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ALSUntangled No. 52: Glutathione

THE ALSUNTANGLED GROUP

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RESEARCH ARTICLE

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ALSUntangled reviews alternative and off-label treatments for ALS on behalf of patients who ask about them. Here we review glutathione treatment, for which we have had 720 requests (1).

Background

Glutathione is a naturally occurring antioxidant which helps cells eliminate damaging free radicals (2). It is part of the "glutathione system" which includes chemicals that help synthesize glutathione as well as chemicals that use glutathione to fight oxidative stress (3). Glutathione exists in different forms including the active (reduced) form referred to as GSH, and the spent (oxidized) form referred to as glutathione disulfide (GSSG); GSH protects cells while rising GSSG indicates worsening oxidative stress (2). GSH itself is available as an oral, intranasal, inhaled or injectable supplement. These formulations are advertised on websites as a treatment for ALS (4,5). Some cysteine-containing supplements such as Immunocal and N-acetylcysteine (NAC) are used to increase intracellular GSH (3,6,7) and so their potential role in treating ALS will also be reviewed here.

Mechanism

Since oxidative stress is believed to play a role in ALS progression (8–10), antioxidants would seem to be plausible treatments. Unfortunately, most antioxidants have failed to slow progression in ALS trials (11). The only exception so far is edaravone which was associated with benefit in one small trial of highly selected patients (12) and is now FDA-approved for the treatment of ALS. Unlike other antioxidants though, studies in people with ALS (PALS) suggest specifically decreased levels of GSH in the blood (13), spinal fluid (14) and even in the motor cortex (15,16). There is also a relationship between levels of different components of the glutathione system and ALS progression; lower levels of GSH relative to GSSG are associated with faster progression (17). All of this is promising but it is not yet clear that taking any form of glutathione or cysteine-containing supplements can actually improve human motor cortex GSH levels or slow human ALS progression. Thus, ALSUntangled assigns glutathione treatment a "mechanistic plausibility" grade of C.

Pre-Clinical

Several studies have manipulated glutathione in cell and animal models of ALS. GSH administration was neuroprotective in motor neuronal NSC-34 cells expressing TDP-43 mutations (18). Increasing GSH via Immunocal delayed disease onset and slowed loss of grip strength in an SOD1 mutant mouse model (6). Increasing GSH via NAC delayed disease onset and slowed loss of motor decline in the same model (19) and in the wobbler mouse model as well (20). On the other hand, genetically increasing or decreasing GSH peroxidase, a component of the glutathione system, did not alter disease onset or progression in the mutant SOD1 mouse model of ALS (21).

Since all of the positive studies described above had methodological flaws (22) including small sample sizes and treatment commencing well before symptom onset (which is not possible in traditional human trials), ALSUntangled assigns a "pre-clinical grade" of C (Table 1).

Cases

On PatientsLikeMe, 58 PALS reported taking some form of glutathione for their ALS (23). Of

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Table 1. TOE grades for GSH in ALS.

	Grade	Explanation
Mechanistic plausibility	C	Numerous observations suggest a role of oxidative stress in driving ALS progression and there are specific reductions in GSH in the blood and motor cortex of PALS. However, it is not year clear that taking any form of glutathione or cysteine-containing supplement can elevate human motor cortex glutathione levels or slow human ALS progression
Pre-clinical	C	Increasing GSH was beneficial in flawed studies in some but not all cell and animal models of ALS
Cases	A	Within a published cohort of validated "ALS reversals" 2 patients were taking glutathione during their recovery (and one of these was also taking NAC)
Trials	F	Small trials of glutathione and acetylcysteine (to raise glutathione) in PALS showed no significant benefits
Risks	B	In previous trials of many different conditions (including ALS), more than 0 but less than 10% of patients taking glutathione or low dose NAC experienced side effects

those who completed detailed treatment evaluations, 3 perceived "major effectiveness," 2 "moderate effectiveness," 4 "slight effectiveness," 9 "none," and 11 "unknown." One PALS reported taking Immunocal for ALS with "unknown" effectiveness (24). Sixty-three PALS reported taking NAC for ALS (25). Of those who completed detailed treatment evaluations, 1 perceived "major effectiveness," 2 "moderate effectiveness," 4 "slight effectiveness," 4 "none," and 9 "unknown." We did not have records to validate the diagnoses or reported improvements in any of these patients.

Within the published cohort of confirmed "ALS reversals" (patients with an independently validated diagnosis and dramatic recovery of lost motor function), 2 were on forms of glutathione (as well as multiple other supplements) during their recovery (26). One of these was also on NAC. As we have stated previously, ALS reversals are not necessarily due to the treatments being taken; there are multiple possible explanations for these cases (26). Nonetheless, based on the 2 validated ALS reversals whose cases are published in a peer reviewed journal (26), we assign a "cases" grade of A (Table 1).

There is one other reported "ALS reversal" on glutathione (27). A 49-year-old male was diagnosed with ALS based on a history of gradual onset, progressive muscle weakness, atrophy and fasciculations, and electromyography (EMG) showing widespread denervation and reinnervation changes. He received an intravenous infusion of glutathione alongside other vitamins and chelation therapy for approximately 3 years. His progression was monitored by strength testing as well as electromyography (EMG). At the end of the treatment, he was declared to have an absence of ALS based on a normal neurological exam and EMG. We do not agree that this patient had ALS. He had no upper motor neuron signs (which should be present in ALS). He had sensory nerve conduction abnormalities and motor conduction blocks on his EMG as well as elevated spinal fluid protein (which are all atypical for ALS). This combination of findings would be more typical of chronic inflammatory demyelinating polyneuropathy, which can improve spontaneously. Additionally, his follow up EMG was reportedly completely normal. To our knowledge, this EMG change is not physiologically possible. Established reinnervation changes on EMG do not resolve or revert to normal, regardless of their cause.

Trials

There have been small clinical trials of GSH (28) and acetylcysteine (29) in PALS. Unfortunately, neither of these trials showed any significant benefits, so we assign a "trials" grade of F (Table 1).

Dosing, costs and risks

Glutathione itself can be taken in many forms including oral, nasal, inhalation, and injection. Oral glutathione is substantially metabolized by the gut and liver so it is not an efficient way to raise blood or CNS levels (30,31). Beyond this, an optimal route or dosage for ALS has not been established. In the PatientsLikeMe cohort taking glutathione for ALS, reported doses range from 1 tablespoon to 2400 mg daily (23). In the above-described ALS trial, the dose was 600mg given intramuscularly each day. Costs depend on the route and dose, with the PatientsLikeMe cohort reporting a range of less than $25 to more than $200 monthly (23). Most forms of glutathione have been well tolerated; less than 10% of participants with a wide range of conditions experienced side effects in short duration trials (28,32–36). In the ALS trial, only 2 out of 32 PALS experienced glutathione side effects (nausea) felt to be related to treatment (28). Inhaled glutathione can cause

transient coughing and bronchoconstriction in asthma patients with sulfite-sensitivity (37). Based on these safety data, we assign glutathione treatment a "risks" grade of B, but caution readers that there has not been much research regarding the safety of long-term glutathione intake.

The most popular cysteine-containing supplement used to increase glutathione levels is NAC. This can be used orally or intravenously, or be inhaled, and again there is no consensus on the optimal route or dose for PALS. The PatientsLikeMe cohort reported using doses between 400mg and 6 g daily (25). NAC at low doses also appears safe and well tolerated. In trials across a variety of different conditions, doses of 1200mg twice daily or less were associated with side effects in less than 10% of patients; higher doses were commonly associated with a variety of non-serious adverse events including headaches, nausea, chills, fever and bronchospasm (38). NAC can interact with nitroglycerin and cause severe hypotension, so this combination should be avoided (38). NAC costs reported by the PatientsLikeMe cohort ranged from $25–49 monthly (25).

Conclusion

As an ALS treatment, glutathione and cysteine-containing supplements that increase glutathione appear reasonably safe, and they have a plausible mechanism, positive preclinical data and 2 interesting case reports. Unfortunately small clinical trials of glutathione itself and of acetylcysteine showed no significant benefit. Given these negative clinical trials, we do not advise PALS to take glutathione or cysteine-containing supplements for their ALS at this time.

Declaration of interest

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