Magnetic Resonance Imaging Predictors of Conversion to Multiple Sclerosis in the BENEFIT Study

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Background: Several studies have confirmed the predictive value of baseline and follow-up magnetic resonance (MR) imaging variables for conversion to clinically definite multiple sclerosis (CDMS), depending on the population, follow-up duration, and treatment intervention. However, the timing of follow-up imaging and the effect of treatment intervention on the predictive value of baseline MR imaging variables require further elucidation.

Objectives: To assess the prognostic value of baseline MR imaging variables for conversion to CDMS over 3 years and whether this was affected by treatment intervention and (2) to assess the increased risk for conversion posed by dissemination in time on follow-up MR imaging.

Design: Cohort study.

Setting: Multicenter randomized clinical trial.

Patients: Four hundred sixty-eight patients with a clinically isolated syndrome who had an initial clinical demyelinating event within the past 60 days who received early treatment (3 years of interferon beta-1b) or delayed treatment (placebo first, followed by 1 year of interferon beta-1b).

Intervention: Magnetic resonance imaging.

Main Outcome Measure: Time to CDMS.

Results: The overall conversion rate to CDMS was 42%. Barkhof criteria with the strongest prognostic value were the presence at baseline of at least 9 T2-weighted lesions (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.15-2.33; P = .006) and at least 3 periventricular lesions (1.66; 1.14-2.41; P = .009). No specific advantage was noted in using a fixed cutoff of at least 3 Barkhof criteria (HR, 1.31; 95% CI, 0.95-1.79; P = .10). The prognostic value of all MR imaging criteria was unaffected by treatment intervention (P ≥ .20 for all). Dissemination in time resulted in increased risk for CDMS only in patients without dissemination in space at baseline and was most informative at the 9-month MR imaging (HR, 2.72; 95% CI, 1.26-5.87; P = .01).

Conclusions: The modified Barkhof criteria showed moderate predictive value for conversion to CDMS, although all patients had received interferon beta-1b therapy for at least 1 year. The predictive value was unaffected by treatment intervention. Follow-up MR imaging was most informative after 9 months in patients without dissemination in space at baseline.


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further elucidation. In 2001, the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study was started, in which 468 patients with a CIS were initially randomized to interferon beta-1b therapy or placebo. The objectives of the present study were (1) to assess the prognostic value of baseline MR imaging variables for conversion to CDMS over 3 years and whether this was affected by treatment intervention and (2) to assess the increased risk for conversion posed by dissemination in time (DIT) on follow-up MR imaging.

METHODS

PATIENTS AND MR IMAGING ACQUISITION

The BENEFIT study was a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, described in more detail by Kappos et al. Briefly, 468 patients aged 18 to 45 years having an initial clinical demyelinating event within the past 60 days were randomized to interferon beta-1b (250 µg subcutaneously every other day) (n=292) therapy or to placebo (n=176) until CDMS was diagnosed or they had been followed up for 24 months. In total, 209 patients (71.6%) in the treatment group and 123 patients (69.9%) in the placebo group received corticosteroid treatment for the initial clinical event. The double-blind study period was extended by an open-label follow-up study in which all patients were offered interferon beta-1b therapy for at least 3 additional years. In total, 418 patients (261 receiving interferon beta-1b and 157 receiving placebo) entered the follow-up study, as 31 patients receiving interferon beta-1b (4 of whom had reached CDMS) and 19 patients receiving placebo (2 of whom had reached CDMS) had dropped out. In the present study, we report the integrated 3-year data for patients who received delayed treatment (placebo first, followed by interferon beta-1b after converting to CDMS or completing 24 months of follow-up) or early treatment (interferon beta-1b for 3 years from the start of the double-blind study).

Magnetic resonance imaging criteria for study entry were at least 2 clinically silent lesions of at least 3 mm on T2-weighted images, at least 1 of which was ovoid, periventricular, or infratentorial. The main outcome measure was time to CDMS, defined as a validated second clinical demyelinating event or as progression of at least 1.5 points on the Expanded Disability Status Scale.

Baseline MR images were obtained as part of the prestudy screening using an oblique axial acquisition plane and gadolinium diethylenetriamine pentaacetic acid (0.1 mmol/kg of body weight) as a contrast agent. The MR imaging protocol included a T1-weighted spin echo before and after contrast administration with repetition times of 400 to 700 milliseconds and echo times of 5 to 25 milliseconds, in addition to a dual-echo T2-weighted spin echo with repetition times of 2000 to 3000 milliseconds and echo times of 20 to 40 milliseconds (first echo) and 60 to 100 milliseconds (second echo). The field of view for all examinations was 25 cm with a 256 × 256-pixel matrix, resulting in a pixel size of roughly 1 × 1 mm². Images were acquired in 2 interleaved sets with a 3-mm gap, resulting in whole-brain coverage with contiguous 3-mm-thick sections.

IMAGE ANALYSIS

Images were centrally evaluated by the Image Analysis Center, Amsterdam, the Netherlands, by raters blinded to treatment allocation. Gadolinium-enhancing lesions were identified according to criteria described by Barkhof et al. Hypointense T1-weighted lesions (black holes) were identified after contrast administration according to criteria derived by van Walderveen et al. and hyperintense T2-weighted lesions were identified using short- and long-echo T2-weighted images according to the criteria described by Barkhof et al. Supratentorial T2-weighted lesions were subclassified as periventricular lesions (in direct contact with the ventricular system), juxtacortical lesions (directly abutting the cortical gray matter), or deep white matter lesions (in neither of the other 2 subclasses). Infratentorial lesions comprised lesions in the brainstem and cerebellum.

STATISTICAL ANALYSIS

Descriptive statistics (number and percentage) of patients fulfilling specific baseline MR imaging variables were calculated for each treatment arm. For time to CDMS, Kaplan-Meier estimates were calculated beginning at study randomization, and corresponding survival curves were plotted. For patients who converted to CDMS within 1080 days, the number and proportion (Kaplan-Meier estimates) were calculated for all dichotomized baseline MR imaging variables, including the cumulative number of positive criteria and the modified Barkhof criteria (≥1 gadolinium-enhancing lesions or ≥9 T2-weighted lesions, ≥1 infratentorial lesions, ≥1 juxtacortical lesions, and ≥3 periventricular lesions). Cox proportional hazards regression models for all patients were used to assess the effect of each baseline MR imaging variable on time to CDMS (adjusted for age, sex, treatment intervention, corticosteroid use, clinical presentation [optic neuritis vs other], and disease onset type [monofocal vs multifocal as described by Uitdehaag et al]) by calculating the hazard ratios (HRs) (95% confidence intervals [CIs]) and corresponding P values. Possible interactions with treatment regimen (early vs delayed) and disease onset type (monofocal vs multifocal) were explored using Cox proportional hazards models (adjusted for treatment intervention, disease onset type, and MR imaging by specific interaction term). Furthermore, Cox proportional hazards models were applied to evaluate the increased risk for conversion to CDMS among patients developing new lesions by 3, 6, and 9 months (all compared with baseline MR images) and were stratified for patients with and without dissemination in space (DIS) at baseline. The presence of at least 1 new lesion on follow-up MR imaging is referred to as DIT. In general, \( P < .05 \) was considered statistically significant; however, because all statistical analyses were exploratory in nature, \( P \) values were not corrected for multiple testing and should be interpreted descriptively. All statistical calculations were performed using commercially available software (SAS version 9.1.3; SAS Institute Inc, Cary, North Carolina; or SPSS version 12.0; SPSS Inc, Chicago, Illinois).

BASELINE MR IMAGING CHARACTERISTICS

At baseline, 64.3% of all patients had DIS (≥3 Barkhof criteria). These results are summarized in Table 1.

PREDICTIVE VALUE OF BASELINE MR IMAGING VARIABLES FOR CONVERSION TO CDMS

After 3 years, the overall conversion rate to CDMS was 42% (51% for patients receiving delayed treatment and 37% for patients receiving early treatment). Table 2 gives
the number and percentage of patients converting to CDMS per baseline MR imaging characteristic. Strong Barkhof criteria predictors of conversion to CDMS were the presence at baseline of at least 9 T2-weighted lesions (46% vs 31% without; HR, 1.64; 95% CI, 1.15-2.33; P = .006) and at least 1 gadolinium-enhancing lesion (48% vs 37% without; HR, 1.56; 1.15-2.10; P = .004). The predictive value of gadolinium-enhancing lesions in-
Table 3. Conversion to Clinically Definite Multiple Sclerosis (CDMS) After 3 Years by Number of Barkhof Criteria

<table>
<thead>
<tr>
<th>No. of Barkhof Criteria</th>
<th>Delayed Treatment (n=176)</th>
<th>Early Treatment (n=292)</th>
<th>Overall (N=468)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>30 (49)</td>
<td>27 (29)</td>
<td>57 (37)</td>
<td>1.31 (0.95-1.79)</td>
<td>.10</td>
</tr>
<tr>
<td>≥3</td>
<td>55 (51)</td>
<td>72 (29)</td>
<td>127 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>54 (48)</td>
<td>54 (33)</td>
<td>108 (39)</td>
<td>1.32 (0.97-1.78)</td>
<td>.08</td>
</tr>
<tr>
<td>≥4</td>
<td>31 (56)</td>
<td>45 (43)</td>
<td>76 (48)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kaplan-Meier estimates at 1080 days.
Hazard ratios (95% confidence intervals) and P values were calculated using Cox proportional hazards regression models (adjusted for age, sex, corticosteroid use, treatment intervention, clinical presentation [optic neuritis vs other], disease onset type [monofocal vs multifocal], and the specific MR imaging variable in the model).

In patients with DIS on MR imaging at baseline (and without CDMS at the time of follow-up MR imaging), DIT on MR imaging was not associated with increased risk of conversion to CDMS regardless of the timing of follow-up MR imaging (P > .18 for all) (Table 4). In patients without DIS on MR imaging at baseline, DIT on MR imaging was associated with increased risk of conversion to CDMS at the 9-month MR imaging (HR, 2.72; 95% CI, 1.26-5.87; P = .01) (Figure 2) and at the 6-month MR imaging (2.24; 1.34-4.42; P = .02) but not at the 3-month MR imaging (1.25; 0.69-2.25; P = .46).

IS THE PROGNOSTIC VALUE OF BASELINE MR IMAGING VARIABLES FOR CONVERSION TO CDMS AFFECTED BY TREATMENT INTERVENTION OR DISEASE ONSET TYPE?

The predictive value of all baseline MR imaging variables for conversion to CDMS was unaffected by disease onset type (P ≥ .24 for all). Similarly, it was unaffected by treatment intervention (P ≥ .20 for all).

COMMENT

In this study, we examined data from a large clinical trial (the BENEFIT study) to evaluate the predictive value of baseline and follow-up MR imaging variables in patients with a CIS. This had certain advantages. First, the population of patients with a CIS studied is one of the largest so far (N = 468) and was recruited from 98 centers worldwide. Second, the MR imaging protocol comprised standardized acquisition variables, which, combined with centralized analysis, prevented center bias in interpretation of the MR imaging data. Third, consider-
the use of 5-mm-thick MR imaging sequences in previous clinical trials, the 3-mm thickness used in this study allowed for ample detection of MS lesions in the brain, as lesion detection increases with decreasing section thickness. It is important to consider the design of the BENEFIT study when comparing the results of our study with those of other large patient cohorts having a CIS. The trial started with a double-blind phase of 2 years in which all patients were randomized to placebo or treatment, followed by an open-label phase in which all patients were offered interferon beta-1b therapy. Our study reports the integrated 3-year data, meaning that all patients received at least 1 year of open-label treatment. This likely lowered the overall conversion rates to the clinical end point (CDMS) and to the radiologic end point (McDonald criteria for MS), as interferon beta-1b exerts an inhibitory effect on the occurrence of a second clinical demyelinating event and on the formation of new lesions. An overall lower event rate will lead to a lower predictive value for any prognostic variable studied.

### Table 4. Conversion to Clinically Definite Multiple Sclerosis (CDMS) After 3 Years Among Patients Having New Lesions Observed at the 3-, 6-, and 9-Month Magnetic Resonance (MR) Imaging With or Without Dissemination in Space (DIS) at Baseline

<table>
<thead>
<tr>
<th>Timing Follow-up MR Imaging</th>
<th>DIS at Baseline</th>
<th>New Lesion</th>
<th>Patients Converting to CDMS, %</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>Yes</td>
<td>Yes (n=126)</td>
<td>46</td>
<td>1.19 (0.80-1.78)</td>
<td>.39</td>
</tr>
<tr>
<td>(n=420)</td>
<td>No</td>
<td>No (n=139)</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No (n=50)</td>
<td>43</td>
<td>1.25 (0.69-2.25)</td>
<td>.46</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No (n=105)</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>Yes</td>
<td>Yes (n=158)</td>
<td>42</td>
<td>1.43 (0.85-2.40)</td>
<td>.18</td>
</tr>
<tr>
<td>(n=385)</td>
<td>No</td>
<td>No (n=85)</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No (n=61)</td>
<td>43</td>
<td>2.24 (1.34-4.42)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No (n=81)</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 9</td>
<td>Yes</td>
<td>Yes (n=157)</td>
<td>36</td>
<td>1.10 (0.64-1.89)</td>
<td>.72</td>
</tr>
<tr>
<td>(n=367)</td>
<td>No</td>
<td>No (n=73)</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No (n=68)</td>
<td>39</td>
<td>2.72 (1.26-5.87)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No (n=69)</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* a Magnetic resonance imaging showing at least 1 new T2-weighted or gadolinium-enhancing lesions by the respective visit compared with the baseline MR image. The number of patients (n) refers to the subpopulation of patients without CDMS at the respective time point.

b Kaplan-Meier estimates at 1080 days.

c Hazard ratios (95% confidence intervals) and P values were calculated using Cox proportional hazards regression models (adjusted for age, sex, corticosteroid use, treatment intervention, clinical presentation [optic neuritis vs other], disease onset type [monofocal vs multifocal], and the specific MR imaging variable in the model).

#### Figure 2.
Dissemination in time (DIT) at the 9-month (M9) magnetic resonance imaging was associated with increased risk for conversion to clinically definite multiple sclerosis (CDMS) in patients without dissemination in space (DIS) at baseline (left panel). In patients with DIS at baseline, DIT was not associated with increased risk for conversion to CDMS (right panel).
Scleroderma Study (ETOMS). However, we found no significant increased risk associated with the presence of 1 or more infratentorial lesions, nor was there any specific advantage in using a fixed cutoff of at least 3 Barkhof criteria. In accord with the CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study) data set, the presence of at least 2 gadolinium-enhancing lesions was a strong predictor of conversion to CDMS, although the predictive value was less distinct than that of the presence of at least 1 gadolinium-enhancing lesion. These conflicting results might be explained by the different trial designs, particularly the variations in inclusion criteria or population studied, treatment regimen, and follow-up duration. Furthermore, the present study used Cox proportional hazards models (with age, treatment intervention, and corticosteroid use as significant covariates in all models), while other analyses did not use covariate adjustment (eg, in the ETOMS data set). The BENEFIT data HRs were 1.31 (95% CI, 0.93-1.79; *P* = .10) for at least 3 Barkhof criteria and 1.32 (0.97-1.78; *P* = .08) for at least 4 Barkhof criteria. Analysis with the same statistical method as that used in the ETOMS data set over 2 years of follow-up results in substantially different HRs and *P* values, namely, 1.37 (95% CI, 0.97-1.94; *P* = .08) for at least 3 Barkhof criteria and 1.48 (1.08-2.04; *P* = .02) for at least 4 Barkhof criteria, showing a significant result for the latter. This indicates that covariate adjustment can have a substantial effect on the results of the statistical analyses.

Dissemination in time was associated with a significantly increased risk for conversion to CDMS only in patients without DIS at baseline (Figure 2). This suggests that follow-up MR imaging is most informative in patients without DIS at baseline and is less so in patients with DIS at baseline. This might be reflective of the interrelationship between DIS, DIT, and CDMS (ie, patients with DIS at baseline already have a higher risk of conversion to CDMS than patients without DIS, and the additional risk of new lesions on follow-up MR imaging might be lower). Clinical variables might influence this interrelation, although in this study both clinical presentation (optic neuritis vs other) and disease onset type (monofocal vs multifocal) showed no effect on time to CDMS. Furthermore, in patients without DIS (and without CDMS up to the respective time point), follow-up MR imaging to determine DIT was associated with increased risk for CDMS, most notably at the 9-month MR imaging and at the 6-month MR imaging but not at the 3-month MR imaging. Based on these data, follow-up MR imaging to determine DIT might best be performed after 9 months in patients without DIS at baseline; however, these results were not corrected for multiple comparisons and should be interpreted descriptively.

We also analyzed whether the predictive value of baseline MR imaging variables was affected by treatment regimen (early treatment vs delayed treatment) by calculating treatment intervention × MR imaging variable interaction. For conversion to CDMS, no variables were statistically significant, indicating that the predictive power of baseline MR imaging variables was unaffected by early treatment. As such, our data are consistent with results from the ETOMS data set, which also reported a lack of power among all MR imaging variables in predicting treatment response. Alternatively, treatment interactions can be interpreted as measures to identify which MR imaging variables predict treatment response (ie, which patients will benefit the most from early treatment). For conversion according to the McDonald criteria for MS, the predictive value of 4 Barkhof criteria was affected by treatment intervention, indicating that this MR imaging measure predicted treatment response.

Our study had several potential limitations. First, patients in our population may not be representative of those seen in daily practice, as only patients with abnormal brain MR images were included, and other neurologic diseases were ruled out by appropriate tests such as cerebrospinal fluid (CSF) analysis or laboratory measures. This is reflected by a slightly higher overall conversion rate to CDMS of 42% over 36 months compared with an overall conversion rate of 32.5% after 85.3 months in a large (N = 532) population of patients with a CIS at a less restricted referral center. Second, we did not investigate the full range of options in the McDonald criteria to ascertain DIS (eg, we did not investigate the combination of positive CSF status and 2 lesions on brain MR imaging). Furthermore, we did not include spinal cord MR imaging, although a recent study showed that (compared with brain MR imaging only) the increased value of spinal cord imaging might be limited, adding only 1% to the sensitivity and specificity of the 2001 McDonald criteria to predict CDMS. Third, we used the more conservative 2001 McDonald criteria because the BENEFIT study was initiated in 2001 rather than the revised 2005 criteria. However, the criteria for lesions on brain MR imaging were unchanged; hence, application of the 2005 revisions would not have altered the results of the present study.

Since introduction of the McDonald criteria in 2001, the diagnosis of MS in patients with a CIS has been made largely on radiologic grounds. New imaging techniques that cross sectionally and longitudinally detect more MS lesions in the brain will unequivocally have an effect on the number of patients fulfilling DIS and DIT criteria, respectively. Recent studies have shown increased detection of MS lesions in various parts of the brain using 3-dimensional (single-slab) sequences and higher field strength (3.0 T). Moreover, specific image contrasts such as double inversion recovery and (phase-sensitive) T1-weighted imaging are more sensitive than conventional methods in visualizing intracortical lesions. Furthermore, image subtraction has been shown to significantly increase the detection of new T2-weighted lesions versus standard comparison of nonregistered images. Future work should examine the precise effects of new imaging sequences, contrasts, and hardware on the predictive value of MR imaging for conversion to CDMS.

In conclusion, MR imaging predictors of conversion to CDMS were assessed in a large population (N = 468) of patients having a CIS with abnormalities on brain MR imaging. In general, the percentage of patients converting to CDMS was higher in the presence (compared with the absence) of all baseline MR imaging variables. In particular, the modified Barkhof criteria showed moderate predictive value for conversion to CDMS, although all
patients were treated for at least 1 year with interferon beta-1b. The predictive value of MR imaging variables was unaffected by treatment intervention. Follow-up MR imaging to determine DIT was most informative after 9 months in patients without DIS at baseline.

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Additional Information: The online-only eAppendix and Table are available at http://www.archneurol.com.

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