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Comparison of the effects of acetyl L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: results of a pilot, randomised, double-blind, crossover trial

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Abstract

Treatment with acetyl L-carnitine (ALCAR) has been shown to improve fatigue in patients with chronic fatigue syndrome, but there have been no trials on the effect of ALCAR for treating fatigue in multiple sclerosis (MS). To compare the efficacy of ALCAR with that of amantadine, one of the drugs most widely used to treat MS-related fatigue, 36 MS patients presenting fatigue were enrolled in a randomised, double-blind, crossover study. Patients were treated for 3 months with either amantadine (100 mg twice daily) or ALCAR (1 g twice daily). After a 3-month washout period, they crossed over to the alternative treatment for 3 months. Patients were rated at baseline and every 3 months according to the Fatigue Severity Scale (FSS), the primary endpoint of the study. Secondary outcome variables were: Fatigue Impact Scale (FIS), Beck Depression Inventory (BDI) and Social Experience Checklist (SEC). Six patients withdrew from the study because of adverse reactions (five on amantadine and one on ALCAR). Statistical analysis showed significant effects of ALCAR compared with amantadine for the Fatigue Severity Scale ($p = 0.039$). There were no significant effects for any of the secondary outcome variables. The results of this study show that ALCAR is better tolerated and more effective than amantadine for the treatment of MS-related fatigue.

Keywords: Multiple sclerosis; Fatigue; Acetyl L-carnitine; Amantadine; Double-blind crossover trial; Fatigue Severity Scale

1. Introduction

Fatigue is one of the most common and disabling symptoms in multiple sclerosis (MS), occurring in more than 60% of patients during the course of the disease [1]. It is described as an overwhelming sense of tiredness, lack of energy or feeling of exhaustion. Its pathophysiology is only partially known. Some data suggest that both central [2–5] and peripheral [6–8] mechanisms may contribute to produce this symptom. Physiologically fatigue is defined as the inability of a muscle or group of muscles to sustain the required or expected force. This may occur because of an inability to sustain the central drive to spinal motoneurons, called central fatigue or because of a loss of force-generating capacity within the muscle itself, called peripheral fatigue. Consequently, the management of fatigue is a complex and difficult task because multiple factors may contribute to produce this symptom. A number of different medications are used to manage fatigue including amantadine, pemoline, aminopyridines and modafinil [9–14]. In a clinical setting, the response to *medications* varies widely from patient to patient. The *medication* most widely used is amantadine. Four short-term studies indicate that fatigue is reduced by amantadine treatment in MS patients who have mild to moderate disability [9,15–17].

Carnitine is a cellular component with a key role in energy metabolism control. Treatment with acetyl L-carnitine (ALCAR) has proved to be effective in the treatment of fatigue in a variety of chronic neurological diseases [18], in chronic fatigue syndrome [19] and in chemotherapy induced fatigue in cancer patients [20].

However, formal investigations of the use of ALCAR for treating MS-related fatigue have not previously been

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reported. The primary intent of this randomised, crossover trial was to compare the effect of ALCAR on the fatigue experienced by MS patients with that of amantadine, one of the first-line therapies currently available for the treatment of MS-related fatigue.

2. Materials and methods

2.1. Study design

This was a single-centre, pilot, randomised, double-blind, crossover trial of two treatment groups of outpatients (amantadine vs. ALCAR) with MS. The study protocol was approved by the Institutional Review Board of "La Sapienza" University in Rome. Informed consent was obtained. Patients were first randomised for the order of treatments and assigned to a 3-month treatment period with either ALCAR, at a daily dosage of 2 g, or amantadine, at a daily dosage of 200 mg, as first drug. Study medication was taken twice daily, morning and evening. After completion of the 3-month period and, following a 3-month washout period, patients were assigned to the alternative treatment for another 3 months, once again followed by a 3-month washout period (Fig. 1). Patients were rated at baseline and every 3 months by means of self-administered tests.

2.2. Patients

Consecutive patients with definite MS [21], diagnosed at the MS Centre of the Department of Neurological Sciences at "La Sapienza" University in Rome, were invited to participate. Patients with both relapsing-remitting MS (RRMS), as defined by a history of relapses and remissions without gradual deterioration, and secondary-progressive MS (SPMS), as defined by an initial RR course with subsequent progressive deterioration for at least 6 months, with or without superimposed relapses [22], were studied. Other inclusion criteria were: age 18 years; EDSS score of 1.0–3.5 for RRMS and 4.0–7.0 for SPMS patients; clinical evidence of fatigue as documented by a score >4 on the Fatigue Severity Scale (FSS); RRMS patients should have been under Interferon β treatment for at least 1 year in order to avoid the frequent occurrence of fatigue in the early stages of Interferon β therapy. SPMS patients were not undergoing disease-modifying therapies. None of the patients had been treated with medication known to influence MS-related fatigue. All medications were discontinued at least 3 months before the beginning of the study. No patients experienced a relapse or were treated with steroids in the 8 weeks prior to the study. The severity of the disease was assessed by the Expanded Disability Status Scale (EDSS) [23].

Compliance with treatments was monitored by means of patient diaries and periodic telephone follow-up between assessments. During the study, patients were not allowed to take any medicines that may have interfered with the evaluation of this treatment program such as antidepressants, anxiolytics, β-blockers and anticonvulsants. Methylprednisolone at high dosage for 3–5 consecutive days was administered intravenously in case of relapse. Patients with relapse had their fatigue assessment postponed for 30 days to avoid any influence of steroids on clinical outcome. The treatment program was discontinued if a patient was not compliant with medicine intake or follow-up visits and evaluations. Any intercurrent illness may have been grounds for discontinuation from the treatment program if the latter had been postponed for more than one month.

2.3. Outcome variables

Since fatigue is a subjective experience we chose self-report instruments to quantify different characteristics of this phenomenon. Efficacy was evaluated at the baseline visit and after each treatment phase using the following self-administered measures: the FSS was the primary efficacy variable in this study [24]. This is a questionnaire, which assesses the effect of fatigue on daily activities and gives information regarding possible triggers of fatigue, and conditions, which might modify the symptom. The scale was explained to the patients by the same physicians (V.T. and E.O.) in a standardized way. It has been shown to have a high degree of internal consistency, validity and sensitivity to change in clinical condition [24]. Secondary outcome measures were: Fatigue Impact Scale (FIS) [25], Beck Depression Inventory (BDI) [26] and Social Experiences Checklist (SEC) [27]. The FIS measures the impact of fatigue on social, cognitive and physical aspects of daily life and it is composed by 40 items with score ranging 0–4 for each item. It was not validated in clinical trials at the time of this study onset. Furthermore, because fatigue is a

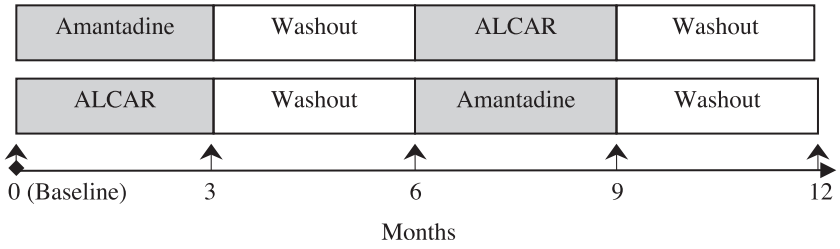

Fig. 1. Study design of a randomised, double-blind, crossover trial of two treatment (amantadine vs. ALCAR) groups of outpatients with both RRMS and SPMS.

symptom used in the diagnosis of depression and most methods of assessing depression are confounded by fatigue, in addition to the two fatigue scales, patients completed the BDI and SEC that assess depressed mood and psychosocial aspects. BDI is a 21-item self-report rating scale for depression. Score range for each item is between 0 and 4. SEC is a self-administered test that measures positive and negative experiences in social interaction. It is composed by 16 items with score included between 1 (any problem in social interactions) and 4 (severe problem in social interactions) for each item.

2.4. Statistical analysis

The statistical analysis was performed using the SPSS 11.0 program (SPSS).

Considering the experimental design (crossover study with two washout periods), changes before–after were computed for each period and entered into an ANOVA for repeated measures. In order to exclude a carry-over effect, washout differences were evaluated against the null hypotheses of no change during washout periods. For each scale, the first measure was entered as covariates for a better control of baseline variability. To evaluate the "sequence effect" (i.e. whether "ALCAR as first" resulted more (or less) effective than "amantadine as first"), the two groups were considered as between-subject factor in the ANOVA. When changes were recoded into dichotomous variables (1 = improvement, 0 = no change or worsening), the effect of ALCAR vs. amantadine was verified by means of the McNemar test.

3. Results

Thirty-six patients with MS (21 RR and 15 SP) were randomised. At baseline, no significant difference was found between the ALCAR-amantadine group and the amantadine-ALCAR group as regards their demographic and clinical characteristics. No significant difference was found between the two groups in any of the self-administered questionnaires (Table 1).

Table 1
Baseline demographic-clinical characteristics and fatigue scores

	ALCAR-amantadine group ($n = 18$)	Amantadine-ALCAR group ($n = 18$)
Baseline demographic-clinical characteristics		
Women/men	12/6	12/6
Relapsing-remitting/ secondary-progressive	10/8	11/7
Age	44.5 (10.9)	43.1 (11.7)
Disease duration (years)	10.2 (6.6)	10.2 (7.0)
EDSS	3.8 (1.9)	3.2 (1.9)
Baseline test scores		
FSS	5.3 (0.6)	5.2 (0.7)
FIS	79.1 (28.9)	86.6 (33.9)
BDI	13.1 (6.1)	11.8 (5.2)
SEC	27.7 (4.8)	27.3 (4.8)

FSS=Fatigue Severity Scale. FIS=Fatigue Impact Scale. BDI=Beck Depression Inventory: SEC=Social Experience Checklist.
Values are number of patients or mean (S.D.). EDSS = Expanded Disability Status Scale.

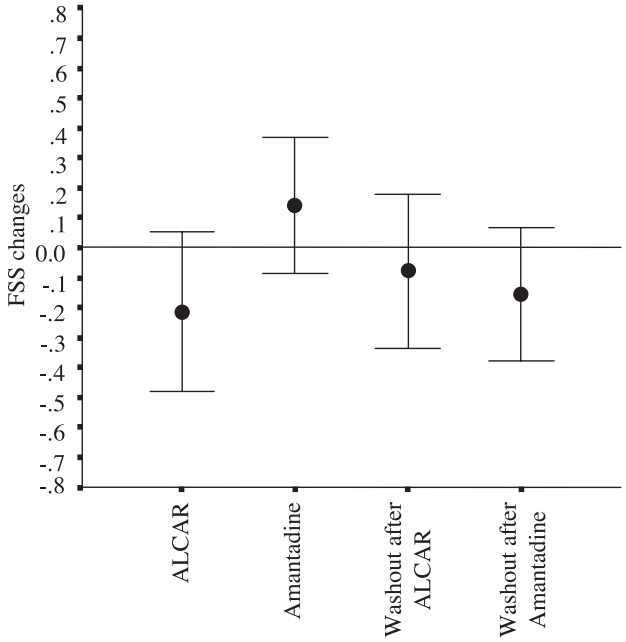

Fig. 2. 95% confidence intervals of absolute changes in the FSS score after each treatment period. The effect of ALCAR on the FSS score was observed to be significantly better than that of amantadine ($p = 0.039$).

Six patients (three RR and three SP) withdrew from the study because of adverse reactions before the evaluation at month 3 of the first study period. One patient treated with ALCAR interrupted the trial because of the development of insomnia and nervousness, whereas five patients treated with amantadine discontinued the study because of nausea and dizziness. Thirty patients completed the study and their tolerability to the drugs was good. No serious adverse events were reported during any treatment phase. Seven patients developed an acute relapse during the study and were treated with high dose of steroids. Among these, four patients had a relapse in the washout periods, two patients during amantadine intake and one patient during ALCAR treatment.

A reduction of FSS score was observed in 70% (21/30) of patients during ALCAR treatment and in 43% (13/30) of patients during amantadine intake (McNemar test, $p = 0.073$). Using a decrease 0.5 in FSS score as a clinically relevant cut-off, we found that 29% of patients improved after ALCAR vs. 21% after amantadine (McNemar test, $p = 0.549$).

As shown in Fig. 2, an FSS reduction was found only after ALCAR administration, whereas a slight FSS increase was observed after treatment with amantadine. FSS score did not change after the two washout periods. When

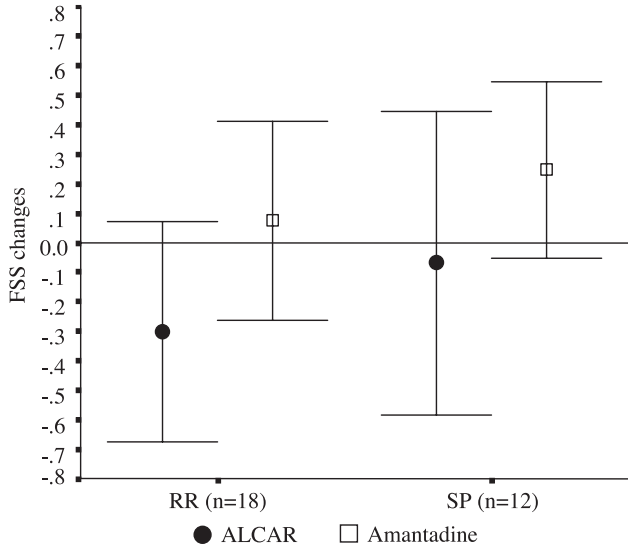

Fig. 3. 95% confidence intervals of absolute changes in the FSS scores during ALCAR and amantadine according to the disease subtypes: RRMS and SPMS. Although there was a trend in favour of ALCAR in both subtypes, the difference did not reach statistical significance.

ANOVA for repeated measures was applied, a significant effect was found [$F(3,81)=4.075$, $p=0.010$]. This was mainly due to the significant difference ($p=0.039$) between the FSS reduction after ALCAR and the slight FSS increase after amantadine.

No significant changes in the other clinical scale (FIS, BDI and SEC) scores were observed.

Changes in FSS scores correlated with changes in SEC ($r=0.41$, $p=0.021$) and BDI scores ($r=0.46$, $p=0.009$) during ALCAR treatment, but not in the amantadine treatment period.

Changes in the FSS score were not related to the baseline clinical-demographic characteristics and fatigue scores. Furthermore, there was no "sequence effect" between ALCAR and amantadine, suggesting that the effects on the FSS score changes were independent of the time-point of drug administration during the treatment program.

When we examined absolute changes in the FSS scores during ALCAR and amantadine intake according to the disease subtypes (RRMS and SPMS), there was a trend in favour of ALCAR in each subtype (Fig. 3). However, this difference did not reach the statistical significance ($p>0.20$, ns), probably owing the small sample size.

4. Discussion

As in chronic fatigue syndrome [19], our study suggests that ALCAR is more effective than amantadine in treating fatigue as result of MS. This study demonstrates a difference between the two drugs on the primary outcome measure (i.e. the fatigue as assessed by FSS). For all secondary endpoints, there is no difference between ALCAR and amantadine.

Of particular significance was the observation that the degree of improvement of fatigue seen with the use of ALCAR, although slight in magnitude, was not associated with the clinical characteristics of patients and the degree of severity of fatigue at baseline. However, the decrease in fatigue induced by ALCAR treatment was associated with an improvement in social interaction and mood profile of patients, while the changes observed during amantadine treatment was unrelated to changes in the secondary outcomes. These findings underscore the role of ALCAR as a potential candidate treatment option to treat MS-related fatigue. Moreover, amantadine was poorly tolerated: five patients were not able to complete the 3-month treatment phase for side effects in contrast with the results found with ALCAR. This agent was very well tolerated. Only one patient stopped treatment with ALCAR because of the occurrence of insomnia and nervousness.

ALCAR (γ-trimethyl-β-acetylbutyrrobetaine) is the acetyl ester of carnitine that plays a key role in the transport of fatty acids from cytosol into the mitochondrial matrix of β-oxidation [28–31].

The ALCAR efficacy may be mediated by its capacity in restoring a normal pattern of energy metabolism both centrally and peripherally.

The effect of ALCAR on fatigue in MS patients could be also consistent with an increased level of stimulating neurotransmitters. A number of experimental studies have demonstrated quite varied properties of ALCAR in enhancing acetylcholine synthesis and exerting a cholinomimetic effect on striatum and prefrontal areas [32,33]. ALCAR promotes synthesis [32] and release [34] of acetylcholine, induces choline acetyltransferase activity [35] and promotes high-affinity uptake of choline [36]. Behavioural evidences, claiming ALCAR action on some cognitive and memory tasks, once again reinforced the cholinergic hypothesis.

Besides the cholinomimetic action, ALCAR can modify other neurotransmitter system functions. ALCAR enhances the glucocorticoid receptor binding in the rat hippocampus [37]. Furthermore, ALCAR may facilitate the release of dopamine at the striatum level [38].

Shug et al. [39] suggested that carnitine does not have a direct neurotransmitter role in the brain, but might play an important role in biochemical pathways involved in excitatory and inhibitory functions in the mammalian brain. A recent study by Kuratsune et al. [40] showed that serum acetylcarnitine is taken up into the brain and utilised for the biosynthesis of glutamate, aspartate and GABA. In the same study, a reduced cerebral uptake of acetylcarnitine was found in several regions of the brain of patients with chronic fatigue syndrome, suggesting that this abnormality might be one of the keys to unveiling the mechanisms of chronic fatigue sensation. A correlation between lower serum acetylcarnitine levels and worse clinical symptoms of fatigue has been previously reported in chronic fatigue syndrome [41], and the administration of acetylcarnitine seems to improve the performance status and fatigue rating score of

patients [42]. Interestingly, the brain regions showing low uptake of ALCAR in chronic fatigue syndrome (prefrontal and temporal cortices, anterior cingulate and cerebellum) have been found to play a role in MS-related fatigue. Roelcke et al. [43] carried out a study using positron emission tomography with fluorodeoxyglucose on MS patients suffering from severe fatigue and found a reduction in metabolic activity in the lateral and medial prefrontal cortex and temporal cortices. Filippi et al. [44], using functional magnetic resonance imaging in MS patients with fatigue, found a significantly lower activation of several cortical and subcortical areas devoted to motor planning and execution, including the ipsilateral cerebellar hemisphere. Thus, one may argue that ALCAR administration may also exert beneficial effects in counteracting neuronal and molecular mechanisms underlying fatigue as result of MS. Investigations of free and total carnitine levels, carnitine metabolism and excretion in MS patients are warranted.

In conclusion, this study demonstrates that ALCAR could reasonably be considered as an additional option in the treatment of MS-related fatigue and an alternative for those MS patients who cannot tolerate the side effects of, or have not experienced satisfactory relief with other commonly used medications for fatigue. The results of this study showed that ALCAR is well tolerated by patients with MS and is more effective than amantadine in the treatment of MS-related fatigue. The interpretation of the results is admittedly limited by the small sample size and larger studies are certainly indicated to confirm these preliminary results and to better understand the mechanisms by which ALCAR may modulate fatigue in MS.

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