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ALSUntangled No. 25: Ursodiol

The ALSUntangled Group

ALSUntangled reviews alternative and off-label treatments for ALS. Here, on behalf of patients who requested it, we review ursodiol as a treatment for ALS.

What is ursodiol?

Ursodiol or ursodeoxycholic acid (UDCA) is classified as a bile acid, which is a derivative of the steroid cholesterol. Bile acids serve many functions in the body, the most prominent of which is the absorption of fat from the intestine. While ursodiol exists in small amounts in the human body, it was originally discovered in bears ('ursa', bear in Latin). Due to its structure ursodiol is more readily dissolved in water and therefore is more easily absorbed than other bile acids. In Chinese medicine bear bile has been used for centuries in the treatment of problems of the gall bladder and liver (1). Synthetic ursodiol was first studied as a pharmaceutical treatment for gallstones in the 1970s (2) and for primary biliary cirrhosis (PBC) in the 1980s (3). The mechanism of action in the treatment of gallstones is through ursodiol's ability to decrease the body's secretion of cholesterol into bile. The mechanism in PBC is less well understood.

Why might ursodiol be useful for people with ALS (PALS)?

The benefits of ursodiol in cholestatic disease extend beyond its ability to regulate cholesterol levels. Multiple studies have demonstrated ursodiol's cytoprotective effects, which have been attributed to antioxidant, anti-apoptotic and immunomodulatory properties.

The antioxidant properties of ursodiol have been demonstrated both through the enhancement of innate antioxidant such as glutathione (4,5), blocking the generation of reaction oxygen species by hydrophobic bile acids (6) and through direct antioxidant effects by hydroxyl radical and ferric iron scavenging (7).

Anti-apoptotic effects of ursodiol have been explained both by blockage of apoptotic pathways (8,9) and promotion of cell survival pathways (10).

In patients with PBC, the immunomodulatory effects of ursodiol have been demonstrated to include decreased antibody production (11), MHC I and II production (12,13), natural killer (NK) activity (14) and eosinophil degranulation (15).

It is these cytoprotective properties that have made ursodiol an attractive potential tool in slowing the loss of motor neurons associated with ALS. However, much of this evidence has been demonstrated in liver disease and hepatocyte cell models. We found only a single recent study suggesting that a glycine-conjugated form of ursodiol, GUDCA, could protect SOD1 mutant motor neuron cultures against apoptosis (16).

Has ursodiol demonstrated benefit in animal models?

We were unable to find any studies of ursodiol in animal models of ALS.

In rodent models of Huntington's disease (HD), there is evidence that a taurine-conjugated form of ursodiol, TUDCA, which has greater solubility than non-conjugated ursodiol, can prevent cell death and improve functional outcomes such as behavior and walking (17). TUDCA also prevented cell damage associated with the presence of amyloid-beta (Aβ) peptide in rat neuronal cultures (18). Aβ peptide is found in the senile plaques of Alzheimer's disease. In rat models of ischemic stroke, brain hemorrhage and spinal cord injury there were fewer signs of neuronal death and better functional outcomes in those rats which had received intravenous (stroke), intra-arterial (hemorrhage) or intraperitoneal (spinal cord injury) TUDCA before or very near the time of laboratory induced injury (19–21). Using a poorly described formulation of ursodiol called 'Yoo's solution' (see below), one group found reduced apoptosis of mouse sensory neurons when treated

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animals were exposed to the chemotherapeutic agent cisplatin (22).

Have there been any trials of ursodiol in PALS?

There are two published trials examining the effect of ursodiol in PALS. In 2010 Parry (23) published a safety and tolerability study of 18 PALS randomly assigned to receive urso-deoxycholic (UDCA) acid at doses of 15, 30, and 50 mg/kg of body weight per day. Based upon their ALSFRS-R score and the requirement of a vital capacity of > 60%, these were PALS in the early stages of the illness. UDCA was generally well tolerated as indicated by the fact that subjects completed the four-week course of treatment and that all side-effects were rated as mild. Common side-effects included constipation (7/18) and diarrhea (5/18), both of which were more common in the highest dose group of 50 mg/kg. All other adverse events occurred only in single individuals without regard for dosing level. To verify that UDCA entered the central nervous system, Parry et al. examined cerebrospinal fluid (CSF) UDCA levels after four weeks of dosing. Patients in this study had a dose dependent increase in UDCA levels in their CSF. No systematic assessments for efficacy were made in this study.

In 2012 Min published the results of a randomized trial in which PALS received oral solubilized UDCA (3.5 g/140 ml/day) or placebo for three months after a run-in period of one month and switched to receive the other treatment for three months after a washout period of one month (24). They reported a statistically significant difference in the rate of change in the Appel ALS rating scale (AALSRS) but no difference in the decline of the revised ALS functional rating scale (ALSFRS-R) or forced vital capacity (FVC) during the treatment period. As the difference in the change of the AALSRS was quite small, and therefore not likely clinically significant, the authors assumed a linearity of this difference in slope over time, such that the treatment may delay a clinically significant change (defined as 20 points) in the AALSRS by 14.9 months. This assumption is questionable as there is evidence suggesting that progression in ALS is actually curvilinear (25). Additionally, as pointed out by the authors, the study suffered from a sizable drop-out rate, which was greater in the treatment group. Oddly, the authors did not perform an intention-to-treat analysis. This error would likely bias the study toward finding a treatment effect, even if one were not present. As in the Parry study, there were more gastrointestinal adverse events in people receiving treatment. In this study there was no attempt made to examine the levels of UDCA in the CSF.

Another potentially concerning aspect of the Min et al. study is the use of an oral solubilized form of ursodiol called 'Yoo's solution' This formulation is produced by Prime Pharm and is likely named after Seo-Hong Yoo, who is listed as an employee of Prime Pharm on one of the papers describing its use (26). Unfortunately, details regarding the formulation are sparse. Min reports that Yoo's solution is 'highly soluble in water with a solubility of 80 mg/ml, and stable from pH 1 to 14 without producing precipitate' (24). References following these claims are provided (22,26); however, these references simply restate these claims without providing data from testing of the chemical properties of the drug.

Within 'stage 1' of a recent placebo controlled trial of ceftriaxone (27), 66 patients were randomized to receive either placebo (21 patients), or ceftriaxone at one of two doses (45 patients). Patients on ceftriaxone had ursodiol 300 mg twice a day started at various times during this 20-week stage. We performed a change point regression analysis (also called a 'hockey stick' analysis) (28) of ALSFRS-R scores in this trial, with the assumption that if ursodiol was effective in slowing progression, there should have been a deflection ('bend') in the slope of the ALSFRS-R scores around the time that it was started. This did not occur, suggesting that ursodiol had no effect on ALSFRS-R progression. In stages 2 and 3, enrollment was increased up to 513 patients, again with one-third randomized to placebo and two-thirds randomized to ceftriaxone, and the study duration was increased to 52 weeks (27). In these stages, all patients started on ceftriaxone were also started on ursodiol 300 mg twice a day at the same time (patients on placebo received an ursodiol placebo). Treatment with ceftriaxone/ursodiol was no better than treatment with placebo/placebo in terms of survival or ALSFRS-R progression in this well-designed study in which all patients who started a treatment were analyzed (29). However, the dose of ursodiol used in the ceftriaxone study was much lower than the doses used in the Parry and Min studies described above.

Other reports of ursodiol in PALS

Within the online community Patients Like Me, 14 members report trying ursodiol for their ALS at doses between 450 mg and 3300 mg daily (30). Of those 10 with reviews, one rated it as having slight effectiveness, and nine rated it as having none. Reported side-effects ranged from mild to severe, and were mostly gastrointestinal.

Google search for 'ALS ursodiol' yielded seven als.net posts in which users with ALS reported taking ursodiol at various doses: two reported slowing in progression, two reported improvements in strength and one reported increased energy (31).

Costs and potential side-effects of ursodiol

Ursodiol is available by prescription and a dose of 500 mg twice a day costs around $100 per month (32).

Side-effects are generally mild and gastrointestinal in nature. More serious side-effects are rare but have been described and include elevated blood glucose, elevated creatinine, leukopenia and skin rash (33).

Conclusions

Ursodiol has interesting mechanisms of action, appears reasonably safe and well-tolerated, has anecdotal reports of benefit in 6/21 of patients who report taking it, and a form of it (Yoo's solution) was associated with slightly slower ALS progression in one out of three outcome measures within a poorly designed study that did not account for large numbers of drop-outs. However, analyses of ursodiol data from the well-conducted randomized, double-blind ceftriaxone trial show that ursodiol 300 mg twice a day is no better than placebo at prolonging survival or slowing ALS progression. Based upon this review, ALSUntangled does not recommend off-label use of ursodiol as a treatment for ALS, at least at doses of 300 mg twice a day. Determining whether higher doses or different formulations are effective will require further well-designed studies.

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