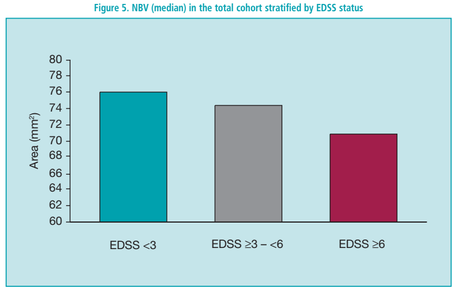
* No additional patients have withdrawn from treatment between 30 and 90 days before MRI, therefore the <90 days analysis revealed no difference compared to the <30 days group

Figure 4. Area of T1 hypointense lesions (black holes) according to the EDSS score in the total patient cohort



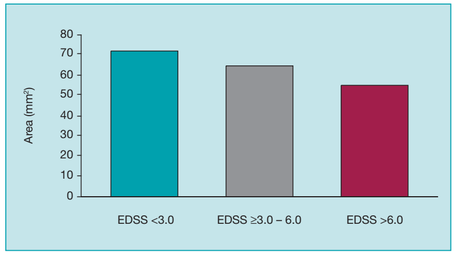
- Median normalised brain volume values were lower in patients with higher EDSS scores (Figure 5). The more disabled patients had smaller brain volumes.

Figure 5. NBV (median) in the total cohort stratified by EDSS status



- This is one of the first studies, in a multicentre setting, to use the cervical cord area at C2 as an outcome measure. For technical reasons not all centres were able to acquire images that could be analysed. A total of 81/192 (42.2%) patients were successfully scanned and evaluated. Although the magnitude of the changes were small, the results demonstrated a clear trend that increased disability is associated with smaller cord area (Figure 6).

Figure 6. Cervical C2 area (median) stratified by EDSS status



Summary

- The majority of the original study patients (88.2%) could still be located after 16 years of treatment and most (89.6%) were alive. New MRI data was obtained from 192 (75.9%) of the participating patients.
- There was a correlation between increasing T2 BOD and worsening disability, with patients having an EDSS score >6.0 having the highest median result.
- The percentage of patients with Gd-enhancing lesions was, as expected, the greatest in patients not currently being treated (>90 day since discontinuation). However, in patients who received the last dose of IFNB-1b for up to 30 days previously, the percentage of patients with Gd-enhancing scans remained decreased, suggesting a sustained treatment effect of IFNB-1b on Gd-enhancing lesions for at least 30 days.
- Patients with the greatest disability, as measured by EDSS score, had the largest area of T1 hypointense lesions (black holes).
- A trend was observed towards higher normalised brain volume values in patients with less disability.
- This was the first multicentre trial assessing cervical C2 area and the scans were obtained from a smaller group of patients than the other MRI parameters. Reduction in cervical C2 area showed a correlation with greater disability.

Conclusions

- T2 burden of disease, T1 hypointense lesions (black holes), normalised brain volume and cervical cord area correlate with increasing clinical disability as measured by EDSS.
- A sustained treatment effect of IFNB-1b was indicated by a reduced percentage of patients with Gd-enhancing lesions in patients who discontinued treatment within the last 30 days and have been on treatment for up to 16 years.
- Additional analyses are ongoing.

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