

## Short Communication

# Ursodeoxycholic Acid May Slow the Progression of Amyotrophic Lateral Sclerosis

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## Abstract

Ursodeoxycholic acid (UDCA) and its taurine-conjugate, tauroursodeoxycholic acid (TUDCA) are bile acids that have been shown to have a wide range of anti-apoptotic, mitochondrial stabilizing and cytoprotective properties. They have been shown to be protective *in vitro* and *in vivo* in a number of models of neurodegenerative diseases. The processes involved in cell death in amyotrophic lateral sclerosis and the known mechanisms of action of UDCA suggest that it could be an effective therapeutic strategy for patients with the disease. Two preliminary studies in small numbers of patients have shown slowing in some, but not all measures of disease progression. Following a pharmacokinetic and CSF penetration study of UDCA in ALS patients we observed that patients who continued to take UDCA long-term survived more than twice as long as those who did not continue the treatment. The preliminary studies along with the observed outcome in our patients suggests that UDCA may be an effective treatment in ALS and is worthy of a more detailed study in a larger cohort of patients.

## ABBREVIATIONS

ALS: Amyotrophic Lateral Sclerosis; UDCA: Ursodeoxycholic Acid; TUDCA: Tauroursodeoxycholic Acid; AALSRS: Appel ALS Rating Scale; ALSFRS-R: ALS Functional Rating Scale-Revised; CSF: Cerebrospinal Fluid; IRB: Institutional Review Board; FVC: Forced Vital Capacity

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is an inexorably progressive disease in which survival is typically three to five years from onset of weakness [1]. The pathogenesis of ALS is incompletely understood but mechanisms involved in motor neuron degeneration may include oxidative damage, mitochondrial dysfunction, neuroinflammation, growth factor deficiency, and glutamate excitotoxicity [2-5]. One or a combination of these mechanisms is presumed to lead to neuronal degeneration. Pharmacological treatment with riluzole, a glutamate modulator, prolongs survival by about three months [6] and has been approved for ALS treatment by regulatory agencies in many countries. There are no other approved pharmacological therapies.

Ursodeoxycholic acid (UDCA) and its taurine conjugate (TUDCA), are potent inhibitors of apoptosis, partly through their

ability to interfere with the upstream pathway of mitochondrial cell death, to inhibit oxygen radical production, to reduce endoplasmic reticulum stress and to stabilize the unfolded protein response [7]. In addition, Sirtuin 1 (SIRT1) is involved in mitochondrial biogenesis and stabilization of endoplasmic reticulum stress. We have recently explored the function of the miR-34a/SIRT1/p53 pathway and its modulation by UDCA in rat liver *in vitro* and *in vivo* [8]. UDCA hampered miR-34a expression, induced SIRT1 expression and inhibited p53 acetylation. In addition, miR-34a over expression resulted in cell death and apoptosis in rat hepatocytes, *via* SIRT1 and p53, and UDCA strongly inhibited this pathway. SIRT1, in particular, constitutes an important target regulated by UDCA mostly at the post-transcriptional level. Interestingly, resveratrol is a SIRT1 activator that attenuated motor neuron loss in ALS [9].

UDCA and its conjugated derivatives have been demonstrated, both *in vitro* and *in vivo*, to have cytoprotective effects in a number of neurodegenerative disorders that are characterized by increased rates of cell death. TUDCA is a potent neuroprotective agent in a transgenic animal model of Huntington's disease [10]. TUDCA was also effective in experimental Parkinson's disease, improving the survival and function of nigral transplants in rat models of Parkinson disease [11], preventing MPTP-induced dopaminergic cell death in mice [12], and partially rescuing

mitochondrial function in the *C. elegans* model of Parkinson's disease [13]. TUDCA has also been shown to suppress apoptosis and preserve function and morphology of photoreceptor cells in mouse models of retinal degeneration [14]. TUDCA has been proposed as having a potential benefit in Alzheimer's disease based on its ability to inhibit glutamate-induced apoptosis in rat cortical neurons [15]. Finally, the glycine conjugate (GUDCA) was effective in a cellular model of mSOD1 neurodegeneration [16].

In humans, UDCA and TUDCA have also shown promise in ALS. Min et al., [17] reported that UDCA slowed the rate of progression as measured by the Appel ALS rating scale (AALSRS) but there was no difference in the rate of deterioration of the revised ALS functional rating scale (ALSFRS-R) or forced vital capacity (FVC). Elia et al., [18] randomly assigned subjects to TUDCA or placebo after measuring the rate of decline of the ALSFRS-R during a three-month run-in period. They showed that the rate of decline for TUDCA-treated subjects was slower compared to the three month run in period whereas the placebo-treated patients continued to decline at the same rate. Both studies confirmed that the treatment was well tolerated with no differences in adverse effects being seen between active-treatment and placebo groups.

We had also previously showed that UDCA was safe and well tolerated in ALS patients and that it penetrated the CSF in a dose-dependent manner [19]. At the completion of our pharmacokinetic study, subjects were offered the option of continuing UDCA free of charge until such time as the final subject had completed the study. Thereafter, the subjects were required to pay for the drug themselves. We here report the outcome of those study subjects who chose to continue to take the drug long-term compared to those who did not.

## MATERIALS AND METHODS

For the original study subjects were recruited from the ALS Clinic at the University of Minnesota and all had probable or definite ALS as defined by the World Federation of Neurology ALS criteria [20]. Eighteen subjects received UDCA at doses of 15, 30, and 50 mg/kg of body weight per day for 4 weeks. At the completion of the study three subjects opted to continue long-term UDCA while 14 did not (one patient was lost to follow-up). Those who did not continue therapy cited inability to pay for the drug or perceived lack of benefit during the four weeks of dosing as reasons for stopping the medication. The original study was approved by the Institutional Review Board (IRB) of the University of Minnesota (IRB# 0304M46721).

This current report is based on a retrospective review of the medical records of those subjects who had participated in the original study, 10 years after that study was completed. Age, duration of disease and two measures of disease severity (ALSFRS-R and FVC expressed as percent of predicted value) were recorded at the time of study enrollment and the duration of survival or time to initiation of permanent invasive artificial ventilation was obtained from the medical records. ALSFRS-R and FVC were not recorded at completion of the original study as this was a short term dosing study to determine blood and CSF concentrations and clinical changes were not anticipated.

## RESULTS AND DISCUSSION

At the time of enrollment in the original study there were no significant differences between those who continued UDCA treatment and those who did not with regard to age or disease severity as measured by the ALS Functional Rating Scale (ALSFRS-R) and forced vital capacity (FVC) (Table 1). Average duration of disease was slightly shorter in those subjects who chose not to continue treatment. The original study showed that UDCA was well absorbed with three times daily dosing and a stable plasma level was seen within eight days of starting administration. UDCA entered the central nervous system, as measured through CSF concentrations, in a dose dependent manner.

Survival in those subjects who continued to take UDCA long-term was more than twice as long as those who did not. Subject 1 who continued on treatment died from the respiratory complications of ALS 103 months from time of diagnosis. Subject 2 died of an unrelated cause (glioblastoma) after 104 months. His FVC had declined only 14% (97% to 83%) during the five years on UDCA and immediately prior to the diagnosis of the glioblastoma he was able to ambulate with the support of a single cane and was independent for activities of daily living. Occurrence of glioblastoma in a patient taking UDCA is not considered to be related to the drug; the medication has been widely prescribed for liver disorders for decades and has been used in Chinese traditional medicine for over 3000 years without reports of glioblastoma. Subject 3 is still alive and ventilator-independent 172 months from time of diagnosis although she is confined to a wheelchair and has a gastrostomy for feeding. In contrast, all subjects who chose not to continue treatment died of respiratory complications or started invasive mechanical ventilation after an average of 49 months from time of diagnosis (range 13-104

**Table 1:** Baseline characteristics at the time of enrollment in the study for each subject who continued on long-term treatment (UDCA) and the average and range for the subjects who stopped treatment at the completion of the study (no UDCA). The subject numbers correspond to the number in the Results section.

	UDCA			No UDCA
	# 1	#2	#3	
Age (range)	55	57	37	55 (37 - 65)
Disease duration in months (range)	37	19	37	18 (4 - 47)
ALSFRS-R (range)	47	43	37	43 (38 - 49)
FVC (range)	88	97	73	91.2 (67 - 115)

**Abbreviations:** UDCA: Ursodeoxycholic Acid. ALSFRS-R: Amyotrophic Lateral Sclerosis Rating Scale – Revised. FVC: Forced Vital Capacity Expressed As Percent of Predicted Value

months). In the subjects who continued to take the drug no new adverse effects were noted.

## CONCLUSION

Although anecdotal, these observations suggest that UDCA had a beneficial effect in slowing progression of ALS and prolonging survival. There were no differences in age or disease severity that could have explained the much longer survival in the patients who continued therapy compared to those who did not. However, the untreated patients did have shorter disease duration at the time of enrollment which raises the possibility that their disease course was more rapid and that could have contributed to the shorter survival. Nonetheless, these observations, particularly when taken in conjunction with the studies reported by Min et al., [17] and Elia et al., [18] provide support for a multicenter pivotal study of UDCA or TUDCA in a much larger cohort of ALS patients.

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