

Biotin in progressive multiple sclerosis – a new lead?

To reverse progressive multiple sclerosis (MS) would be an extraordinary claim. The current global effort, exemplified by the Progressive MS Alliance,¹ would be delighted by news of any interventions that truly delay progression. Indeed, the dawn may finally be breaking, with chinks of light radiating from reports of ocrelizumab in primary progressive MS (PPMS)² or siponimod in secondary progressive MS (SPMS).³ These drugs, given over 2-3 years, delayed the confirmed progression of MS by about 20-25%. These are in stark contrast to the long list of failed attempts over the last 25 years which have been so sadly archived.⁴

Yet, the report in this edition of MSJ contains exactly that claim.⁵ Reversal of progression in progressive MS, by high dose biotin (300mg/day). The readers would expect careful scrutiny.

So why biotin? It has acquired a number of names of the years: vitamin H, B7 and coenzyme R. Leafing through biochemistry books, it is water soluble and composed of a ureido (tetrahydroimidizalone) ring fused with a tetrahydrothiophene ring (C₁₀H₁₆N₂O₃S₁). Foods with relatively high biotin content include peanuts, leafy green vegetables and liver. It is a cofactor for four carboxylases: acetyl-CoA carboxylase, pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase, and propionyl-CoA carboxylase. Deficiency symptoms include hair loss and dermatitis. Rare biotin-dependent genetic multiple carboxylase defects can occur, characterised by seizures and myoclonus accompanied by immune defects. So why the role in MS? The authors postulate that biotin may be activating these carboxylases to enhance fatty acid synthesis and support myelin repair and/or enhancing neuronal energy production to protect against hypoxia-driven axonal degeneration. How did they come to find biotin? In an earlier open pilot study of 23 patients, treated for variable lengths of time, they report improvement, including reductions in the Expanded Disability Status Scale (EDSS). It seemed a plausible lead to follow.

The next step is to examine the trial structure in detail. A standard plan in progressive MS might be to assume a phase 2 MRI marker of disease progression, such as whole brain atrophy changing by 0.5%/year over 2 years; or in phase 3, clinical progression by 35-45% over 3 years. These constructs would yield 2-arm trial cohort sizes of c150 or 1000 respectively. In this trial (n=154, in a 2:1 randomisation ratio), and on the basis of their original work, the authors inverted this and looked for proportions *improved* over 9 months, which are confirmed 3 months later.

What is an event? The definitions are: improvement in EDSS of ≥ 0.5 or ≥ 1.0 depending on the base level (6.0-7.0 or 4.5-5.5) or a $\geq 20\%$ decrease in timed 25-foot walk (T25FW). How is the trial powered? The assumption, from initial work is that 40% of biotin patients will improve and 10% on placebo. The key patients contributing to the primary endpoint are listed in their table 2. This is the meat of the paper and it is worth spending some time analysing it in detail. There is some discontinuity, with only 2 patients being concordant with an improvement both in EDSS and T25FW; 8 are solely due to EDSS improvement, leaving 3 with walking gains alone. All are on biotin, none are placebo. In terms of the magnitude of the EDSS change in the high ranges, 4 patients required an entry score of 6.5 to improve to at least 6.0, which of course is a major step over a 9+3 month trial – changing from walking 20m with 2 sticks, to 100m with 1 stick. The readers might be concerned by the lack of third party assessment. However, to move back from 6.5 to 6.0 would be extraordinary, though highly welcome, could this be a symptomatic effect? Figure 3 shows that the improvement tends to come early, at about 3 months, perhaps supporting this thesis.

Does the trial contain any possible confounders apart from the lack of independent assessors? By chance, the arms are not balanced in terms of the disability subgroups. In the lower range EDSS 4.5-5.5, potentially the easier to improve or the most fluctuant, the active:placebo ratio was 27%:14%. Or vice versa: 6.0-7.0, i.e., the hardest to improve, the proportions were 73% versus 86%.

Finally of course, we eagerly await the full MRI analysis. This report contains the T2 data which shows new lesions in 23% of those on biotin versus 13% on placebo. Atrophy would be perhaps

more interesting, though to see a slow-down at 12 months would in itself be demanding and more advanced (maybe metabolic) parameters might be more insightful.

Therefore in summary, the bar for slowing MS progression is high, to reverse it is higher still. We celebrate this report, but unfortunately know that it is work only half-done. To come must be a large and long phase 3 trial. If that confirms this finding, we, and especially our patients with progressive MS, will be truly celebrating.

References

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Conflicts of interest

JC declares none relevant to this article