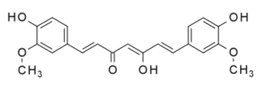
Cured By Curcumin? Results from a Widely-Inclusive, Historically-Controlled, Virtual Pilot Trial of Theracurmin

Richard Bedlack,[1] Xiaoyan Li,[1] Michelle Ward,[1] Subhara Raveendran,[2] Lam Vo,[2]

1. Duke University Medical Center - Durham NC, USA
2. PatientsLikeMe (PLM)-Cambridge MA, USA

Background

Curcumin is a polyphenol naturally found in turmeric and curry powder.



It could theoretically slow ALS progression via effects on neuroinflammation, oxidative stress, protein aggregation and the gut microbiome. In a cell model of ALS, curcumin treatment reduced hyperexcitability, markers of oxidative stress & protein aggregation, and improved mitochondrial function. In two small flawed human trials, curcumin treatment was associated with improved ALS outcomes. Nine "ALS Reversals" are associated with forms of curcumin. When taken orally, curcumin is safe and well-tolerated. (ALS and FTD 2018;19:623-629). We recently finished a pilot trial Theracurmin, a water-soluble form of curcumin that was associated with improvements in a trial in patients with cognitive impairment (Am J Geriatric Psychiatry 2017;17:S1064).

Hypotheses

1. Theracurmin decreases the rate of ALSFRS-R progression by 50% relative to historical controls.
2. Theracurmin increases the frequency of ALS reversals (defined by an improvement of 4 or more points in the ALSFRS-R over the course of 6 months) to at least 2%.
3. Theracurmin alters the gut microbiome in people living with ALS.
6. The novel features of this pilot trial will be associated with improved participant enrollment compared to prior more traditional ALS trials where this is 2 participants per site per month (ALS 2008;9:257-265).
7. The novel features of this pilot trial will be associated with improved participant retention compared to prior more traditional ALS trials where the retention out rate is 78% (Neurology 2013;15:1350-1355)

Methods

Like our previous trial of Lunasin (ALS and FTD 2019;20:285-293) , this single-center trial featured broad inclusion criteria, historical controls, virtual data collection, and real-time results. Participants measured their ALSFRS-R score, perceived side effects, burdens and effectiveness,, and recorded these monthly on PLM. They and a healthy control from the same household also mailed in saliva and stool samples at 3 time points over 6 months. The protocol was published online (https://alsreversals.com/wp-content/uploads/2021/06/ROAR2v16cc.pdf).

Enrollment & Retention

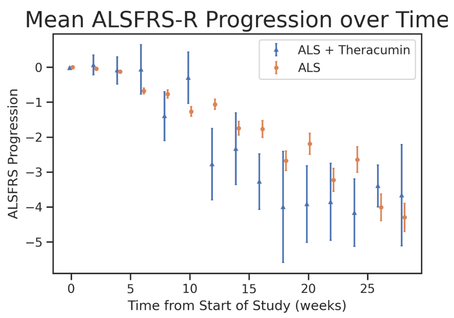
We enrolled 50 patients in 16 months (enrollment rate 3.1 patients per site per month). Participants were primarily white (n=43) males (n=31), with a mean age of 61 years (range 39-81 years). Thirty-eight participants were on Riluzole, one was also on Edaravone. Participants' disease duration was longer than most trials, including some with ALS for 10 years. Thirty-five participants (70%) completed the 6-month study.

Effectiveness

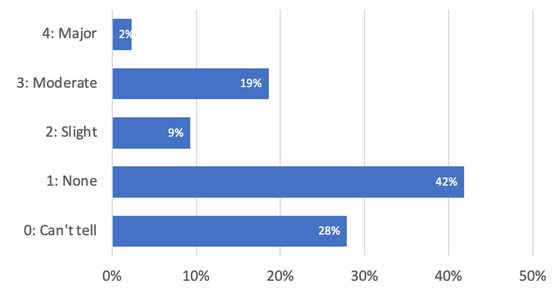
The following table summarizes available ALSFRS-R scores at different time points during the study.

Timepoint	N	Min	Max	Mean	Std. Dev.
Week1	39	16	45	34.79	6.502
Week2	36	18	45	34.83	6.691
Week3	39	16	44	33.44	7.192
Month1	43	18	46	34.65	7.04
Month2	41	13	46	32.66	8.788
Month3	37	11	44	31.84	9.338
Month4	36	16	45	31.97	7.977
Month5	32	17	44	31.53	8.493
Month6	30	14	42	31.63	8.307

ALSFRS-R decline was compared to matched historical controls, similarly to previous PLM studies (Nature Biotechnology 2011;29:411-414, ALS and FTD 2019;20:285-293).



There was no significant slowing in ALSFRS-R progression relative to historical controls. No participant had an ALS reversal. Participants were also invited to rate their own perceptions of effectiveness throughout the study. Choices included “none,” “slight,” “moderate” and “major.” Of the participants who completed this outcome, 79% perceived little or no effectiveness at any time point.



Adverse Events

There were 2 serious adverse events, both considered unrelated to treatment (1 pulmonary embolus, 1 death due to ALS progression). Twenty-three participants reported non-serious adverse events (some reported multiple adverse events), as shown in this table:

Non-Serious Adverse Event	Number of Participants Reporting
Diarrhea or Loose Stools	11
Hot flashes	3
Covid infection	3
Itching	2
Increased weakness	2
Malaise	1
Rash	1
Anxiety	1
Flu-like symptoms	1
Constipation	1
Abdominal pain	1
Headache	1
Cramps	1

Burdens, Affordability, Adherence

Most participants reported no burden, good affordability, and being very adherent with taking Theracurmin.

Treatment evaluation	Not at all	A little	Somewhat	Very	Null
Adherence %	1%	1%	5%	93%	
Burden %	96%	4%	0%		
Affordability %	19%	0%	1%	73%	6%

Microbiome

Analyses of saliva and stool microbiome are underway. These will compare patients to healthy controls and evaluate the effect of Theracurmin treatment on the microbiome.

Conclusions

1. Theracurmin was safe and well tolerated.
2. Theracurmin did not measurably slow progression.
3. None of our 50 participants had an ALS reversal.
4. Despite occurring during a pandemic, this trial had an above-average enrollment rate and included a very diverse population.
5. Retention rate was about average for a 6-month ALS trial.
6. Missing data were more common in this trial than our previous one (ALS and FTD 2019;20:285-293.
7. This efficient design could serve as a model for larger “de-centralized” trials or expanded access programs using products that appear reasonably safe.

Acknowledgements

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