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ALSUntangled No. 47: RT001

Richard Bedlack

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RESEARCH-ARTICLE

ALSUntangled No. 47: RT001

THE ALSUNTANGLED GROUP

ALSUntangled reviews alternative and off-label therapies on behalf of persons with ALS (PALS). Here, we review the use of Retrotope's RT001 in PALS.

Overview

RT001 is an orally administered compound being developed by the pharmaceutical startup company Retrotope (1) for patients with Friedreich's ataxia, an inherited neurodegenerative disease. The company website suggests broad potential usefulness in other neurodegenerative disorders including ALS. Chemically, RT001 is a modified polyunsaturated fatty acid (PUFA) with an omega-6 structure (1). Two of the normal hydrogen atoms have been replaced with deuterium atoms (D-PUFA). Mechanistically, this change allows it to reduce the oxidative stress-induced damage in a unique way as described below. RT001 is not FDA-approved yet for any disease and is currently only available through Retrotope's clinical trials and expanded access programs. An expanded access program for PALS was recently created (2).

Mechanism

Several lines of evidence suggest that oxidative stress might play a role in the pathophysiology of sporadic ALS (3). Unfortunately, previous clinical trials of antioxidants have been disappointing, showing either no benefits (4–6) or, on one occasion, a possible benefit to a subset of PALS (7).

Excess free radicals are the molecular cause of cellular oxidative stress. Free radicals are toxic to cells because they damage DNA and key cellular proteins; however, they also have important physiologic roles in cell signaling and pathogen defense. Most antioxidants work by neutralizing a single free radical. Retrotope postulates that RT001 might be more effective than other antioxidants because it works at the level of lipid (i.e. fatty acid) peroxidation (1). Lipid peroxidation is a chemical reaction in which a free radical converts a fatty acid into a fatty acid peroxide. This chemical reaction also results in another free radical that can peroxidize more fatty acids. This process continues as a self-propagating chain reaction that results in extensive lipid peroxidation. The many resulting fatty acid peroxides are unstable and can form additional free radicals, thus multiplying the initial oxidative stress and causing more cellular injury (8). Deuterium atoms are heavier than hydrogen atoms, therefore peroxidation of D-PUFAs is slower than peroxidation of PUFAs. The slower lipid peroxidation of D-PUFA may lessen or interrupt some of the downstream cellular damage associated with oxidative stress (1). Cell culture studies and animal models of Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease support the idea that RT001 and other D-PUFAs decrease oxidative stress (1, 9–17), but we could not find experimental evidence that D-PUFAs were more potent in a biological context compared to most other antioxidants.

Based on the ability of RT001 to lower markers of oxidative stress in multiple neurodegenerative disease pre-clinical animal models, ALSUntangled assigns a "Mechanism" grade of B (Table 1).

Pre-clinical models

We learned of a single unpublished study of RT001 in the G93A SOD1 mutant mouse model (18). No benefit was seen in this study. This outcome is odd because antioxidants typically prolong survival and slow disease progression in this mouse model (19). Based upon this lack of effect, ALSUntangled assigns a "Pre-Clinical Models" grade of F (Table 1).

Cases

We learned of 3 PALS taking RT001 as part of an expanded access program (18). Only one of these patients has been on the compound for more than 1 month. In the six months prior to taking RT001, his ALSFRS-R score declined quickly, from 30 to 15. At this point, his FVC was 60% of predicted and he had unintelligible speech. After 4 months

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Table 1. Table of evidence for RT001.

	Grade	Explanation
Mechanism	B	RT001 has been shown to lower brain oxidative stress in several animal models of neurodegenerative disease.
Pre-Clinical Models	F	The only available study in an ALS model showed no benefits.
Cases	D	One PALS taking RT001 for 4 months had small improvements in ALSFRS-R score, FVC and speech. We did not independently confirm his diagnosis or improvements.
Trials	U	No clinical trials of RT001 in PALS have been conducted.
Risks	U	Experience in PALS is limited at this time.

on RT001, his ALSFRS-R score had improved to 18, his FVC improved to 73% of predicted and his speech was now intelligible. This is difficult to interpret as this is only one PALS, the ALSFRS-R and FVC improvements were small enough to be consistent with the natural course of ALS, and we did not have records to independently confirm this person's diagnosis or improvements. We found no other cases in our Google and PatientsLIkeMe searches. Based upon the single report of improvement, which we were unable to independently verify, ALSUntangled assigns a "Cases" grade of D (Table 1).

In addition to ALS, Retrotope has initiated RT001 expanded access programs for Progressive Supranuclear Palsy and Infantile Neuroaxonal Dystrophy (20, 21). Some patients in these programs are reportedly showing signs of possible improvement, but it is not clear that these cases are relevant to PALS.

Trials

We found no trials of RT001 enrolling PALS. Therefore, ALSUntangled assigns a "Trials" grade of U (Table 1).

Of potential interest, there has been a small, short-duration trial in patients with Friedreich's ataxia, another neurodegenerative disease in which oxidative stress is believed to play a prominent role. Nineteen patients were randomized to receive RT001 at either 1.8 or 9 grams per day, or the same weight of a non-deuterated PUFA, for 28 days. A statistically significant improvement in maximum exercise capacity was observed in the RT001 (i.e. D-PUFA) groups relative to the PUFA groups. Positive trends in walking speed and other measures were also noted in the RT001 groups relative to the PUFA groups (22).

Risks

RT001 has never been carefully studied in PALS. One of the 3 PALS in the expanded access program reportedly experienced some nausea which resolved when the dosage was reduced from 3.6 to 1.8 g daily (18). In the Friedreich's ataxia trial, the dose of 1.8 grams daily was well-tolerated with no reported adverse events. However, over half of the patients taking 9 g of RT001 per day had diarrhea and one patient of very low body weight required hospitalization due to diarrhea (22).

RT001 is enzymatically metabolized to arachidonic acid with deuterium on the 13th carbon in humans (22). This form of deuterated arachidonic acid has been shown in a mouse cell line to decrease the production of important cell signaling molecules known as prostaglandins and leukotrienes (23). In one of the mouse models of Alzheimer's Disease described in "mechanisms," levels of one prostaglandin were assayed and reported to decrease in the brain with the administration of RT001 (14). The effect of chronically lowering levels of prostaglandins and leukotrienes in PALS is not known. Based on the lack of experience with RT001 in PALS, ALSUntangled assigns a TOE "Risks" grade of U.

Dosing and costs

The optimal dose of RT001 for PALS has not been established. From the limited data available so far (see "risks" section), lower doses (1.8 grams daily) seem to be better tolerated than higher doses (9 grams daily). RT001 has recently been made available for use by PALS through an expanded-access program (2). PALS receiving care at Massachusetts General Hospital, Columbia University or California Pacific Medical Center can work with their physician to receive RT001 from Retrotope for no charge (18).

Conclusions

RT001 has a novel mechanism for reducing oxidative stress that could theoretically work better than

more traditional antioxidants. In the small trial of patients with Friedreich's ataxia, it seems to be safe and well-tolerated at lower dosages but can cause nausea and diarrhea at higher doses. At the time of this writing, there is very little efficacy or safety data in PALS. An expanded access program is underway which allows PALS at certain clinics to try this compound free of charge. Data resulting from this expanded access program will help the planning of a possible future clinical trial.

Authors

ALSUntangled Reviewers who contributed to this paper include the following: Jesse Crayle (lead author), Richard Bedlack (senior author), Carmel Armon, Paul Barkhaus, Michael Bereman, Mark Bromberg, Greg Carter, Merit Cudkowicz, Terry Heiman-Patterson, Carlayne Jackson, Gregory Kenoyer, Pamela Kittrell, Chris McDermott, Kathy Mitchell, Kristiana Salmon, Dane Ward, Paul Wicks.

Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

Disclosures of interest

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