Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: THE ALSUNTANGLED GROUP (2020): ALSUntangled 53: Carnitine supplements, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2020.1726565

To link to this article: https://doi.org/10.1080/21678421.2020.1726565

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020; 0: 1–7

RESEARCH ARTICLE

ALSUntangled 53: Carnitine supplements

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ALSUntangled reviews alternative therapies on behalf of persons with ALS (PALS). Here we review the use of carnitine supplements.

Overview

Carnitine is a special type of amino acid found in human cells. It plays a key role in transporting fatty acids into mitochondria where they are used to make energy for cells. Carnitine exists in several different forms including acetyl-L-carnitine (ALCAR), L-carnitine (LC) and propionyl-L-carnitine (PLC). Most people's bodies make all the carnitine they require from the ingested amino acids lysine and methionine (1). A small number of people cannot make enough carnitine due to medical problems such as inborn errors of metabolism, hemodialysis, or certain medications they are taking. It is widely accepted that carnitine supplements are useful in these patients (2,3). PALS do appear to have altered metabolism of carnitine; however, they have been reported to have normal levels of carnitine (4,5). It remains uncertain whether carnitine supplements can help PALS.

Mechanisms

There are six reported actions of carnitine that may be relevant in ALS including enhancement of exercise performance, reduction of oxidative stress, aiding in mitochondrial energy production, protecting motor neurons against excitotoxicity, promotion of regrowth and survival of neurons and the neuromuscular junction, and increasing the heat shock protein response.

Enhanced exercise performance

Some but not all trials in PALS suggest that exercise is associated with slower disease progression (6). Trials in healthy volunteers (7,8) and patients with chronic obstructive pulmonary disease (9, COPD) suggest that LC supplementation may enhance the benefits of exercise, possibly through decreasing exercise-induced muscle damage and increasing blood flow to muscles (7). Thus, it is theoretically plausible that carnitine supplements might enhance the benefits of exercise for PALS.

Reduced oxidative stress

We previously reviewed the role of oxidative stress in ALS and the possible protective role of the Nrf2-ARE antioxidant pathway (10). In pre-clinical studies, LC (11) and PLC (12) have been reported to have direct antioxidant activity. ALCAR can upregulate levels of Nrf2 and the antioxidants glutathione (GSH) and heme oxygenase 1 (HO-1) and can decrease markers of oxidative stress (13–17). A number of human trials (non-ALS) that tested supplementation with LC (18–25) or PLC (26–29) reported lowered blood biomarkers of oxidative stress. In trials with ALCAR supplementation, the effect was less clear (30,31). Based on these observations, it is theoretically plausible that carnitines might reduce oxidative stress in PALS but to date no data exist to support this hypothesis. While most antioxidants have failed to slow ALS progression in trials (32), one (edaravone) was associated with a small benefit in highly selected patients (33).

ALSUntangled Reviewers who contributed to this paper include the following: Jesse Crayle (lead author), Richard Bedlack (senior author), Carmel Armon, Paul Barkhaus, Benjamin Barnes, Ettore Beghi, Michael Benatar, Michael Bereman, Tulio Bertorini, Mark Bromberg, Robert Bowser, James Caress, Greg Carter, Jonathan D. Glass, Volkan Granit, Terri Heiman-Patterson, Leanne Jiang, Pamela Kittrell, Christopher McDermott, Natasha Olby, Lyle Ostrow, Sabrina Paganoni, Gary Pattee, Meraida Polak, Elisabetta Pupillo, Jeffrey Rothstein, Kristiana Salmon, Ashley Whyte-Rayson, and Paul Wicks.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

Correspondence Richard Bedlack Email: richard.bedlack@duke.edu

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2020.1726565

Table 1. Table of evidence for *L*-carnitine (LC).

	Grade	Explanation
Mechanism	A	LC improved blood biomarkers of antioxidants and oxidative stress in several human trials.
Pre-Clinical	C	A single flawed study in a peer-reviewed journal showed benefits of LC administration to the mutant SOD1 mouse model of ALS.
Cases	F	Neither of the 2 PALS we found taking LC reported any benefit.
Trials	F	A single very flawed pilot trial of LC in PALS found no benefit.
Risks	B	Mild-moderate gastrointestinal distress and/or rarely a fishy body odor may be experienced in <5% of patients.

Table 2. Table of evidence for acetyl-*L*-carnitine (ALCAR).

	Grade	Explanation
Mechanism	A	ALCAR increased blood ATP levels suggestive of increased mitochondrial energy production in a single human study.
Pre-Clinical	D	Two research groups showed benefits of oral ALCAR in two different mouse models of ALS. Neither of these studies have been published in a peer-reviewed journal.
Cases	C	One PALS with a validated diagnosis experienced substantial and sustained functional improvement ("ALS reversal") on a multi-compound regimen that included ALCAR.
Trials	D	A single randomized double-blinded placebo-controlled clinical trial reported benefits in PALS; however, violations of protocol in subject selection, as well as, post-hoc sub-analysis of the results requires that the results be interpreted with caution.
Risks	B	Mild-moderate gastrointestinal distress and/or rarely a fishy body odor may be experienced in <5% of patients.

Enhanced mitochondrial energy production

Mitochondria produce energy for cells by metabolizing various compounds obtained from food. Alterations in neuronal mitochondrial function, resulting in impaired intracellular energy production, are hypothesized to be important in ALS pathophysiology (34,35). In a clinical trial of healthy participants, intravenous supplementation with ALCAR, PLC, and to a lesser extent LC increased blood levels of the energy equivalent ATP (36). It should be noted though that even if carnitine supplementation can improve mitochondrial energy production, this does not mean it will have clinical benefits for PALS. Prior efforts to improve mitochondrial function with other theoretically promising pharmaceuticals failed to show benefits (34,35).

Protection against excitotoxicity

A large body of data suggests that excitotoxicity (overstimulation of motor neurons from excess glutamate) may contribute to ALS progression (37). In pre-clinical studies, LC and ALCAR were able to protect neurons from glutamate-induced excitotoxicity (38–40). This protection may occur via direct interaction with glutamate receptors (38) or by stimulation of inhibitory interneurons called Renshaw cells (41). One FDA approved drug that decreases excitotoxicity (riluzole) conclusively demonstrated prolonged survival in ALS trials (42).

Neurotrophic effects

One of the oldest theories on ALS pathophysiology is that it is caused by the loss of some "trophic" factor that normally supports fetal motor neuron growth and/or differentiation (43). ALCAR (39,44,45) and in some studies LC (45) have demonstrated neurotrophic properties in cell cultures stressed by the removal of growth factors. ALCAR was also associated in rats with enhanced recovery following peripheral nerve or spinal cord injuries (46–49). Unfortunately, even if ALCAR and LC are neurotrophic in PALS it is not clear whether these will slow progression; previous trials of neurotrophic factors have failed to do so (43).

Increased heat shock proteins

We previously discussed the potential role of misfolded protein aggregation in possibly contributing to ALS progression (10). Misfolded protein aggregation could be targeted by increasing the expression or activity of specialized proteins called "heat shock proteins (HSPs)" that help or "chaperone" misfolding-prone proteins to fold properly (50,51). In cell cultures, ALCAR can increase HSPs (13,14) and rats given oral ALCAR had increased expression of HSPs in their cortical, striatal, hippocampal, and cerebellar neurons (16). In an open-label human trial, a HSP response enhancer called arimoclomol significantly slowed ALSFRS decline relative to historical controls (52). In a subsequent phase 2 randomized trial of PALS possessing specific *SOD1* mutations that are associated with rapid disease progression, effects on the rate of decline of the ALSFRS-R and survival duration directionally favored arimoclomol; while of a magnitude that is clinically meaningful, the observed effects were not statistically significant (53).

Mechanisms summary

To us, the most promising data within these six mechanisms are the reported ability of LC and

Table 3. Table of evidence for propionyl-*L*-carnitine (PLC).

	Grade	Explanation
Mechanism	A	PLC improved blood biomarkers of antioxidants and oxidative stress in several studies and increased blood ATP levels suggestive of increased mitochondrial energy prodution in a single study.
Pre-Clinical	U	We found no studies testing PLC in pre-clinical models of ALS.
Cases	U	We found no cases of PALS taking PLC.
Trials	U	We found no trials testing PLC that enrolled PALS.
Risks	B	Mild-moderate gastrointestinal distress and/or rarely a fishy body odor may be experienced in <5% of patients.

PLC to reduce markers of oxidative stress, and of ALCAR and PLC to increase ATP levels. These biomarker changes were measured in human trials. Therefore, ALSUntangled assigns a Table of Evidence (TOE) "mechanisms" grade of A for LC (Table 1), ALCAR (Table 2) and PLC (Table 3).

Pre-Clinical models

ALCAR and LC have been studied in mouse models of ALS. Oral ALCAR increased survival in one breeding line of SOD1 G93A mutant mice but not another breeding line ((54), cited in (55)). In the wobbler mouse model of motor neuron degeneration, oral ALCAR was found to possibly slow progression in males (56). Neither of these studies have been published in a peer-reviewed journal nor have they been independently replicated. A single paper described a series of experiments in which oral LC administered to SOD1 G93A mutant mice from an early age delayed disease onset and improved survival (57). Subcutaneous LC starting at symptom onset also improved survival (57). This study was generally well-designed but does have several flaws as per established guidelines (58) including not reporting observer blinding, small animal numbers for some of the experiments, and only testing LC in a single animal model. This study has not been independently replicated. We found no studies testing PLC in models of ALS. Based on this information, ALSUntangled assigns a TOE "pre-clinical models" grades of C for LC (Table 1), D for ALCAR (Table 2), and U for PLC (Table 3).

Cases

In the online community PatientsLikeMe (PLM), 51 PALS reported taking ALCAR and 16 PALS reported taking LC. Twelve PALS taking ALCAR and 2 PALS taking LC rated their perceived effectiveness. Two PALS taking ALCAR reported no effectiveness. The other PALS trying either ALCAR or LC reported "unknown effectiveness (59,60). No PALS reported taking PLC. One verified case of an "ALS reversal" occurred on a cocktail of supplements and medications that included oral ALCAR; however, it is not known if ALCAR contributed to this improvement in ALS disease (61). Based on the above cases, ALSUntangled assigns TOE "cases" grades of F for LC (Table 1), C for ALCAR (Table 2), and U for PLC (Table 3).

Trials

There has been one trial of oral ALCAR in PALS (55). This was a randomized double-blinded placebo-controlled trial in which 82 PALS took 1000 mg ALCAR or placebo three times a day (3000 mg total daily dose of ALCAR) for 48 weeks. All PALS in the study were also on riluzole. The study measured ALSFRS-R scores, FVC (a measure of breathing function), muscle strength, and deaths during the study. The results showed that the PALS taking ALCAR were less likely to lose the ability to take care of themselves and had slower decline in ALSFRS-R total scores. The ability for self-care (62) was defined as a score of at least 3 out of 4 on the ALSFRS-R subscores for swallowing, cutting food and handling utensils, and walking. Additionally, the results suggested that loss of respiratory function (FVC), loss of muscle strength, and time to death was slowed in the group taking ALCAR. Despite these results, the results of this study are difficult to interpret because 21 of the 82 enrolled PALS did not meet study eligibility criteria. Further statistical analyses that considered only the PALS that met study eligibility criteria showed that although there was a trend toward PALS taking ALCAR as less likely to lose the ability to take care of themselves, this did not reach statistical significance. The lack of significant results may have been from the very small sample size. This trial has never been replicated. Of potential interest, ALCAR has also been shown to possibly have benefits in Alzheimer's Disease clinical trials (63).

There has also been a trial of LC in PALS (64). This was an open-label pilot trial in 1992 that randomized 30 PALS to "vitamin B and carnitine" of unspecified dosage or the amino acid threonine. The study enrolled 15 PALS in each arm, with treatment ongoing for 12 months. The results showed no difference in the decline of Norris Scale scores (an ALS functional rating scale; 65) between the two treatment arms. The results are difficult to interpret due to no true placebo arm, low enrollment that limited statistical power, and moderately high drop-out in both study arm. It is also possible that the trial participants did not receive an adequate dose of LC.

There have been no trials of PLC in PALS. Based on the above information, ALSUntangled assigns a TOE "trials" grades of F for LC (Table 1), D for ALCAR (Table 2), and U for PLC (Table 3).

Risks

In reviews and meta-analyses of oral carnitine supplementation in human clinical trials, the supplement-associated side effects are occasional nausea, vomiting, diarrhea, and rarely an unpleasant body and urine odor. The total frequency of side effects in those taking carnitine supplements is less than 5% greater than placebo. This appears to be consistent for LC (66,67), ALCAR (63,68), and PLC (69). In clinical trials that reported side effect profiles, intravenous LC (70–75), intravenous ALCAR (41), intravenous PLC (75–80) and intramuscular ALCAR (81) all appear to have minimal to no side effects similar to oral dosing.

It has been suggested that carnitine supplementation could lead to negative health outcomes in the long-term by increasing levels of trimethylamine *N*-oxide (TMAO; 82,83). This is because LC is metabolized by gut bacteria to trimethylamine (TMA) which is absorbed by the gut and converted into TMAO by the liver. Similar to LC, TMAO is also found naturally in animal product foods. Mouse and cell studies have suggested a direct role of TMAO in leading to atherosclerosis, kidney disease, and diabetes (84); correlating with this, atherosclerosis has been shown to worsen in a mouse model of atherosclerosis following LC supplementation (83). Many clinical studies in individuals with cardiovascular disease risk have shown an increased risk of all-cause mortality with increasing blood concentrations of TMAO (85). A single clinical study showed higher blood LC levels to be associated with cardiovascular disease (83). In spite of this possibly causal association, clinical trials have suggested that LC supplementation lowers the risk of all-cause mortality following a myocardial infarction (86) and has some benefit in heart failure (67) and type 2 diabetes mellitus (87,88). Abnormalities of energy metabolism in PALS (35) likely changes this risk, but the relationship is unknown.

In the small trials to-date with PALS, the side effects of oral ALCAR appeared to be similar to placebo (55) and no side effects were reported with oral LC (64), but these trials were not long enough to assess all possible cardiovascular adverse events in PALS. Based on the above information, ALSUntangled assigns a TOE "risks" grades of B to each LC (Table 1), ALCAR (Table 2), PLC (Table 3).

Dosing and costs

Carnitine supplements are typically taken orally but have been administered by intramuscular or intravenous injections. The clinical trial showing some possible benefit of ALCAR in PALS used 1000 mg ALCAR by mouth three times per day (55); similar total daily doses of LC (7,67,88) and PLC (26–28,69) have been used in other human clinical trials. The optimal dosage or form of carnitine for use in ALS is not clear; however, it is unlikely that individual doses over 1000 mg will lead to greater absorption (89,90). The pharmacokinetic data supports dosing multiple times per day (91,92). Because of the possible benefits of ALCAR in PALS (55), similarly dosed clinical trials that have suggested increased CSF levels of ALCAR (93,94), and the evidence presented in the above "mechanisms" section, we believe oral ALCAR is the most promising of the carnitine supplements. A month's supply of oral ALCAR at 1000mg three times daily (3000 mg total daily dose) will cost approximately $15 per month depending on the brand selected (95). We found no evidence in the literature comparing brands.

Conclusions

In conclusion, there are good theoretical mechanisms for carnitines, some pre-clinical evidence for LC and ALCAR, and a single clinical trial that suggested ALCAR could slow disease progression in PALS. All three carnitines appear to be well-tolerated, generally safe and inexpensive. We believe that there is a need for future clinical trials of carnitines in PALS to further elucidate their efficacy. Until there is further data, we cannot endorse any of these supplements as a definite way to slow ALS progression; however, oral ALCAR at 1000mg three times daily (3000 mg total daily dose) appears to be a theoretically promising supplement available for PALS whom would like to self-experiment.

Declaration of interest

ALSUntangled is sponsored by the ALS Association. Richard Bedlack has research support from ALSA, MNDA, Cytokinetics, Orion and Ultragenyx, and consulting support from ALSA, Biogen, Brainstorm Cell, Biohaven, ITF Pharma, Mallinkrodt, New Biotic and Woolsey Pharma.

Paul Wicks (PW) is an employee of PatientsLikeMe and holds stock options in the company. PW is an associate editor at the Journal of Medical Internet Research and is on the Editorial Boards of The BMJ and BMC Medicine. The PatientsLikeMe Research Team has received research funding (including conference support and consulting fees) from Abbvie, Accorda,

Actelion, Alexion, Amgen, AstraZeneca, Avanir, Biogen, Boehringer Ingelheim, Celgene, EMD, Genentech, Genzyme, Janssen, Johnson and Johnson, Merck, Neuraltus, Novartis, Otsuka, Permobil, Pfizer, Sanofi, Shire, Takeda, Teva, and UCB. The PatientsLikeMe R&D team has received research grant funding from Kaiser Permanente, the Robert Wood Johnson Foundation, Sage Bionetworks, The AKU Society, and the University of Maryland. PW has received speaker fees from Bayer and honoraria from Roche, ARISLA, AMIA, IMI, PSI, and the BMJ.

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