Correlation of clinical, MRI, and OCT outcomes in the 11-year follow-up from BENEFIT: BENEFIT 11

AUTHORS

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Introduction

- Approximately 85% of patients with multiple sclerosis (MS) present with a single demyelinating episode known as a clinically isolated syndrome (CIS)[1]
  - Disease-modifying therapies (DMTs) for patients with CIS may delay conversion to clinically definite MS (CDMS) and improve clinical outcomes[2-4]
- Patients with CIS who had early treatment with interferon beta-1b in the BENEFIT trial maintained an overall favorable disease course, with some clinical differences that favored treatment start at CIS, including lower annualized relapse rate (ARR), higher Paced Auditory Serial Addition Task (PASAT) score, and longer time to CDMS[5]
  - The 11-year follow-up from this trial provides an opportunity to assess the relationship between long-term clinical outcomes and structural assessments by magnetic resonance imaging (MRI) and optical coherence tomography (OCT)
- The objective of this analysis was to assess correlations between clinical, MRI, and OCT outcomes over 11 years

Methods

- Patients with CIS who had ≥2 clinically silent brain lesions on MRI were randomized to interferon beta-1b 250 µg (early treatment) or placebo (delayed treatment) subcutaneously every other day
  - Patients remained on placebo until conversion to CDMS or for 2 years, whichever occurred first
- 11 years after initial randomization, all patients were approached to undergo cross-sectional follow-up that included clinical, MRI, and OCT assessment
  - Cross-sectional MRI was conducted using blinded central reading of 1.5 or 3-T scans for assessments including (but not limited to) number and volume of T1, T2, and gadolinium-enhancing (Gd+) lesions, cortical thickness and number of cortical lesions, normalized thalamic volume, normalized brain volume, and mean upper cervical cord area (MUCCA)
  - OCT analysis was conducted at those sites with Heidelberg SPECTRALIS® OCT instruments and Nsite® Analytics™ for SPECTRALIS®
    - Readings were completed by a central reading site
    - Assessments included peripapillary global retinal nerve fiber layer (G-RNFL) thickness, total macular volume (TMV), macular ganglion cell inner plexiform layer (GCIP) thickness, and papillomacular bundle-retinal nerve fiber layer (PMB-RNFL) thickness
- Correlations of clinical parameters with MRI and OCT at Year 11 were assessed with Kendall's tau or Spearman's rank coefficients
  - Clinical parameters included ARR, Expanded Disability Status Scale (EDSS), Kurtzke Functional Status Scale (KFSS), Multiple Sclerosis Functional Composite (MSFC), PASAT score, and Symbol-Digit Modality Test (SDMT)
  - Correlation was also assessed between mental processing speed (the sum of the *z* scores for PASAT and SDMT adjusted for education status, age, and sex) and selected MRI parameters

Results

Patient disposition

- Of the 468 patients originally randomized, 278 (71.3% of patients at participating centers) participated in BENEFIT 11
  - Early treatment: 167 patients (57.2% of the original cohort)
  - Delayed treatment: 111 patients (63.1% of the original cohort)
- Year 11 MRI (Table 1) and OCT (Table 2) assessments were conducted in 191 patients (68.7%) and 86 patients (30.9%, 2 patients missing data), respectively
  - Little difference between the early and delayed treatment groups with regard to MRI and OCT findings was noted with the exception of a difference in median (Q1-Q3) number of T1-hypointense lesions: 4.0 (1.0-11.0) in the early and 2.0 (1.0-6.0) in the delayed group
    - A negative binomial regression model adjusted for T2 hyperintense lesions at screening showed that the numerical difference in number of T1-hypointense lesions at Year 11 was driven by the imbalance in T2 lesion number at screening (risk ratio [95% CI] 1.02 [1.02, 1.03], $P < 0.0001$)

MRI correlations

- MRI correlations are shown in Table 3
- Significant positive correlations in the overall BENEFIT 11 population were observed between:
  - ARR and volume of T1 lesions ($r = 0.212$)
  - ARR and volume of T2 lesions ($r = 0.216$)
  - Expanded Disability Status Scale (EDSS) score and T1 hypointensity volume ($r = 0.281$)
  - EDSS and T2 volume ($r = 0.244$)
- Significant negative correlations in the overall BENEFIT 11 population were observed between:
  - ARR and MUCCA ($r = –0.208$)
  - EDSS and MUCCA ($r = –0.194$)
  - MSFC and T1 lesion volume ($r = –0.183$) and T2 lesion volume ($r = –0.213$)
- Mental processing speed correlated negatively with number of T1 lesions ($r = –0.176$) (Table 4)

OCT correlations

- OCT correlations are shown in Table 5
- Significant positive correlations in the BENEFIT 11 population were observed between:
  - PASAT and minimum G-RNFL thickness ($r = 0.271$)
- Significant negative correlations in the BENEFIT 11 population were observed between:
  - ARR and minimum G-RNFL thickness ($r = –0.233$) and PMB-RNFL thickness ($r = –0.239$)
  - T1 lesion volume and minimum G-RNFL thickness ($r = –0.255$) and PMB-RNFL ($r = –0.340$)
  - T2 lesion volume and G-RNFL ($r = –0.307$) and PMB-RNFL ($r = –0.392$)
- No significant correlations were found between OCT parameters and EDSS, KFSS, MSFC, SDMT, normalized brain volume, mean cortical thickness, normalized thalamic volume, or visual acuity (either eye)

Table 1. MRI assessments at Year 11

	Early treatment		Delayed treatment		Total BENEFIT 11 population	
	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)
Hypointense lesions on T1, n	7.1 (8.9)	4.0 (1.0-11.0)	4.7 (6.6)	2.0 (1.0-6.0)	6.2 (8.2)	3.0 (1.0-9.0)
Volume of hypointense T1 lesions, mm³	1044.8 (2294.8)	234.5 (34.0-1042.5)	470.9 (742.5)	189.0 (30.0-566.0)	814.7 (1855.1)	215.0 (31.0-887.0)
New lesions on T2, n[a]	6.0 (11.4)	2.0 (0.0-6.0)	4.9 (8.0)	2.0 (0.0-6.5)	5.6 (10.2)	2.0 (0.0-6.0)
Volume of hyperintense lesions on T2, mm³	4232.9 (5920.4)	2237.0 (618.0-5473.0)	3139.9 (4447.5)	1640.5 (911.0-3419.0)	3793.4 (5390.9)	1760.0 (775.0-4738.0)
Cortical lesions, n	3.6 (4.4)	2.0 (0.0-5.0)	3.4 (4.7)	1.5 (0.0-4.0)	3.5 (4.5)	2.0 (0.0-5.0)
Mean cortical thickness, mm	2.689 (0.360)	2.625 (2.420-2.980)	2.747 (0.390)	2.660 (2.420-3.070)	2.713 (0.373)	2.640 (2.420-2.980)
Normalized brain volume, cm³	1496.6 (135.4)	1527.0 (1444.0-1595.0)	1502.1 (114.2)	1514.0 (1429.0 -1575.5)	1498.7 (127.2)	1519.0 (1433.0-1585.0)
Normalized thalamic volume, mm³	9321.6 (1796.5)	9839.0 (8801.0-10603.5)	9097.0 (2160.0)	9613.0 (8433.0-10462.0)	9233.2 (1944.7)	9752.0 (8639.0-10477.0)
MUCCA, mm²	76.75 (8.69)	76.35 (71.30-81.10)	78.08 (9.75)	77.20 (73.30-84.50)	77.28 (9.13)	76.60 (72.00-83.00)

[a]T2 lesions new since MRI assessment at Year 5.
MRI, magnetic resonance imaging; MUCCA, mean upper cervical cord area.

Table 2. OCT assessments at Year 11 (median [Q1, Q3])

	Early treatment		Delayed treatment		Overall	
	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
G-RNFL (12°), µm	92.0 (83.0, 100.0)	95.0 (85.0, 100.0)	90.0 (82.0, 101.0)	89.0 (79.0, 101.0)	91.5 (83.0, 101.0)	93.0 (85.0, 100.0)
GCIP, µm	80.0 (72.5, 85.5)	80.0 (72.0, 86.0)	80.0 (69.0, 85.0)	78.0 (71.0, 84.0)	80.0 (71.0, 85.0)	79.5 (72.0, 85.0)
TMV, mm³	8.47 (8.07, 8.82)	8.37 (8.07, 8.75)	8.46 (7.96, 8.75)	8.37 (8.14, 8.72)	8.47 (8.03, 8.82)	8.37 (8.10, 8.75)
PMB-RNFL (12°), µm	46.0 (38.0, 50.0)	48.0 (40.0, 55.0)	47.5 (39.0, 53.0)	51.0 (37.0, 56.0)	46.5 (39.0, 51.5)	49.0 (39.5, 55.5)

G-RNFL, global retinal nerve fiber layer; GCIP, ganglion cell inner plexiform layer; OCT, optical coherence tomography; PMB-RNFL, papillomacular bundle-retinal nerve fiber layer; TMV, total macular volume.

Table 3. Correlations of MRI and clinical parameters at Year 11

	EDSS		ARR		MSFC		PASAT	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Mean cortical thickness, mm	–0.013	NS	–0.002	NS	–0.007	NS	–0.086	NS
Normalized thalamic volume, mm³	–0.129	NS	–0.125	NS	0.139	NS	0.103	NS
MUCCA, mm²	**–0.194**	**.0137**	**–0.208**	**.0083**	0.031	NS	0.049	NS
T1 lesion volume, mm³	**0.281**	**.0003**	**0.212**	**.0069**	**–0.183**	**.0267**	–0.123	NS
T2 lesion volume, mm³	**0.244**	**.0018**	**0.216**	**.0058**	**–0.213**	**.0094**	–0.149	NS

ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite; MUCCA, mean upper cervical cord area; NS, not significant; PASAT, Paced Auditory Serial Addition Task.
Statistically significant correlations are shown in **bold**.

Table 4. Correlations of MRI parameters with mental processing speed at Year 11

	Early Treatment		Delayed Treatment		Overall	
	r	*P* value	*r*	*P* value	*r*	*P* value
T1 lesion number	–0.054	NS	**–0.355**	**.0057**	**–0.176**	**.0355**
Cortical lesion number	0.017	NS	**–0.415**	**.0011**	–0.153	NS
T1 hypointense lesions volume, mm³	–0.061	NS	**–0.320**	**.0135**	–0.164	NS
Normalized brain volume, cm³	0.037	NS	0.137	NS	0.074	NS
Mean cortical thickness, mm	–0.050	NS	**0.295**	**.0233**	0.096	NS
Normalized thalamic volume, mm³	0.025	NS	0.194	NS	0.094	NS
Mean upper spinal cord area, mm²	0.125	NS	0.225	NS	0.143	NS

NS, not significant.
Statistically significant correlations are shown in **bold**.

Table 5. Correlations of OCT and clinical and MRI parameters

	GCIP		G-RNFL (12°)		PMB-RNFL (12°)		TMV	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
EDSS	–0.127	NS	–0.081	NS	–0.202	NS	–0.185	NS
MSFC	0.056	NS	0.105	NS	0.182	NS	0.202	NS
ARR	–0.159	NS	**–0.233**	**.0396**	**–0.239**	**.0347**	–0.134	NS
PASAT	0.141	NS	**0.271**	**.0197**	0.226	NS	0.219	NS
SDMT	0.083	NS	0.037	NS	0.076	NS	0.170	NS
KFSS	–0.109	NS	–0.155	NS	–0.138	NS	–0.088	NS
T1 lesion volume	–0.166	NS	**–0.255**	**.0422**	**–0.340**	**.0059**	–0.188	NS
T2 lesion volume	–0.191	NS	**–0.307**	**.0136**	**–0.392**	**.0014**	–0.176	NS
Normalized brain volume	0.085	NS	0.039	NS	0.214	NS	0.045	NS
Mean cortical thickness	0.044	NS	–0.152	NS	0.098	NS	–0.108	NS
Normalized thalamic volume	0.135	NS	0.187	NS	0.151	NS	0.090	NS
Visual acuity, right eye	0.145	NS	0.025	NS	0.142	NS	0.050	NS
Visual acuity, left eye	–0.020	NS	–0.032	NS	0.020	NS	–0.009	NS

ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; G-RNFL, global retinal nerve fiber layer; GCIP, ganglion cell inner plexiform layer; KFSS, Kurtzke Functional Status Scale; MRI, magnetic resonance imaging; MSFC, Multiple Sclerosis Functional Composite; NS, not significant; OCT, optical coherence tomography; PASAT, Paced Serial Auditory Addition Task; PMB-RNFL, papillomacular bundle-retinal nerve fiber layer; SDMT; Symbol-Digit Modality Task; TMV, total macular volume.
Statistically significant correlations are shown in **bold**.

Discussion

- Results from BENEFIT 11 confirmed the relationship between MRI measures of disease and long-term outcomes
  - Significant correlations of lesion volume with EDSS, ARR, and MSFC as well as with minimum G-RNFL and PMB-RNFL were found, while MUCCA significantly correlated with EDSS and ARR
  - All correlations identified were somewhat weak ($r < 0.4$)
  - These findings highlight the importance of monitoring MRI activity for assessing disease status
- Cognition, as measured by mental processing speed, was related to lesion number
  - Further exploration of the relationship between processing speed and MRI could be undertaken by assessing the effects of lesions in specific brain regions
- Results also indicated that patients with more active disease tended to have smaller cervical spinal cord volumes
  - This measure is thought to reflect the neurodegenerative aspects of MS and was shown to be related to measures of disease severity in a cohort of patients with RRMS[6]

Conclusion

- Long-term follow up from the BENEFIT trial confirmed the relationship between MRI metrics and disease outcomes after 11 years, particularly with regard to lesion activity and MUCCA

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- X Montalbán has received speaking honoraria and travel expenses for scientific meetings and has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Bayer, Biogen Idec, EMD, Genentech, Genzyme, Merck Serono, Neuro-Tec, Novartis, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall.
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