Vitamin D and the Development and Evolution of Permanent Black Holes Among Patients with Clinically Isolated Syndrome

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Abstract

Objective: To assess the relationship between vitamin D [25(OH)D] and irreversible brain tissue damage characterized by the occurrence of persistent T1- hypointensities (permanent black holes [PBHs]) in patients with clinically isolated syndrome (CIS) who were followed for 5 years.

Methods: BENEFIT was a randomized trial comparing early versus delayed interferon beta-1b (INFB-1b) treatment in patients with a first event suggestive of MS (CIS). Serum 25(OH)D concentrations were measured at baseline, 6, 12, and 24 months. 465 of the 468 patients had at least one 25(OH)D measurement and had lesion follow-up for at least 1 year. We calculated a season-adjusted 25(OH)D and estimated the association between the time-dependent cumulative average of 25(OH)D and the number of new PBHs after 6 months. We modeled lesion counts using negative binomial models and logistic regression models to assess the proportion of lesions evolving into PBHs accounting for intra-patient correlation using generalized estimating equations. We also assessed the association between 25(OH)D and number of lesions of a specific type at initial presentation (nodular Gadolinium [Gd]-enhancement, ring-like Gd-enhancement, T1-isointense, T2 lesions or T1-hypointense lesions). Analyses were adjusted for age, sex, treatment, baseline T2 lesions, and CIS onset type.

Results: A total of 3789 new lesions developed over the 5 year follow-up period with 383 developing into PBHs (10%). Average 25(OH)D levels were significantly inversely correlated with the number of PBHs from the 6-month to five-year MRI; patients with serum 25(OH)D levels $\geq$50 nmol/L experienced a 55% lower absolute rate of PBHs (95% CI: 0.29 to 0.71; P=0.006) than those $<$50 nmol/L. We also observed a marginal association between serum 25(OH)D and the proportion of T2 lesions evolving into PBHs (0.71; 95% CI: 0.50 to 1.01; P=0.056, comparing patients with $\geq$50 nmol/L vs those ¡50 nmol/L).

Conclusions: Our results that higher levels of 25(OH)D were associated with lesser accumulation of irreversible brain tissue damage support the importance of adequate vitamin D status in delaying MS progression.

Background

- Several previous studies have suggested vitamin D is strongly associated with lower rates of multiple sclerosis (MS) activity characterized by the development of fewer T2 lesions or Gd-enhancing lesion or overall T2 lesion burden.
- However, results for vitamin D on global neurodegenerative processes reflected by grey and white matter volume loss or increases in clinical disability in MS are more variable.
- Persistent T1 hypointense lesions (persistent black holes (PBHs) represent an additional measure to characterize neurodegeneration as PBHs are more strongly associated with clinical disability and brain volume loss than Gd-enhancing or T2 lesions.

Objective

To characterize the role of vitamin D [25(OH)D] and irreversible brain tissue damage characterized by the occurrence and evolution of PBHs in patients with clinically isolated syndrome (CIS).

Specifically, we hypothesized that higher levels of 25(OH)D were associated with

- fewer overall PBH lesions
- lesser conversion of T2 lesions or Gd-enhancing lesions into PBHs

Methods

Study Population: The Beteferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) was a randomized trial designed to assess early versus late initiation of interferon beta-1b in patients with clinically isolated syndrome (CIS). Eligible patients presented with a first episode of neurologic dysfunction highly indicative of MS and at least 2 clinically silent lesions on magnetic resonance imaging (MRI) and were randomized INFB-1b (n=292) or placebo (n=176) followed by INFB-1b at MS conversion. Patients were then subsequently followed in a preplanned prospective study for up to 5 years.

Measurements of 25(OH)D: Samples collected at baseline, 6 month, 12 month and 24 months. Individuals with at least two measurements of 25 (OH)D were included in the study – 417 patients had at least 2 samples, 396 had at least 3 and 303 provided all 4 samples. Serum 25(OH)D was measured using enzyme-linked immunosorbent assay. We season-adjusted 25(OH)D values to remove extraneous seasonal variation and to obtain an estimate of an individual's long term vitamin D status.

Assessment of PBHs: MRI scans were performed at baseline and at three, six, nine, 12 months and annually thereafter. Following the baseline measurement, new Gd-enhancing lesions and new T2 lesions were classified by mutually exclusive subtypes (nodular Gd-enhancement on enhanced T1-weighted images; ring-like Gd-enhancement on enhanced T1-weighted images; isointense-T2 lesion on enhanced T1-weighted images or hypointense T2 lesion on T1-weighted images). We defined a lesion as T1 hypointense if the signal intensity was $\leq$ neighboring grey matter and considered a lesion to be a PBH if the hypointensity was confirmed at the last available scan (where each potential hypointensity needed to be observed for a period of at least 1 year).

Statistical Analysis: Following season-adjustment, we modeled 25(OH)D using a time-dependent cumulative average, updating 25(OH)D using the 6, 12 and 24 month measurements to assess the association between 25(OH)D and the number of new PBHs that developed after the 6 month MRI assessment. We considered 25(OH)D as a continuous (per 50 nmol/L) and categoricial (using $<$50nmol/L or $\geq$50 nmol/L) measurements. We modeled lesion counts using negative binomial models and logistic regression models to assess the proportion of lesions evolving into PBHs and accounted for intra-patient correlation using generalized estimating equations. We also assessed the association between 25(OH)D and number of lesions of mutually exclusive subtypes at initial presentation, locations and sizes and adjusted analyses for age, sex, treatment, baseline T2 lesions, and CIS onset type.

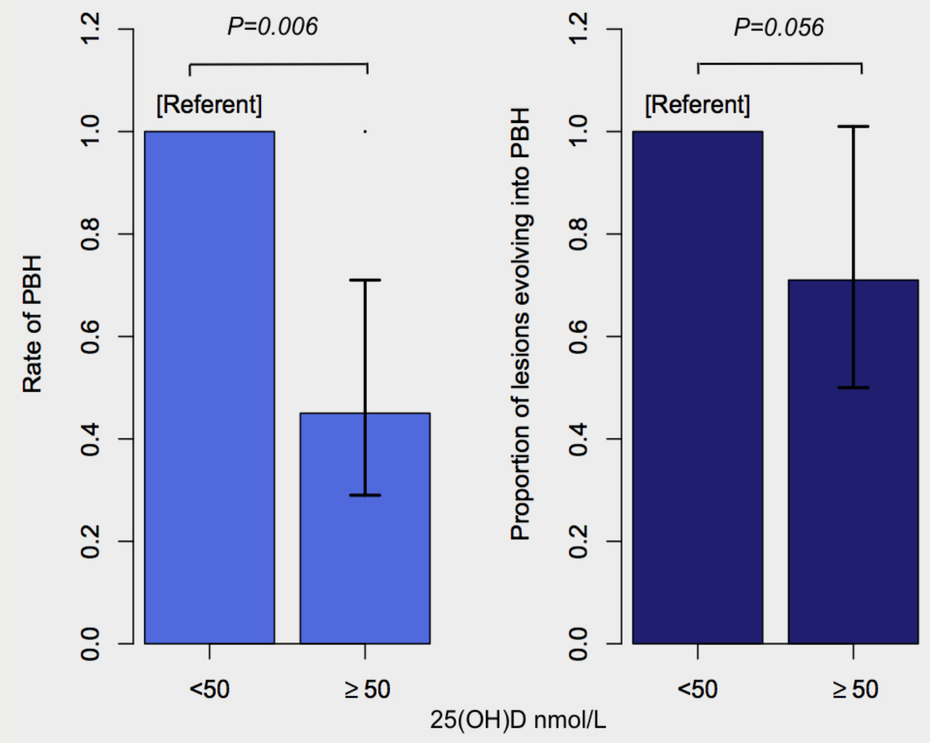
Results

Table 1: Baseline Characteristics across categories of 25(OH)D.

Characteristic	25(OH)D level $<$50nmol/L	25(OH)D level $\geq$50nmol/L
25(OH)D, nmol/L	38.4	63.8
Age, years	31.6	30.2
Female, %	71	67
EDSS	1.5	1.5
BMI, kg/m^2	24.9	23.8
Monofocal onset, %	48.1	48.6
No. of T2 Lesions (median)	17.5	16
Brain Volume (centralized) cm^3	1049.6	1059.3

- Overall, between categories of 25(OH)D included patients were roughly similar with respect to age, gender, EDSS (Table 1). Patients with higher 25(OH)D levels tended to have a lower BMI and higher centralized brain volume.
- We observed generally similar associations between $\geq$50nmol/L 25(OH)D levels and specific type of lesion at presentation (for Gd-enhancing lesions with nodular presentation: 0.64; 95% CI: 0.47-0.98; for Gd-enhancing lesions with ring presentation: 0.79; 95% CI: 0.47-1.35; for new T2 lesions with T1 hypointensity: 0.54; 96% CI: 0.32-0.91; for new T2 lesions isointense on T1: 0.63; 95% CI: 0.47-0.85.

Figure 1: Association between 25(OH)D and PBH Measures Among BENEFIT Participants



- The multivariable-adjusted relative rate of PBH comparing individuals with 25(OH)D levels $\geq$50nmol/L with those with ¡50nmol/L was 0.45, 95% CI: (0.29, 0.71). Among individuals who developed lesions over follow-up, results suggested a lesser proportion of such lesions converted to PBH in individuals with higher levels of 25(OH)D levels (Figure 1; 0.71; 95% CI: (0.51-1.01).
- Results were slightly stronger between $\geq$50nmol/L 25(OH)D levels and rate of PBH among those in the early INFB-1b treatment group; however, the interaction was not significant (P=0.44; among the early treated: 0.42; 95% CI: 0.25-0.72; among the delayed treated: 0.56; 95% CI: 0.28-1.14) and using a continuous increment for 25(OH)D.

Conclusion

- Higher 25(OH)D levels were associated with a lesser accumulation of irreversible brain tissue damage characterized by a slower rate of PBH development and a marginally lower proportion of new lesions occurring that evolved into PBH.
- Our results suggest vitamin D may also contribute to preventing neurodegenerative processes in MS.

Disclosures

KC Fitzgerald; KL Munger have no disclosures.
MS Freedman has received compensation from Actelion, Bayer Healthcare, Biogen Idec, Celgene, EMD Canada, Genzyme, Glycominds, Roche, Merck Serono, Novartis, Opexa, Sanofi-Aventis, and Teva Canada Innovation for consulting services, and has received research/educational grants from Bayer HealthCare and Genzyme. He also participates in a Genzyme-sponsored speaker?s bureau.
H-P Hartung has received honoraria for consulting and speaking at symposia from Bayer Pharma AG, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Sanofi-Aventis, with approval by the rector of Heinrich-Heine University.
X Montalbn 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, Neurotec, Novartis, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall.
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D Pleimes is a salaried employee of Myelo Therapeutics GmbH. He was a salaried employee and is currently a paid consultant for Bayer Pharma AG/Bayer HealthCare Pharmaceuticals. DP owns stock in Bayer AG, the owner of Bayer Pharma AG/Bayer HealthCare Pharmaceuticals.
R Sandbrink is a salaried employee of Bayer Pharma AG/Bayer HealthCare Pharmaceuticals. RS owns stock in Bayer AG, the owner of Bayer Pharma AG/Bayer HealthCare Pharmaceuticals.
L Kappos'institution, the University Hospital Basel, has received research support and payments that were used for research support for Prof Kappos? activities as principal investigator and member or chair of planning and steering committees or advisory boards in trials sponsored by Actelion, Bayer HealthCare, Bayer Schering, Biogen Idec, BioMarin, CLC Behring, Elan, GeNeuro, Genmab, Genmark, GlaxoSmithKline, Lilly, Merck Serono, Novartis, Novo Nordisk, Peptimmune, Sanofi-Aventis, Santhera, Roche, Teva, UCB, and Wyeth, Prof Kappos has received grants from the Swiss MS Society, Swiss National Research Foundation, the European Union, Gianni Rubatto Foundation, and the Novartis and Roche research foundations.
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