High-dose biotin in progressive multiple sclerosis: A prospective study of 178 patients in routine clinical practice

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Abstract

Background: A recent controlled trial suggested that high-dose biotin supplementation reverses disability progression in patients with progressive multiple sclerosis.

Objective: To analyze the impact of high-dose biotin in routine clinical practice on disability progression at 12 months.

Methods: Progressive multiple sclerosis patients who started high-dose biotin at Nantes or Rennes Hospital between 3 June 2015 and 15 September 2017 were included in this prospective study. Disability outcome measures, patient-reported outcome measures, relapses, MRI data, and adverse events were collected at baseline, 6 months and 12 months.

Results: 178 patients were included. At baseline, patients were 52.0±9.4 years old, mean Expanded Disability Status Scale (EDSS) score was 6.1±1.3, mean disease duration was 16.9±9.5 years. At 12 months, 3.8% of patients had an improved EDSS score. Regarding the other disability scales, scores either remained stable or increased significantly. 47.4% of patients described stability, 27.6% felt an improvement, and 25% described a worsening. Four patients (2.2%) had a relapse. Of the 74 patients (41.6%) who underwent an MRI, 20 (27.0%) had new T2 lesions, eight (10.8%) had gadolinium-enhancing lesions. Twenty-five (14%) reported adverse event.

Conclusion: In this study, high-dose biotin did not seem to be associated with a clear improvement in disability.

Introduction

Multiple sclerosis (MS) is the leading cause of nontraumatic disability in young adults. It has a prevalence of 1/1000 and affects more than 2 million people worldwide. Progressive forms of MS can be either active, if there is clinical or radiological inflammatory activity, or nonactive, as recently defined by Lublin et al.[1] The mechanisms underlying MS progression are poorly understood. It has been suggested that axonal degeneration is linked to virtual hypoxia resulting from an increased energy demand from demyelinated axons and a reduction in axonal ATP production owing to mitochondrial injury.[2]

Although some disease-modifying therapies (DMTs) such as mitoxantrone, siponimod, and anti-CD20 antibodies have shown some efficacy in patients with active progressive disease, [3,4,5,6] there is still a dearth of therapies for nonactive progressing patients. Biotin is a water-soluble molecule that is usually classified as a B-complex vitamin, and reduced levels are found in the cerebrospinal fluid of patients with MS.[7] It is a cofactor for four carboxylases: acetyl-CoA carboxylase, pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase, and propionyl-CoA carboxylase. These four carboxylases are involved in key steps of energy metabolism and fatty acid synthesis. Through the metabolic activation of these enzymes, biotin may have a neuroprotective effect in two ways. First, it may increase the supply of precursors for fatty acid synthesis, and thus promote myelin repair. Second, it may increase production of ATP, and so reverse virtual hypoxia through enhanced energy production in neurons.[8,9] Its adequate intake is 30 µg per day for a healthy adult.[10]

MD1003 is an oral formulation of high-dose pharmaceutical-grade biotin. A double-blind 12-month study found that 12.6% of patients with progressive MS receiving high-dose biotin (100 mg three times daily) achieved a notable improvement in their disability, as scored by the Expanded Disability Status Scale (EDSS) or Timed 25-Foot Walk (T25-FW), compared

with none of the placebo-treated patients (p = 0.005).[11] These findings were consistent with those of a previous pilot study.[12]

Our study aimed to determine whether similar benefits could be observed in routine clinical practice, and whether these benefits extended to functional disability, mobility, and quality of life.

Methods

Patient selection and data collection

Two French MS centers (Nantes and Rennes University Hospitals) participated in this study. These centers systematically collect prospective data on all their patients with MS, using European Database for Multiple Sclerosis (EDMUS) software.[13] Data confidentiality and safety are ensured in accordance with the recommendations of the French Data Protection Authority (CNIL), which approved the use of the EDMUS database in these centers.

Patients with primary progressive MS (PPMS) or secondary progressive MS (SPMS) who were started on high-dose biotin (300 mg per day) between 3 June 2015 and 15 September 2017 at one of the two university hospitals were systematically included in the study. The biotin was made available under the French Temporary Authorization for Use (TAU) scheme. As this specific TAU required nominative registration, patients were automatically enrolled. The censoring date was 28 September 2018. The study was registered on ClinicalTrials.gov (no. NCT03302806). All participants provided their written informed consent.

Data were collected at baseline and at the 6-month and 12-month follow-up visits by treating neurologists. Sociodemographic variables included age and sex. Clinical variables recorded were date of MS onset, duration of MS, type of progressive MS (PPMS or SPMS), previous and currently prescribed DMTs, EDSS score 12 months before the start of high-dose biotin, at

baseline and at 12 months, history of relapses, and Clinical Global Impression (CGI) scale at 12 months. There was a time window of ± 3 months for collecting the follow-up data at 12 months.

When patients underwent MRIs as part of their follow up, their scan data were collected. Adverse events (AEs) were also systematically collected by treating neurologists at each visit, using a specific form.

For patients followed at Nantes Hospital, we also systematically collected the following data at baseline and 12 months: T25-FW time, Symbol Digit Modalities Test (SDMT), Nine-Hole Peg Test (NHPT), quality of life measures (three-level version of the EuroQoL five-dimensional questionnaire (EQ-5D-3L) and Two Lives Scale (TLS Coping 10)), and Twelve Item MS Walking Scale (MSWS-12).

Primary outcome

The efficacy of high-dose biotin was assessed as an improvement in disability at 12 months (defined as decrease of ≥ 0.5 EDSS point if baseline score was 6 or more, or ≥ 1 EDSS point if baseline score was 5.5 or less).

Secondary outcomes

We compared (i) disability and dexterity (EDSS score, T25-FW time and NHPT), (ii) processing speed and sustained attention (SDMT), (iii) quality of life (EQ-5D-3L and TLS Coping 10), and (iv) mobility (MSWS-12) between baseline and 12 months. Other outcomes were the CGI score at 12 months, and clinical and radiological activity (relapse occurrence and MRI data).

Finally, safety and tolerance were assessed by collecting any AEs.

Statistical analysis

Statistical analysis was performed using paired z tests to compare EDSS, T25-FW, SDMT, NHPT, TLS Coping 10 and MSWS-12 scores between baseline and 12 months, and McNemar's chi-Square test to compare EQ-5D-3L scores between baseline and 12 months. All results are presented as mean ± SD. Statistical analysis was performed using Stata 14.2. The significance threshold was set at $p = 0.05$. Intention to treat analysis was performed in this study. Thus, the entire cohort of 178 patients was included in the efficacy and safety analyses.

Results

Patients' characteristics

A total of 178 patients with progressive MS (102 from Nantes Hospital and 76 from Rennes Hospital), aged 24-74 years ($M = 52.0 \pm 9.4$ years) were included in the study (Fig. 1). Their clinical and demographic characteristics are summarized in Table 1. Among these patients, 84 had PPMS and 94 had SPMS. At the time of high-dose biotin initiation, mean disease duration was 16.9 ± 9.5 years and the mean EDSS score was 6.1 ± 1.3. A total of 44 (24.7%) patients were treated with a concomitant DMT. The concomitant DMT was started at the same time as the biotin (± 3 months) in four patients. The mean interval between the introduction of the DMT and the start of high-dose biotin was 36.6 ± 33.4 months. The annualized relapse rate for the 12 months before biotin was 0.05 ± 0.2. In the previous year, 9 patients (among 174 patients, i.e 5,2%) had a relapse. Eighty-eight patients had an MRI within the previous year, and among us 5 (i.e 5,7%) presented radiological evidence of activity (defined by an MRI with at least one gadolinium-enhancing lesion).

Efficacy of high-dose biotin

Primary outcome

Twenty-six (14.6%) patients stopped treatment before 12 months, while 152 (85.4%) continued treatment for at least 12 months. Mean treatment duration was 10.9 ± 2.9 months. Data concerning EDSS at baseline or at 12 months were missing for 21 of the 178 patients. Among the 157 patients with available data, six (3.8%) exhibited an improvement in disability at 12 months. All of them had SPMS. Three of them were receiving a concomitant DMT. None of these patients had started the concomitant DMT at the same time as the high-dose biotin. Two of them had been concomitantly taking mycophenolate mofetil for 36 months and 93 months respectively, while the third had been taking glatiramer acetate for 24 months.

Secondary outcomes

We found that the EDSS score rose from 5.8 ± 1.3 at 12 months before high-dose biotin initiation to 6.0 ± 1.3 at baseline ($p < 0.0001$). The fact that the EDSS score at biotin initiation was higher than it had been the previous year explains why the high-dose biotin treatment was started. However, 12 months into the high-dose biotin treatment, we observed a further significant increase in the EDSS score (6.3 ± 1.3 at 12 months vs. 6.1 ± 1.3 at baseline, $p < 0.0001$) (Fig. 2A).

When we looked at the proportions of patients whose condition improved, stabilized or worsened between M-12 and baseline and between baseline and M12, we failed to find any significant difference ($p = 0.29$, chi-square test): 4.2% of patients improved (between M-12 and baseline), compared with 3.8% (between baseline and M12); 65.7% of patients remained stable (between M-12 and baseline), compared with 73.9% (between baseline and M12); and 30.1% of patients worsened (between M-12 and baseline), compared with 22.3% (between

baseline and M12). Among the 41 patients whose symptoms had worsened before starting biotin, 12 continued to worsen, 25 were stable, and four improved. Among the 84 who had been stable in the preceding year, 67 remained stable, 2 improved, but 15 worsened after starting biotin (see supplementary table).

Concerning the T25-FW, we observed a significant increase at 12 months compared with baseline (46.6 ± 59.0 s at 12 months vs. 39.4 ± 53.3 s at baseline, p = 0.0005) (Fig. 2B). However, among the 87 patients with available data for T25-FW at baseline and at 12 months, nine (10.3%) improved their T25-FW time (defined as a ≥ 20% decrease), and 12 (14.1%) patients improved either their EDSS score or their T25-FW time, but no patient improved both (among the 85 patients with EDSS and T25-FW data available at baseline and at 12 months).

NHPT scores remained stable (29.5 ± 25.2 s at 12 months vs. 30.7 ± 36.1 s at baseline, *ns*) (Fig. 2C), and there were no significant difference in mobility, as evaluated by scores on the self-report MSWS-12 scale (74.7 ± 25.4 at 12 months vs. 76.4 ± 18.6 at baseline, ns).

In terms of processing speed and sustained attention, we observed no significant difference in SDMT scores at baseline and 12 months (37.6 ± 12.2 good answers at 12 months vs. 37 ± 11.0 at baseline, ns) (Fig. 2D).

Regarding quality of life, there was a significant improvement in the pain and discomfort dimension of the EQ-5D-3L (p = 0.0015). The other EQ-5D-3L dimensions (mobility, self-care, usual activities, anxiety/depression) remained stable (Table 2), as did scores on the TLS Coping 10 (6.0 ± 1.7 at 12 months vs. 5.9 ± 1.7 at baseline, ns).

For the CGI score, at 12 months, 47.4% of patients described stability (CGI score = 4), 27.6% felt an improvement (CGI score < 4), and 25% described a worsening (CGI score > 4) (Fig. 3). Among the six patients whose EDSS score improved, four reported an improvement in the

CGI score at 12 months and one described stability. Information was unavailable for the remaining patient.

At 12 months, four patients had had a relapse (2.2%) and the mean annualized relapse rate was 0.02 ± 0.1 (vs. 0.05 ± 0.2 for the previous 12 months, ns).

A total of 74 patients (41.6%) underwent an MRI during the follow up, 7.3 ± 5.1 months after the start of high-dose biotin. Time since the previous MRI was 24.3 ± 22.8 months. We found radiological disease activity for 22 (29.7%) of them : 20 patients (27.0%) had new T2 lesions, eight (10.8%) had at least one gadolinium-enhancing lesion, and 6 (8.1%) had both (two of these patients had a clinical relapse). Finally, 16/35 (45.7%) of the patients whose condition worsened underwent an MRI scan during the follow up, compared with 48/122 (39.3%) of the stable/improved patients (p = 0.499, chi-square test). In patients with an available follow-up MRI, we found clinical or radiological activity (relapse, new T2 lesions, or at least one gadolinium-enhancing lesion) in 8/16 (50%) patients with worsening MS, compared with 14/48 (25%) of stable/improved patients.

Tolerance and safety during high-dose biotin treatment

A total of 25 (14%) patients reported at least one AE during treatment, leading to definitive treatment discontinuation in five cases (2.8%) (Table 3). Most of the AEs were considered to be mild. The most common AE was the disruption of thyroid assays (four patients; 2.2%). Three cases or asthenia and three cases of edema were reported (each 1.7%). There were two cases of weight gain, two of sleep disorders, and two of rash. No patient died during treatment. One atrioventricular blockage, one suicide attempt, and one acute limb ischemia occurred under high-dose biotin, but were not considered to be related to the treatment.

High-dose biotin was stopped before 12 months in 26 patients (14.6%) because of an unsatisfactory therapeutic effect (*n* = 8, 4.5%), patients' wish to discontinue treatment (*n* = 5,

2.8%), progression of the disease (*n* = 5, 2.8%), suspected AE (*n* = 5, 2.8%), deterioration in general status (*n* = 1, 0.6%), difficulty coming to the hospital for treatment (*n* = 1, 0.6%), or for unknown reasons (*n* = 1, 0.6%).

Discussion

We evaluated the impact of high-dose biotin in patients with progressive MS, in routine clinical practice, on disability, mobility, processing speed and sustained attention, and quality of life. To our knowledge, our observational prospective study was the largest real world study to analyze the effectiveness and safety of high-dose biotin in patients with progressive MS.

In our observational study, we found a lower impact of high-dose biotin than in the pivotal controlled trial.[11] Only six patients (3.8%) in the cohort presented an improvement in disability, as measured with the EDSS score (in contrast to 9.7% in the pivotal trial). It seems surprising that in the pivotal trial, none of the patients in the control group had an improvement in disability, given that progressive MS may fluctuate and improvements in disability may occur naturally. Indeed, in one PPMS cohort, Tremlett et al. reported an EDSS improvement at 12 months in 23.8% of patients, and a 6-month sustained EDSS improvement in 8.4% of patients[14]. This was in accordance with our study, as 4.2% of patients had a spontaneous improvement in their EDSS score in the 12 months before starting high-dose biotin.

In our study, EDSS scores increased significantly under high-dose biotin at 12 months, and the progression was close to the EDSS progression observed in the placebo group of the pivotal trial (mean EDSS increased from baseline by 0.2 in our study, and by 0.13 in the placebo group of the pivotal study)[11], and was also consistent with previous placebo data in progressive MS trials.[11,15,16] Our results are in accordance with another prospective

observational study featuring a smaller cohort, which did not report any improvement in EDSS with high-dose biotin.[17]

Surprisingly, in our study, we found that a higher proportion of patients improved on the T25-FW, as 10.3% presented an increase of at least 20% in their T25-FW time, compared with only 4.9% in the pivotal trial. When we consider improvements in EDSS or T25-FW, 14.1% of the patients with MS in our study presented a disability reversal (as in the pivotal trial).

Our results concerning processing speed and sustained attention failed to reach significance, contrary to the data reported by Donze et al.[18], who observed an improvement in the SDMT score after 12 months of treatment for the group of patients with a baseline EDSS score of 6-6.5. However, in their cohort, patients were assessed for SDMT at baseline, 3, 6 and 12 months, suggesting a potential learning effect.

There was no significant improvement in quality of life, except for the pain and discomfort dimension of the EQ-5D-3L, which interestingly improved significantly. Another important outcome was the CGI score, with more than a quarter of patients feeling that their condition had improved under high-dose biotin. These last two results point to a symptomatic or placebo effect of high-dose biotin.

The annualized relapse rate under high-dose biotin was low in our study, but we found evidence of radiological disease activity in 29.7% of the patients who underwent an MRI during the follow up. MRI scans were not systematically carried out in our study, and the results must be interpreted with considerable caution, even if scans were performed in the same proportion of worsening patients as of stable/improved patients. In addition, the time since the previous MRI was sometimes long (M = 24.3 ± 22.8 months), making the comparison with the previous imaging less relevant. However, our results were consistent with the new MS-specific lesions observed in 23.4% of MD1003-treated patients (vs. 13.0% of placebo-treated patients, $p = 0.36$) in the pivotal trial.[11]

Other studies have recently reported an unexpectedly high rate of clinical or radiological disease activity under high-dose biotin.[19,20,21,22] Distinct changes in immune cell frequencies in patients treated with high-dose biotin have also been observed and associated with clinical or MRI deterioration.[23]

There are several possible explanations for the differences between our results and those reported in the pivotal trial, especially concerning the rate of EDSS improvement. First, there was a higher proportion of patients with PPMS in our cohort (47.2%) than in the cohort of MD1003-treated patients in the pivotal trial (40.8%), as well as a longer MS duration (16.9 ± 9.5 years vs. 14.8 ± 8.9 years) and a significant longer T25-FW time (39.4 ± 53.3 s vs. 21.8 ± 27 s), suggesting that our cohort probably had a more advanced disease. The notion that there is less of a response to high-dose biotin in more disabled patients is supported by the results of the subgroup analysis of the pivotal trial.[11] Second, there was a smaller proportion of patients with a concomitant DMT in our study (24.7% vs. 40.8% in the cohort of MD1003-treated patients), which may partly explain the higher proportion of patients whose disability improved in the pivotal trial. Third, contrary to the pivotal trial, we did not exclude patients with clinical or radiological evidence of inflammatory activity within the previous 12 months, and this too may partly explain the significant disability worsening in our study.

We noticed relatively good tolerance of high-dose biotin: AEs were mostly mild or moderate, and included mainly asthenia, edemas, skin problems and disruption of thyroid assays (as previously reported).[24,25] Only 2.8% of patients had to stop treatment because of these AEs.

On account of its real world status, our study had several methodological limitations. It was an observational study, with no randomization or placebo arm. MRI scans were not systematically carried out in our study, making it difficult to know the true proportion of patients with radiological activity under high-dose biotin. Finally, our cohort had a more

advanced and disabling disease than the cohort of MD1003-treated patients in the pivotal trial, which may partly explain the different results.

In conclusion, this observational study is, to date, the largest prospective real world analysis of high-dose biotin in patients with progressive MS, collecting data on disability, quality of life, mobility, dexterity, processing speed and sustained attention. High-dose biotin does not seem to be associated with a clear improvement in disability, even if it may have an impact on quality of life in terms of pain and discomfort. Our study could provide useful insights on the limitations of high-dose biotin treatment of progressive MS in the real world. The demonstration of the usefulness of this drug in these patients needs additional scientific data from well-designed randomized controlled trials: an ongoing randomized clinical trial (SPI2 study) may help researchers to reach a conclusion on the real impact of high-dose biotin.

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Table 1. Clinical and demographic characteristics of our cohort.

Women (%)	111 (62.4)
Age in years **Mean ± *SD*** **Median (range)**	 52.0 ± 9.4 51 (24-74)
Disease phenotype	
PPMS (%)	84 (47.2)
SPMS (%)	94 (52.8)
Duration of MS in years **Mean ± *SD*** **Median (range)**	 16.9 ± 9.5 16 (0-50)
EDSS **Mean ± *SD*** **Median (range)**	 6.1 ± 1.3 6 (3-9.5)
Concomitant DMT (%)	44 (24.7)
Mycophenolate mofetil, n(%)	20 (11.2)
Rituximab (%)	7 (3.9)
Glatiramer acetate (%)	4 (2.2)
Natalizumab (%)	3 (1.7)
Fingolimod (%)	3 (1.7)
Interferon beta (%)	3 (1.7)
Cyclophosphamide (%)	2 (1.1)
Dimethylfumarate (%)	1 (0.6)
Methotrexate (%)	1 (0.6)

Table 2. Changes in quality of life measured with the three-level version of the EuroQoL five-dimensional questionnaire (EQ-5D-3L).

Mobility		M12		
		No problems	Problems	$p = 1$
M0	No problems	1	2	
	Problems	2	75	

Self-care		M12		
		No problems	Problems	$p = 0.3$
M0	No problems	44	10	
	Problems	5	21	

Usual activities		M12		
		No problems	Problems	$p = 1$
M0	No problems	3	6	
	Problems	5	66	

Pain/Discomfort		M12		
		No problems	Problems	$p = 0.0015$
M0	No problems	4	0	
	Problems	12	64	

Anxiety/Depression		M12		
		No problems	Problems	$p = 1$
M0	No problems	23	8	
	Problems	8	41	

Table 3. Description of the adverse events reported in our study.

Type of adverse event	Number of patients	Treatment stopped
Disruption of thyroid assays	4	0
Asthenia	3	0
Edema	3	1
Weight gain	2	0
Sleep disorders	2	1
Cutaneous eruption rash	2	1
Arthralgia	1	1
Nausea	1	1
Spasms	1	1
Sweating	1	1
Pruritus	1	0
Eczema	1	0
Increase in bladder-sphincter disorders	1	0
Atrioventricular block	1	0
Increase in cognitive disorders	1	0
Suicide attempt	1	0
Acute limb ischemia	1	0
Weight loss	1	0
Total	28 adverse events (for 25 patients)	7 adverse events (for 5 patients)

Figure legends

Figure 1. Cohort follow up. 178 patients were included in the study: 26 patients stopped treatment before 12 months, and the remaining 152 continued treatment for at least 12 months.

Figure 2. Changes in disability and executive functions between initiation of biotin treatment and 12-month follow up.

(A) Expanded Disability Status Scale (EDSS) scores increased from 5.8 ± 1.3 12 months prior to initiation of biotin treatment to 6.0 ± 1.3 at baseline (n = 143, $p < 0.0001$, paired z test). Twelve months after the start of high-dose biotin, EDSS scores had increased significantly, from 6.1 ± 1.3 at baseline to 6.3 ± 1.3 at 12 months (n = 157, $p < 0.0001$, paired z test).

(B) Timed 25-foot Walk (T25-FW) time increased from 39.4 ± 53.3 s at baseline to 46.6 ± 59.0 at 12 months (n = 87, $p = 0.0005$, paired z test).

(C) Nine-Hole Peg Test (NHPT) scores remained stable between initiation of high-dose biotin (30.7 ± 36.1 s) and 12-month follow up (29.5 ± 25.2 s) (n = 87).

(D) Symbol Digit Modalities Test (SDMT) scores remained stable between initiation of high-dose biotin (37.0 ± 11.0 good answers) and 12-month follow up (37.6 ± 12.2 good answers) (n = 85).

Figure 3. Clinical Global Impression scale at 12 months.

47.4% (n = 74) of patients reported stability (CGI score = 4), 27.6% (n = 43) felt an improvement (CGI score < 4), and 25% (n = 39) described a worsening (CGI score > 4).

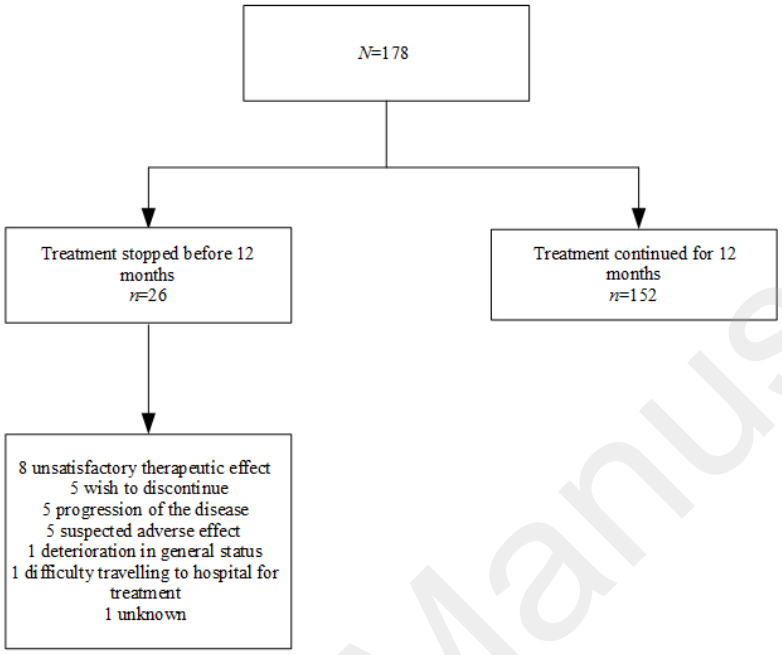
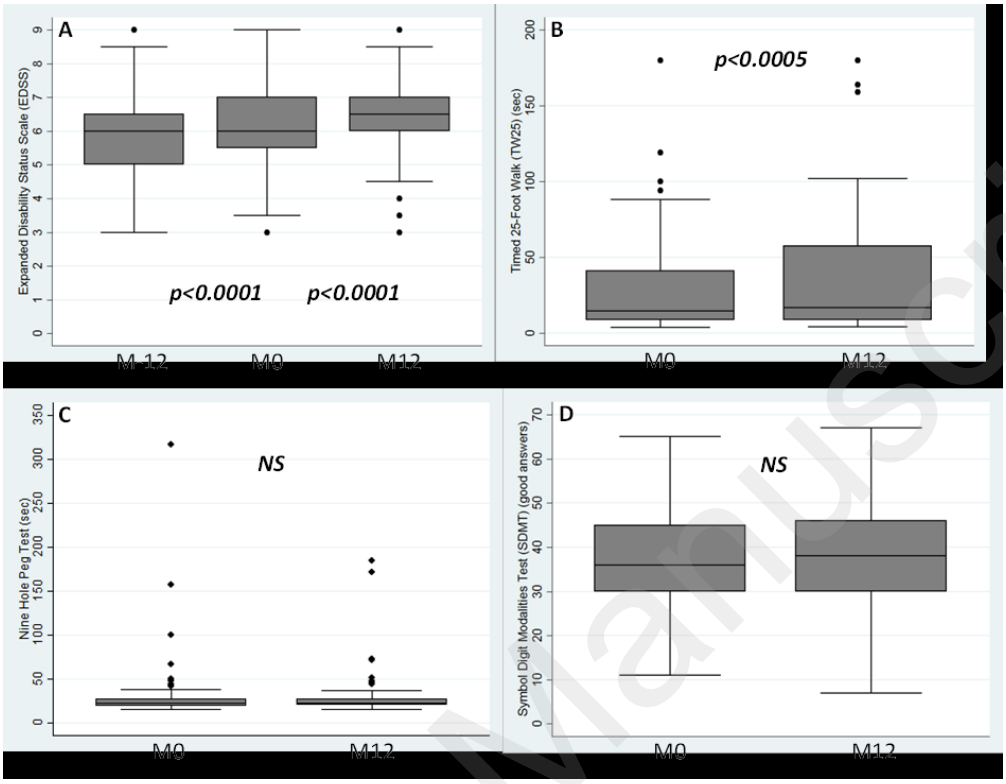
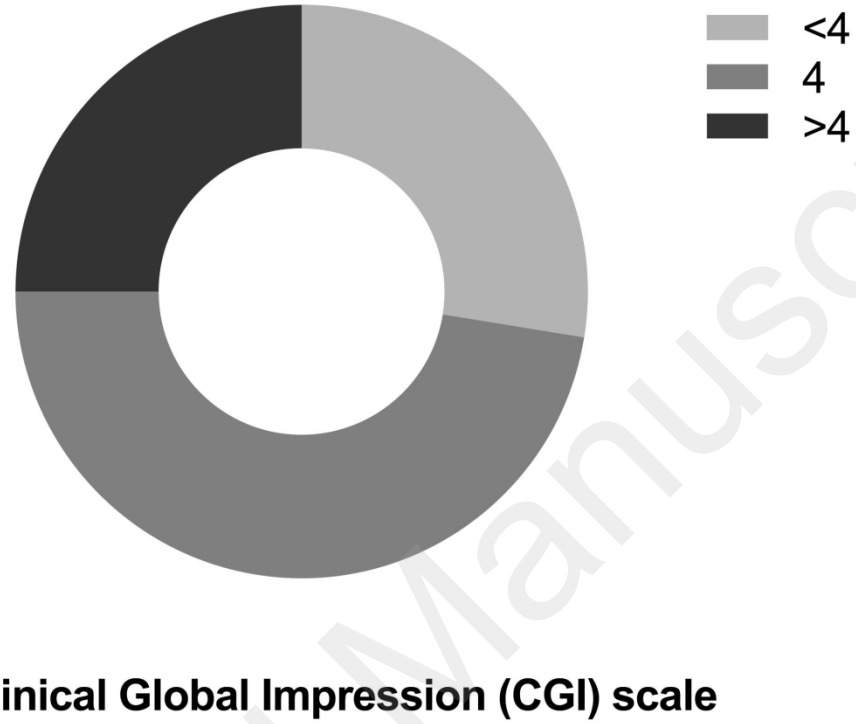


Figure 1



159x123mm (150 x 150 DPI)

Figure 3



185x157mm (300 x 300 DPI)

Supplementary table. The before and after table : disability progression before and after the start of high-dose biotin.

EDSS		AFTER M0 M12			
		Improved	Stabilized	Worsened	Total
BEFORE M-12 M0	Improved	0	5	1	6
	Stabilized	2	67	15	84
	Worsened	4	25	12	41
	Total	6	97	28	131