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Research Article

ALPHA LIPOIC ACID AS ADD-ON THERAPY TO SUBCUTANEOUS INTERFERON B-1A FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS: A PILOT STUDY

Valentina Durastanti*, Emanuele Tinelli, Simone Di Rezze, Alfredo Berardelli and Enrico Millefiorini

Sapienza Università di Roma, Italy

ABSTRACT

Objectives: Treatment of relapsing-remitting multiple sclerosis (RRMS) with interferon (IFN) β-1a is only partially effective in reducing relapses and progression of disability. Alpha lipoic acid (ALA)–a naturally occurring compound that is essential in energy metabolism−has been shown to exert significant anti-inflammatory, antioxidant, and neuroprotective effects. We designed the current pilot study to assess the efficacy of ALA as add-on therapy to subcutaneous (sc) IFN β-1a in RRMS patients.

Methods: We enrolled 13 patients with RRMS in a 2-year, placebo-controlled, double-blind, randomized trial of ALA (400 mg given orally twice daily for the first year and 200 mg twice daily for the second year) as add-on treatment to sc IFN β-1a (44 μg, three times weekly). After starting treatment with sc IFN β-1a, patients were randomly assigned to ALA (n = 7) or placebo (n = 6) for two years. Changes in clinical measures from baseline to the end of the study served as the primary outcome for analysis, whereas secondary outcomes were modifications in MRI parameters.

Results: At the end of follow-up, no significant between-group differences were observed for both changes in clinical measures and MRI parameters.

Conclusions: Although we found no beneficial effect of ALA as add-on therapy to sc IFN β-1a in RRMS patients, our pilot results should be interpreted cautiously because of the small sample size. Future larger studies are needed to investigate whether higher ALA doses could be beneficial.

Key words: Relapsing-remitting multiple sclerosis; Interferon β-1a; Alpha-lipoic acid; Add-on therapy

Abbreviations:

MS: Multiple Sclerosis; CNS: Central Nervous System; RRMS: Relapsing-Remitting Multiple Sclerosis; sc: Subcutaneous; IFN: Interferon; ALA: Alpha-Lipoic Acid; BBB: Blood-Brain Barrier; EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; T25W: Timed 25-foot Walk; 9HPT: 9-Hole Peg Test; PASAT: Paced Auditory Serial Addition Test; MSFC: MS Functional Composite; MSIS-29: Multiple Sclerosis Impact Scale; BDI: Beck Depression Inventory; MRI: Magnetic Resonance Imaging; T2W: T2-Weighted; FSE: Fast Spin-Echo; T1W: T1-weighted; IR-SPGR: 3D-Inversion Recovery Spoiled Gradient Recalled Echo

*Corresponding author: Valentina Durastanti, Sapienza Università di Roma, Italy, E-mail: valentina.durastanti@uniroma1.it

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by diffuse neurodegeneration and demyelination in the white and gray matter, believed to be triggered by a complex interplay of genetic susceptibility and environmental factors (Goodin DS, 2014; Tullman MJ, 2013).

Current disease-modifying drugs can reduce relapses and may delay disability progression in patients with relapsing-remitting MS (RRMS) (Marta M, et al. 2012), the most common disease course at the time of diagnosis (Goodin DS, 2014). Among them, subcutaneous (sc) interferon (IFN) β-1a has been shown to be a valid treatment approach in RRMS because of its favorable benefit/risk profile, improved pharmacokinetic and Pharmacodynamic characteristics, and reduced therapy-related adverse effects (Sanford M, et al. 2011; Murdoch D, et al. 2005). Because RRMS is characterized by disseminated and heterogeneous perivascular inflammatory processes with involvement of auto reactive T cells, B lymphocytes, and macrophages coupled with an enhanced oxidative stress (Gilgun-Sherki Y, et al. 2004; Chiurchiù V, 2014) combination therapy of IFN β-1a with anti-oxidant compounds may be more effective than IFN β-1a alone.

Alpha lipoic acid (ALA) – a naturally occurring iron chelator with potent antioxidant properties – has therapeutic potential for treating CNS disorders because it can pass easily across the blood-brain barrier (BBB) (Shay KP, et al. 2009; Gomes MB, et al. 2014). Notably, it was earlier reported that oral ALA treatment may be clinically useful in MS. In a seminal study conducted in 37 subjects, (Yadav et al. 2005) have shown that ALA supplementation as monotherapy is generally well-tolerated and appears to reduce serum levels of Proinflammatory markers (matrix metalloproteinase-9 and soluble intercellular adhesion molecule-1). In a recent double-blind, randomized controlled clinical study, Khalili et al.11 investigated the effect of daily consumption of ALA on oxidative stress parameters in a sample of 52 RRMS patients. Compared with placebo, consumption of ALA resulted in a significant improvement of total antioxidant capacity in RRMS patients, although no significant effect was seen on other markers of oxidative stress (including superoxide dismutase, glutathione peroxidase, and malondialdehyde) (Khalili M, et al. 2014). In a related study, the same research group demonstrated that ALA significantly reduced circulating levels of several, but not all, Proinflammatory cytokines in RRMS patients, albeit with no effect on Expanded Disability Status Scale (EDSS) scores (Khalili M, et al. 2014).

The available data on the potential usefulness of ALA in RRMS are mostly limited to its use as monotherapy. The question as to whether ALA is indicated in combination with current disease-modifying drugs to further reduce the clinical disability and the brain lesion burden remains open. We therefore undertook the current pilot study to assess the efficacy of ALA as add-on therapy to sc IFN β-1a in RRMS patients. Changes in clinical measures served as the primary outcome for analysis, whereas secondary outcomes were modifications in MRI parameters.

METHODS

PARTICIPANTS

This research was designed as a 2-year, placebo-controlled, double-blind, randomized trial of ALA (400 mg given orally twice daily for the first year and 200 mg twice daily for the second year) as add-on treatment to sc IFN β-1a (44 μg, three times weekly) in RRMS. The inclusion criteria were as follows: 1) diagnosis of RRMS according to the McDonald 2001 criteria (McDonald WI, et al. 2011); 2) age at inclusion between 18 and 50 years; 3) disease duration of less than 10 years; 4) EDSS score ≤ 3.5; 6) less than 6 months of sc IFN β-1a administration; 7) no evidence of relapses or need of steroid treatment within 60 days of enrollment; and 8) no use of immunosuppressive and immunomodulating drugs within 6 months and 1 year of enrollment, respectively. Patients with a positive history of psychiatric diseases, neurological conditions other than RRMS, previous head trauma, alcohol or drug abuse, pregnancy or breastfeeding, and major physical diseases (cancer, cardiovascular disorders, renal, respiratory, or liver failure) were excluded. All subjects were Caucasian of Italian descent. The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Before the study, each participant was informed about the purpose of the research and signed informed consents were obtained.

MATERIALS

ALA supplements for oral use were provided by Laborest SpA (Nerviano, Milan, Italy). IFN β-1a for sc use (Rebif®) was obtained from Merck Serono S.A. (Geneva, Switzerland).

PROCEDURES

After starting treatment with sc IFN β-1a, the study patients (n = 13) were randomly assigned to ALA (n = 7) or placebo (n = 6) for two years. Randomization was performed using a computer program and clinical staff had no access to the randomization sequence. The active arm received ALA (400 mg given orally twice daily for the first year and 200 mg twice daily for the second year) as add-on treatment to sc IFN β-1a (44 μg, three times weekly), whereas the placebo arm received an identical oral placebo. Active ALA tablets and placebo were indistinguishable, so that neither the subjects nor the investigators could identify which subjects were randomized to the same regimen. Assessments of the outcomes were performed at baseline and at the end of the study.

Primary Endpoint: Clinical Measures

The changes from baseline for the following variables served as primary endpoints: 1) EDSS (Kurtzke JF, 1983), 2) MS Functional Composite (MSFC) (Fischer JS, et al. 1999), 3) Fatigue Impact Scale (FIS) (Benito-León J, et al. 2007), 4) Multiple Sclerosis Impact Scale (MSIS-29) (Hobart J, et al. 2001) and 5) Beck Depression Inventory (BDI) (Beck AT, et al. 1961). The EDSS is an MS-specific scale consisting of a neurological assessment quantifying disability in eight functional systems. The assessment of these functional systems yields a sum score ranging from 0 (no neurological impairment) to 10 (death due to MS) (Kurtzke JF, 1983). The MSFC comprises quantitative functional measures of three key clinical dimensions of MS: leg function/ambulation (timed 25-foot walk; T25W), arm function (9-hole peg test; 9HPT) and cognitive function (paced auditory serial addition test; PASAT) (Fischer JS, et al. 1999). The FIS was used to assess the impact of fatigue on daily functioning, with higher scores indicative of an increased fatigue impact (Benito-León J, et al. 2007). MS-specific health related quality of life was examined with the MSIS-29, that examines both the physical (20 items) and psychological (9 items) impact of MS (Hobart J, et al. 2001). High scores on MSIS-29 indicate a greater impact of MS. Finally, symptoms of depression were screened by the BDI, a validated 21-question multiple-choice, self-report inventory (Beck AT, et al. 1961).

Secondary Endpoint: MRI Parameters

Magnetic resonance imaging (MRI) imaging was performed on a 1.5 Tesla whole-body Signa Excite MRI scanner (General Electric Medical Systems, Milwaukee, WI, USA). The following sequences were acquired in the axial plane: 1) T2-weighted (T2W) Fast Spin-Echo (FSE); 2) T1-weighted (T1W) FSE, and 3) T1W 3D-Inversion Recovery Spoiled Gradient Recalled Echo (IR-SPGR). Additional T1W images were acquired within 15 min after injection of a single dose of gadopentate dimeglumine (Magnevist®; Berlex Labs, Cedar Knoller, NJ, USA) at 0.1 mmol/Kg of body weight. After acquisition, images in DICOM format were transferred to a Linux workstation for post-processing analysis. Lesion load (expressed by the number and volume of T2 hyper-intense and T1 hypo-intense non-acute lesions) was computed using a semi-automated technique based upon the local threshold on a MEDx platform. Using the Freesurfer software (version 3.0.2, https://surfer.nmr.mgh.harvard.edu), the averaged image obtained from three anatomical IR-SPGR was used for measuring both the volume of subcortical structures and cortical thickness.

DATA ANALYSIS

Categorical variables were expressed as counts and percent frequency and compared using the Fisher's exact test. Continuous variables are given as medians and interquartile ranges. Between-groups comparisons were performed using the nonparametric Mann-Whitney U test. The changes in outcome measures before and after treatment were compared with paired Student's t-tests. All calculations were performed with the STATA 12.1 statistical package (StataCorp, College Station, TX, USA). Two-tailed values <0.05 were considered statistically significant.

RESULTS

The baseline characteristics of the two study groups are depicted in Table 1. The two treatment arms were well-balanced in terms of sex, age, age at onset, disease duration, and compliance to treatment.

Table 1: Baseline characteristics of the two study groups.

	sc IFN β-1a plus ALA (n = 7)	sc IFN β-1a plus placebo (n = 6)	P value
Males subjects, n (%)	2 (28.6)	1 (18.7)	1
Age, years	33 (26-43)	28.5 (22.5-44.3)	0.47
Age at onset, years	26 (24-29)	21 (19.8-29.5)	0.13
Disease duration, years	4 (1-9)	6 (1-13.3)	0.66
Compliance to treatment, %	97.5 (96-100)	97.8 (94.5-98.9)	0.94

Abbreviations: IFN: Interferon; ALA: Alpha-Lipoic Acid; sc: subcutaneous. Data are expressed as counts (percentages) or medians (interquartile ranges), as appropriate. P values were calculated with the Fisher's exact test or the Mann-Whitney U test, as appropriate.

Primary Endpoint: Clinical Measures

EDSS, MSFC, FIS, MSIS-29, and BDI scores did not differ between the two study groups at baseline. We found no differences between treatment groups in terms of changes of EDSS, MSFC, FIS, MSIS-29, and BDI scores from baseline to the end of the study (Table 2). Similarly, the changes in the T25W, 9HPT, and PASAT dimensions of MSFC were similar in the two study groups (data not shown).

Table 2: Changes in clinical measures (primary outcome) from baseline to the end of the study.

	sc IFN β-1a plus ALA (n = 7)	sc IFN β-1a plus placebo (n = 6)	P value
EDSS			0.36
Baseline	1 (0-2)	1.03 (1-2.1)	
End of the study	1 (0-2)	1.5 (0.8-1.5)	
MFSC			0.89
Baseline	-0.1 (-0.4-0.3)	0.2 (-0.3-0.4)	
End of the study	0 (-0.2-0.4)	0.4 (0.2-0.6)	
FIS			0.61
Baseline	16 (11-27)	25.5 (1.8-35.8)	
End of the study	8 (5-35)	12.5 (0.8-23.8)	
MSIS-29			0.57
Baseline	41 (35-45)	42.5 (33-47.8)	
End of the study	34 (32-38)	42.5 (32.5-52.3)	
BDI			0.47
Baseline	4 (2-8)	3 (0.8-5.8)	
End of the study	2 (1-6)	2 (0-4.3)	

Abbreviations: IFN: Interferon; ALA: Alpha-Lipoic Acid; sc: Subcutaneous; EDSS: Expanded Disability Status Scale; MFSC: Multiple Sclerosis Functional Composite; FIS: Fatigue Impact Scale; MSIS-29: Multiple Sclerosis Impact Scale; BDI: Beck Depression Inventory. Data are expressed as medians (interquartile ranges). P values were calculated with paired Student's t-tests.

Secondary Endpoint: MRI Parameters

The MRI volumetry of subcortical structures (i.e., amygdala, thalamus, caudate, putamen, globus pallidus, hippocampus, cerebellar cortex) did not differ between the two study groups at baseline. We found no differences between treatment groups in terms of changes of MRI parameters from baseline to the end of the study (Table 3). Similarly, the changes in the cortical thickness were similar in the two study groups (data not shown).

Table 3: Changes in MRI volumetry of subcortical structures (secondary outcome) from baseline to the end of the study.

	sc IFN β-1a plus ALA (n = 7)	sc IFN β-1a plus placebo (n = 6)	P value
Amygdala, cm			0.39
Baseline	2.3 (2.0-3.0)	2.7 (2.3-3.2)	
End of the study	2.3 (2.2-2.7)	2.5 (2.1-2.8)	
Thalamus, cm			0.47
Baseline	5.2 (4.9-6.2)	5.9 (5.3-7.6)	
End of the study	5.2 (4.5-6.0)	5.7 (5.4-6.6)	
Caudate, cm			0.77
Baseline	3.3 (3.0-3.7)	3.3 (2.9-3.8)	
End of the study	3.2 (2.7-3.7)	3.2 (2.3-3.7)	
Putamen, cm			0.25
Baseline	8.5 (7.7-8.9)	9.0 (8.5-10.1)	
End of the study	9.3 (6.9-10.2)	9.4 (6.4-10.6)	
Globus pallidus, cm			1.00
Baseline	2.7 (2.6-3.4)	2.8 (2.5-3.5)	
End of the study	2.9 (2.3-3.5)	2.9 (2.5-3.4)	
Hippocampus, com			0.47
Baseline	7.2 (6.5-7.8)	7.2 (6.2-7.9)	
End of the study	7.2 (6.6-7.5)	7.4 (6.9-7.7)	
Cerebellar cortex, com			0.88
Baseline	8.9 (8.4-9.5)	9.5 (8.6-9.8)	
End of the study	8.7 (8.1-9.2)	8.7 (6.6-9.8)	

Abbreviations: IFN: Interferon; ALA: Alpha-Lipoic Acid; sc: Subcutaneous. Data are expressed as medians (interquartile ranges). P values were calculated with paired Student's t-tests.

DISCUSSION

The potential to obtain additive (i.e., an effect representing the sum of two individual treatments) or synergistic (i.e., an effect greater than the sum of the two treatment effects alone) results through add-on therapies is generally intriguing (Sorensen PS, et al. 2011).The combination of ALA and sc IFN β-1a represents a very attractive regimen in patients with RRMS for at least two reasons. First, the two compounds have different mechanisms of action. Specifically, the use of ALA is directed at counteracting the oxidative processes that represent a major source of damage in MS (Gilgun-Sherki Y, et al. 2004; Chiurchiù V, 2014; Shay KP, et al. 2009; Gomes MB, et al. 2014; Yadav V, et al. 2005; Khalili M, et al. 2014), whereas the beneficial effects of IFN β-1a may stem from its immunomodulatory and anti-inflammatory properties as well as its effects on the endothelial cells of the BBB (Marta M, et al. 2012). Second, ALA is inexpensive, crosses the BBB, and side effects associated with its chronic or elevated supplementation are very rare (Shay KP, et al. 2009).

We therefore reasoned that a combination of ALA with sc IFN β-1a should be superior to sc IFN β-1a alone to reduce the progression of disability and the burden of CNS lesions at follow-up. However, the effects of combining two compounds remain difficult to predict, even if their mechanism of actions appears to be complementary. Because the effect of add-on approaches can only be assessed empirically (Sorensen PS, et al. 2011), herein we utilized a pragmatic placebo-controlled design to address the potential usefulness of ALA as add-on therapy to sc IFN β-1a in RRMS patients. The overall aims and design of our study were therefore aimed to compare ALA in addition to sc IFN β-1a to sc IFN β-1a administered as monotherapy.

The most important finding of our pilot research is that oral ALA did not confer additional benefits to sc IFN β-1a therapy over placebo. Accordingly, there were no clinically worthwhile differences between groups in terms of disability, functional measures of key clinical dimensions of MS, fatigue, quality of life, and depression. Moreover, the two study groups did not differ significantly in terms of MRI volumetry of subcortical structures and changes in the cortical thickness from baseline to the end of the study. Contrary to our hypothesis, however, there were no differences between the two treatment groups in both the primary and secondary outcome measures. In the absence of significant treatment effects and a reduction in costs or resource utilization, our preliminary results do not provide support for the use of ALA as add-on therapy to sc IFN β-1a in RRMS patients.

However, there are several limitations to this study that should be kept in mind. We recognize that a significant weakness is the limited sample size. Our study should be considered as an exploratory pilot project and replication in larger cohorts is required to extend our preliminary observations. Moreover, our research was conducted in Caucasian individuals, so results cannot be simply extrapolated to populations with different ethnic backgrounds. Finally, we cannot exclude the possibility that higher dosages of ALA can be required to obtain significant therapeutic effects when given as add-on therapy to sc IFN β-1a. Nonetheless, an important strength of the study is the combined used of both clinical and MRI endpoints.

In summary, we found no beneficial effect of ALA as add-on therapy to sc IFN β-1a in RRMS patients. Although these two compounds do not seem to provide neither additive nor synergistic effects when combined, our pilot results should be interpreted cautiously because of the small sample size. Moreover, the use of higher doses or ALA in future larger studies may be worthwhile.

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