Neurotherapeutics (2020) 17:968–970
https://doi.org/10.1007/s13311-020-00907-5

COMMENTARY

# The Rise and Fall of High-Dose Biotin to Treat Progressive Multiple Sclerosis

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Published online: 5 August 2020


**Key Words** Biotin · multiple sclerosis · progressive MS · MS relapse

Currently, effective treatments for patients with progressive multiple sclerosis (PMS) are an unmet need. Pivotal trials of ocrelizumab in primary progressive MS (PPMS) and siponimod in secondary progressive MS (SPMS) demonstrated efficacy, but the magnitude of benefit was modest and appeared to be predominantly in participants with recent or ongoing focal lesion activity [1, 2]. Biotin is a co-factor for four essential carboxylases expressed in oligodendrocytes and neurons. Administration of high-dose biotin (HDB) has been hypothesized to promote myelin repair and protect against virtual hypoxia-driven axonal degeneration and, as a result, might represent a novel treatment strategy for PMS [3].

A small, open-label pilot study of HDB in PMS showed clinical disability improvement measured as decrease in the Expanded Disability Status Scale (EDSS) [4]. In the randomized, double-blind, placebo-controlled MS-SPI trial, which enrolled 154 participants with PP or SP MS, 13 of 103 (12.6%) participants treated with HDB demonstrated disability reversal, measured as improved EDSS or timed 25-ft walk (T25FW) at 9 months and confirmed at 12 months, compared to 0 of 51 of participants treated with placebo [3]. HDB appeared well-tolerated and safe. An important point raised in this trial, however, was interference with certain laboratory tests in patients taking HDB. There were 11 cases of apparent hyperthyroidism (low thyroid-stimulating hormone) in patients taking HDB, which was determined to be due to biotin interference with laboratory tests that utilize biotinylated antibodies. Besides thyroid-stimulating hormone, other common tests sensitive to interfere by HDB include tests for vitamin D, creatine kinase, troponin, and prostate specific antigen [5].

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In MS-SPI, MS relapses occurred in 4.9% of participants in the HDB-treated group and 7.8% of the placebo group during the initial double-blind phase, and in 7.7% of the HDB-treated participants and 4.8% of the placebo participants in the extension phase. However, MRI scans performed at month 12 detected new lesions in 23.4% of HDB-treated participants and 13% of placebo-treated participants; 8.5% of HDB-treated participants had enlarging lesions and 4.3% had at least one gadolinium-enhancing lesion compared to no placebo-treated participants. These MRI changes were unanticipated and raised concern about potential pro-inflammatory effects of HDB.

The results of a second phase 3 trial of HDB in PMS, SPI2, recently were presented [6]. The primary endpoint of this 27-month study was proportion of participants with improvement of disability at month 12 confirmed at month 15 measured as improvement in either the EDSS or the T25FW. Secondary endpoints included time to confirmed EDSS worsening, Clinical Global Impression of Improvement, and percentage change in T25FW from baseline. There were no significant differences between the treatment groups for any of the primary or secondary endpoints. Confirmed relapses occurred in 20 of 331 (6.0%) participants treated with HDB compared to 25 of 311 (8.0%) participants treated with placebo. Annualized relapse rates (ARRs) were 0.0362 in the HDB group and 0.0478 in the placebo group. MRI results have not yet been reported.

In the current issue of *Neurotherapeutics*, Branger et al. report a prospective observational study to evaluate the risk of relapse in PMS patients taking HDB [7]. They studied a French cohort of patients enrolled in a national registry, excluding patients who had a relapse in the previous year. They followed patients after HDB initiation in the exposed group and for 103 months after progression onset in non-HDB exposed patients, as this was the mean time between progression onset and HDB initiation in the former group. This study

employed three statistical methods of analysis: a case-crossover design of patients who received HDB, and propensity score (PS) matching and inverse probability of treatment weighting (IPTW) to compare cases with controls. In the first analysis, they compared the number of relapses in the period between the onset of the progressive phase and HDB initiation to the period between HBD initiation and the last observation. For the PS matching analysis, age at progression, sex, form of PMS, and EDSS at progression were incorporated in the model, and cases were matched in a 1:1 ratio with controls. Time to relapse was compared in a survival analysis using a Cox model. Finally, an IPTW analysis using a Cox model was used to compare the time to relapse in the cohorts.

The study included 42 patients who received HDB and 440 controls. Overall, 26.2% of HDB-treated patients had relapses. In the case-crossover analysis of HDB-treated patients, ARR was $0.04 \pm 0.08$ prior to treatment and $0.39 \pm 0.77$ after HDB initiation—incident rate ratio 7.4 using a Poisson regression model ($p < 0.0001$). In the PS matching analysis, the risk of having a relapse was significantly higher in the HDB group compared to the control group (hazard ratio 4.3, $p = 0.01$), as well as in the IPTW analysis (hazard ratio 5.1, $p < 0.0001$). One weakness of this study was that the PS matching did not include the duration of the progressive phase, time since the last relapse, disease-modifying therapy status, or MRI data. Additionally, MRI, which would be expected to be more sensitive to focal lesion activity compared to clinical relapses, was not included as an outcome.

A possible association of increased disease activity with HDB use has been explored since the MRI results of the initial SPI trial were reported [8]. The results of the study of Branger et al. are in line with some but not all other reports. A case report published in 2020 describes a patient with PPMS who exhibited worsening disability with MRI showing a large, contrast-enhancing lesion 16 months after initiating HDB therapy [9]. An Italian group reported a cohort of 41 patients with PMS treated HDB for a mean duration of 13.7 months [10]. They found that ARR in the year prior to HDB treatment was 0.10 and increased to 0.27 while on treatment [10]. This study included 2 patients with no history of relapses previously. In addition to 3 patients experiencing a clinical relapse, they reported 4 patients with asymptomatic MRI activity. A French group reported a cohort of 107 patients with PMS who had been relapse-free for 5 years prior to starting HDB [11]. They found that 5 (4.7%) patients had a clinical relapse as well as active MRIs within 8–11 months after treatment initiation. Not all studies have reported increased relapses with HDB. Another French cohort study that also used PS matching and IPTW found no increased relapse rates in HDB-treated patients ($n = 2628$) compared to controls ($n = 654$) [12]. Also, as noted above, no increase in relapses was seen in the SPI2 study [6].

The mechanism by which HDB might increase MS disease activity is unclear. It has been hypothesized that it competes with the metabolism or transport of B vitamins, including riboflavin, which are involved in cellular functioning [9]. Interestingly, there is a case report of a participant in the SPI trial who 5 months after initiating HDB developed myopathy and dropped head syndrome. She had extensive workup revealing severe lipid storage suggesting a metabolic myopathy [13]. Dropped head syndrome has been associated with riboflavin transporter defects, which may be caused by the HDB competing with its metabolism and transport [13]. HDB was held, and she improved over 6 months.

Thus, whether HDB is efficacious in PMS and/or whether it causes relapses is uncertain at this time. Both issues are clinically relevant. Many centers, including our own, have treated a sizable number of patients with HDB because it was considered to be low risk and potentially beneficial for patients with few therapeutic options. Reviewing electronic medical record data from our comprehensive MS clinic, 350 patients with a diagnosis of MS were prescribed HDB from August 2016 to June 2020. Considering the negative results of the SPI2 trial, along with at least some studies reporting increased risk of relapse or increased MRI activity, our clinical practice will likely shift away from routine use of HDB. This is unfortunate given the lack of robustly effective treatment options for PMS that slow progression and/or reverse disability. We look forward to the results of ongoing studies of several novel strategies.

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

**Funding Information** CH Goldschmidt is supported by Sylvia Lawry Physician Fellowship Award FP-1807-31728 from the National Multiple Sclerosis Society.

## Compliance with Ethical Standards

**Disclosures** CH Goldschmidt reports no disclosures. JA Cohen reports personal compensation for consulting for Adamas, Atara, Bristol-Myers Squibb, Convelo, MedDay, and Mylan, and serving as an Editor of *Multiple Sclerosis Journal.*

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