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ALSUntangled 43: copper

THE ALSUNTANGLED GROUP

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RESEARCH ARTICLE

ALSUntangled 43: copper

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ALSUntangled reviews alternative therapies on behalf of persons with ALS (PALS). Here we review the use of copper for ALS, for which we have had over 250 requests (1). We will review copper in the form of a dietary supplement, which has been a popular topic in ALS forums (2), as well as the copper complex diacetylbis(N(4)-methylthiosemicarbazonato) copper(II) also known as CuATSM. This oral bioavailable molecule, which has long been used to image hypoxic tissues, recently gained publicity after researchers at University of Melbourne and Oregon State University published promising results in using it to treat an ALS animal model (3).

Overview

Copper is an element required for the function of many enzymes. The human body cannot synthesize copper and therefore must get it through dietary sources. Ingested copper is absorbed mainly through the small intestine (4). It gets transported to the liver where it is bound to ceruloplasmin before being released into the blood. It can then cross the blood brain barrier via copper transporters (4). Central nervous system (CNS) copper regulation is complex, involves interactions with many different proteins, and is important for cellular responses to oxidative stress and metal toxicities, proteostasis, and synaptic neurotransmission (4–6). Copper deficiency due to lack of adequate intake or impaired absorption can lead to anemia, neutropenia, osteoporosis, impaired growth, and neurological problems including neuropathy and myelopathy (4,7). There are three case reports of copper deficiency mimicking ALS (8); in two of these there was a prior history of GI surgery which might have caused malabsorption. Genetic defects affecting copper transport or binding proteins lead to a variety of other neurodegenerative diseases, highlighted by Menkes disease (4,5,9).

Mechanisms

Most PALS have normal serum copper levels, but some may have copper dysregulation. The strongest evidence for this hypothesis comes from mouse models of type 1 familial ALS (FALS1), which are caused by mutations in superoxide dismutase 1 (SOD1). SOD1 protein normally binds copper, and this binding helps stabilize the shape (conformation) of the protein. Demetalation, which may occur from specific mutations impairing copper binding or dysfunction in carrier proteins (called chaperones), results in misfolded SOD1 which can form neurotoxic protein aggregates (5,9–12). SOD1 normally participates in the distribution of intracellular copper. Failure of mutant SOD1 to deliver copper to the mitochondria can impair neuronal energy production and increase oxidative stress (3,13). Demetalation of mutant SOD1 can also result in increased copper concentrations in the spinal cord (14).

Three observations argue that the copper dysregulation seen in mutant SOD1 mice might play an important role in driving their disease progression. First, animals co-expressing human "copper chaperone for SOD1" (CCS) have copper deficient mutant SOD1 and markedly accelerated disease progression (15). Second, treatment with

ALSUntangled Reviewers who contributed to this paper include the following: Victoria Rice (who wrote the first draft), Richard Bedlack, Robert Bowser, Paul Wicks, Dallas Forshew, Stephen Kolb, Jeffrey Rothstein, Eric Valor, Greg Carter, Terry Heiman-Patterson, Carmel Armon, Mark Bromberg, Pamela Kittrell, Jim Caress, Tulio Bertorini, Nicholas Maragakis, Kristiana Salmon, Christopher McDermott, Jon Glass, Rup Tandan, Gary Pattee, Erik Pioro, Sabrina Paganoni, Fernando Viera, Veronica Peschansky, Ceri Weber, Neta Zach.
Correspondence: Richard Bedlack, E-mail: richard.bedlack@duke.edu

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Table 1. TOE for oral copper supplements.

	Grade	Explanation
Mechanism	D	In the setting of normal serum copper, it is unlikely that simply taking extra copper would ameliorate complex CNS copper dysregulation
Pre-clinical	U	We found no pre-clinical data on copper supplements in ALS models
Cases	F	Neither of the 2 PALS we found taking copper supplements reported any benefits
Trials	U	We found no trials of copper supplements in PALS
Risks	D	Very high doses (30–60mg/d for 3 years) can result in cirrhosis of the liver

Table 2. TOE for CuATSM.

	Grade	Explanation
Mechanism	B (for SOD1 ALS), C (for other types of ALS)	CuATSM can ameliorate CNS copper dysregulation and alter progression in animal models of SOD1 ALS; relevance in other types of ALS is less certain
Pre-clinical	A	Multiple well-designed studies in peer reviewed publications show that CuATSM can slow progression in ALS animal models
Cases	D	A few PALS have reported benefits, but they were on combinations of treatments and we did not have records to validate their diagnoses or improvements
Trials	U	There is a small pilot trial underway but results are not available yet
Risks	U	The only safety data we found on repeated doses in PALS is subjective and comes from small numbers

CuATSM, which specifically releases copper into cells that have a defective electron transport chain, slows mouse disease progression (3,16–19). Finally, treatment with chelators that lower spinal cord copper levels can also slow mouse disease progression (9).

Whether modulating copper delivery is mechanistically relevant to PALS without SOD1 mutations remains unclear. One study suggests that people with sporadic ALS also have elevated levels of copper (and other metals) in the motor area of their spinal cords (20). However, a small human trial of a copper chelator showed no benefit (21). Given how complex CNS copper regulation is, it seems unlikely that simply taking oral copper would be useful to PALS with normal serum copper levels. We therefore assign a Table of Evidence (TOE) "Mechanism" grade of D for oral copper supplements (Table 1). On the other hand, CuATSM may allow delivery of copper to specific brain areas in need. In a PET-imaging study, for example, radiolabeled CuATSM accumulated much more in brains of 12 ALS patients than in nine healthy age-matched control subjects (22). The level of retention of CuATSM directly correlated with the disease severity of the ALS patients. Given this, and the pre-clinical data described above and below, we assign CuATSM a TOE "Mechanism" grade of B for ALS caused by SOD1 mutations, and C for other types of ALS (Table 2).

Preclinical data

We found no studies evaluating the use of a copper supplement in pre-clinical ALS models. We therefore assign copper supplements a TOE "Pre-Clinical" grade of U (Table 1).

We found several studies evaluating the effect of CuATSM on mutant SOD1 mice with and without CCS coexpression (3,16–19). These are summarized in Table 3. Based on these studies we assign CuATSM a TOE "Pre-Clinical" Grade of A.

Data in PALS

Cases

Within the Patients Like Me (PLM) community of 11,000 PALS, five reported taking a copper supplement as a treatment for their ALS. Of these, two completed detailed treatment reports (23). A 49-year-old male took 1mg of an unnamed copper supplement per day. He rated the treatment as having no effectiveness and no side effects. A 63-year-old male took 10mg of an unnamed copper supplement per day. He couldn't tell if there was any effectiveness and he reported having the side effect of burping, rated as mild. Based on this information, we assign copper supplements a TOE "Cases" grade of F.

Four PALS on PLM reported taking CuATSM, and two of them completed detailed treatment reports (24). A 49-year-old male took 12 mg daily and reported "slight" effectiveness. A 41-year-old male took 12mg daily during which he reported "slight" effectiveness, then increased to 18 mg daily and reported "moderate" effectiveness. Neither noted any side effects. We did not have records on any of these patients to confirm their diagnoses or reported improvements. ALSUntangled also received emails from a group of seven PALS taking oral CuATSM. None of these patients reportedly has anSOD1 mutation or family history of ALS. These PALS began taking CuATSM at different times and at varying doses with the lowest dose

Table 3. Pre-clinical studies of CuATSM in ALS models.

Reference	Model	Treatment (vs. comparison)	Starting age	Rater blinding	Key outcomes
(3)	G93A mutant SOD1 x CCS mice	CuATSM 30 mg/kg BID (vs. untreated)	Arm 1 = continuous treatment, Arm 2 = stopped at weaning, Arm 3 = stopped at weaning then restarted at symptom onset	Yes	All 3 arms associated with delayed symptom onset, increased survival
(3)	G93A mutant SOD1 mice	CuATSM 100 mg/kg BID (vs. vehicle)	Arm 1 = 5 days, Arm 2 = 50 days	Yes	Both arms associated with delayed symptom onset, improved survival
(16)	G93A mutant SOD1 mice	CuATSM 30 mg/kg daily (vs. vehicle)	50 days	Yes	CuATSM delayed symptom onset, slowed motor progression, trend toward improved survival
(17)	G93A mutant SOD1 mice	CuATSM 30 mg/kg daily (vs. vehicle)	Arm 1 = 140 days, Arm 2 = 200 days	Yes	Both arms associated with delayed symptom onset, improved survival
(18)	G37R mutant SOD1 mice	CuATSM 30 mg/kg daily (vs. vehicle)	40 days	Yes	CuATSM associated with improved survival, delayed symptom onset, preserved spinal motor neuron counts, increased concentration of metallated mutant SOD1
(19)	G37R mutant SOD1 mice	CuATSM at several doses with and without riluzole (vs. riluzole treated, vehicle treated)	Some at 38-41 days, others "post-symptom onset"	Yes	CuATSM associated with delayed symptom onset, improved survival relative to riluzole or vehicle

being set at 6 mg/day. They are also taking many other supplements and medications such as magnesium, niacinamide, testosterone and Edaravone making it difficult to differentiate effects from CuATSM versus other treatments. No side effects were reported and five out of seven patients are said to have had stable neurological function for the last five to six months. One patient had an elevated creatinine kinase level before starting CuATSM and after three weeks taking CuATSM, his level was down within the normal range. PALS on placebo can have six month periods of clinical stability (25), and creatinine kinase levels can vary spontaneously over the course of ALS (26), so these results are of uncertain significance. Since we did not have records to validate the diagnoses or outcomes in this cohort, we assign CuATSM a TOE "cases" grade of D.

Trials

We found no trials of copper supplements in PALS. There is a small pilot trial of CuATSM underway, but results are not yet available (27). We thus assign copper supplements and CuATSM TOE "Trials" grades of "U."

Dosing, risks, and costs

As mentioned above, there are no studies looking at copper supplementation in ALS models or PALS having normal serum copper levels. Thus, there is no way to know what, if any, dose might be useful. The recommended daily allowance of copper for adults is 0.9–1.3 mg/d, with a safe upper limit of 10 mg/d (4). Very high dose supplementation (30–60 mg/d for 3 years) can result in severe cirrhosis of the liver (28). We thus assign copper supplements a TOE "Risks" grade of D. Oral supplementation at the recommended daily allowance would cost less than $1 per month (29).

Single doses of radiolabeled CuATSM, used to image various types of tumor hypoxia, appear safe (30,31). However, the only safety data we found on repeated doses of CuATSM in PALS is described in the Cases section above. Since this data is subjective and comes from very small numbers of PALS, we assign CuATSM a "Risks" grade of U. The ongoing CuATSM ALS trial includes oral dose escalation, ranging from 3 mg/d to 48 mg/d, chronic administration and objective outcomes (27). CuATSM is available for purchase on the Internet at a cost of around $300 for 25 mg (32); thus, depending on the dosage used, this could cost $9,000 per month or more.

Conclusions

Copper dysregulation may play a role in ALS progression, particularly for the form caused by

SOD1 mutations. Given the complexity of this problem, simple copper supplements are unlikely to be useful to PALS with normal serum copper levels. We do not recommend using these. CuATSM, on the other hand, has more promising potential mechanisms of action, and several positive pre-clinical studies in mutant SOD1 ALS models. There are even a small number of PALS reporting benefits from it, though in our opinion the described benefits are thus far of uncertain clinical significance. At this time, the safety of repeated doses of CuATSM is unknown, as is the optimum daily dose, and it appears to be very expensive. Until trials clarify dosing and safety, as well as effectiveness in patients with and without SOD1 mutations, we do not recommend using CuATSM for ALS.

Declaration of interest

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