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ALSUntangled 38: L-serine

The ALSUntangled Group

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RESEARCH ARTICLE

ALSUntangled 38: L-serine

THE ALSUNTANGLED GROUP*

ALSUntangled reviews alternative therapies for patients with ALS. Here we review L-serine, for which we have had more than 1090 requests (1).

Overview

Serine is a "non-essential" amino acid which humans can synthesise (2). Serine exists in 2 forms: L-serine and its mirror image D-serine (2). L-serine is used in making proteins, while D-serine has other roles including acting as a neuromodulator (2). Both forms of serine can cross the blood brain barrier and enter the central nervous system (3).

Mechanism

Some, though not all, investigators believe that certain cases of sporadic ALS may be caused by exposure to a chemical called BMAA (B-methylamino-L-alanine, 4). This was first proposed as an explanation for the ALS Parkinsonism dementia complex (ALS/PDC) of Guam and supported when the chemical was found in autopsies of affected Chamorros (original studies reviewed in 4). It was later extended more broadly when BMAA was found in autopsies of people outside Guam who died from ALS (reviewed in 4). Proponents of the hypotheses point out that BMAA can be incorporated into proteins in place of L-serine, resulting in proteins that misfold, aggregate, and are ultimately neurotoxic (5). In cell cultures (5), flies (6,7) and vervets (8), application of L-serine can block incorporation of BMAA into proteins, limiting protein misfolding, aggregation, and neurotoxicity.

The BMAA ALS hypothesis has been criticised, mainly for 2 reasons. First, some studies have failed to find BMAA in autopsies of Chamorros who died from ALS/PDC (9), or from people outside Guam living with or having died from ALS (10). Proponents of the hypothesis questioned the sensitivity of the methods used in some of these studies (reviewed in 4). Second, it has been pointed out that BMAA induced "neurotoxicity" would not explain the long latency between exposure and ALS onset, especially cases where exposure to the toxin may not even be present anymore when the disease begins (11,12).

Based on this information, ALSUntangled assigns a TOE "Mechanism" grade of B (Table 1).

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Note: this paper represents a consensus of those weighing in. Every investigator in this group does not necessarily share the opinions expressed in this paper.

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Table 1. TOE Grades for L-Serine in ALS.

	Grade	Explanation
Mechanism	B	Shown in peer reviewed publications to act on a relevant mechanism in non-traditional pre-clinical ALS models
Pre-Clinical	C	Multiple peer reviewed publications report that L-serine can block the toxic effects of BMAA in cell and animal models, but it is not clear that these are models of ALS, nor that L-serine can reverse damage that has already been done
Cases	D	Subjective reports of benefit without validated diagnoses and/or benefits
Trials	D	One small pilot trial showed a trend toward benefit
Risks	C	At least 10% of exposed patients experienced GI side effects (no hospitalisations or deaths)

Pre-clinical data

Traditional ALS models are based on genetic mutations inserted into animals (13) or cells obtained from patients with the disease (14). We are unaware of L-serine being tested in these. Models of BMAA-induced neurotoxicity exist (15–22), and share some features with human ALS. For example, human lung fibroblasts, human umbilical vein endothelial cells and human neuroblastoma cells that are exposed to BMAA suffer from protein aggregation and apoptosis (5) as is seen in ALS motor neurons (23,24). As mentioned above, L-serine blocks these pathological changes (5). Vervets chronically exposed to BMAA develop neurofibrillary tangles and Beta-amyloid deposits in their brains, as is seen in humans with the ALS/Parkinson's/Dementia Complex of Guam (8). Co-administration of L-serine ameliorates these changes (8). Based on this information, ALSUntangled assigns a TOE "Pre-Clinical" grade of C (Table 1).

While the above-described results support using L-serine to prevent damage to cells and the nervous system caused by BMAA exposure, it is important to note they have not addressed its ability to reverse neurodegeneration that is already present.

Data in PALS

Cases

On the PatientsLikeMe website, 18 people state that they tried L-serine to treat their ALS, 8 of whom completed a total of 11 evaluations on it (25). Dosages used ranged from 0.5g to 35g twice daily. In terms of perceived effectiveness, 1 person rated it as "moderately effective," 1 "slightly effective," 1 "not effective," and 8 "unknown effectiveness." Only 1 person reported a side effect (constipation). Across several threads on L-serine in the ALS Forums (ex. 26) we found 8 people who reported taking L-serine for ALS at dosages of up to 30g daily. Three of these reported improvements, including subjectively improved strength or progression rate. No one reported significant side effects. Across several threads on L-serine in the ALS TDI Forum (ex. 27) we found 5 people who reported taking L-serine for ALS at dosages of up to 15g twice a day. No one reported any benefits and one person reported "brain fog" on this. Based upon this information, ALSUntangled assigns a TOE "Cases" grade of D (Table 1).

Trials

Recently, a small safety trial of L-serine in PALS was published (28). Twenty PALS were randomly assigned to dosages of 0.5, 2.5, 7.5 or 15g twice a day, with safety and tolerability measures obtained in a double-blind manner over 6 months of treatment. CSF, plasma and urine concentrations of L-serine and BMAA were measured by mass spectroscopy. Disease progression was measured by comparison of ALSFRS-R score and FVC decline relative to 430 historical controls from the placebo group of several trials with similar inclusion criteria. L-serine at all doses appeared reasonably safe and well tolerated. While there were 3 deaths, all were attributed to ALS progression and deemed unrelated to L-serine. There were 3 drop outs (2 related to GI side effects); this 15% dropout rate is consistent with previous ALS trials periods of similar duration (29). Increasing doses of L-serine were associated with increasing levels in the CSF, blood and urine. BMAA was detected in a single patient. The study was not powered to detect efficacy, though there was a trend toward a dose-related decrease in slope of decline in ALSFRS-R scores. Changes in FVC did not differ between PALS treated with L-serine and historical controls. Problems with this trial include its very small sample size, lack of concomitant placebo group, and the fact that the majority of participants did not have measureable BMAA in their CSF, blood or urine (meaning it is not clear whether this is the right subset of ALS to target). Based on all this, ALSUntangled assigns a TOE "Trials" grade of D (Table 1).

Risks and Costs

The above-described small pilot trial is the best source of systematically gathered safety information on L-serine (28). In this trial, 3 out of 20 enrolled participants developed GI side effects including bloating, nausea, and loss of appetite (28). No other adverse events were noted. No serious adverse events related to L-serine were detected in this trial

or in any of the individual case reports we found on the Internet. Based on this information, ALSUntangled assigns a TOE "Risks" grade of "C" (Table 1).

Depending on the dosage, L-serine can be reasonably inexpensive and can be purchased from the exact same supplier used in the above-described trial (30).

Conclusion

L-serine is a reasonably inexpensive, widely available nutritional supplement that has a plausible mechanism by which it could help a subset of patients who might have ALS from BMAA-toxicity. A small Phase I trial showed that L-serine up to 15 g twice daily is relatively well tolerated. A larger follow up trial is planned and will shed further light on its safety and utility as an ALS therapeutic. Unfortunately, since it is challenging to reliably measure BMAA in PALS, it will be difficult to identify the subset most likely to respond. Until a reliable assay for measuring BMAA exposure in living people arises, or a follow up trial confirms safety and demonstrates benefit independent of this, we cannot recommend L-serine as a treatment for ALS.

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