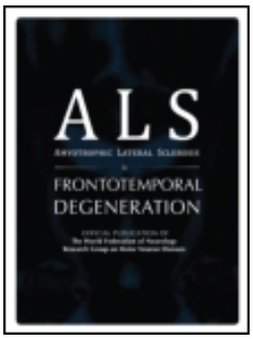

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ALSUntangled No. 31: Protandim

The ALSUntangled Group

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ORIGINAL ARTICLE

ALSUntangled No. 31: Protandim

THE ALSUNTANGLED GROUP

ALSUntangled reviews alternative therapies on behalf of patients with ALS (PALS). Here we review the use of Protandim for ALS, for which we have had more than 700 requests (1).

Overview

Protandim is an oral tablet derived from five different plants: Silybum marianum (milk thistle), Withania somnifera (Ashwagandha), Camellia sinensis (green tea), Curcuma longa (turmeric) and Bacopa monniera (2). It can activate an intracellular molecule called Nrf2 (nuclear factor erythroid 2-related factor) (3). Once activated, Nrf2 can bind to another molecule called ARE (antioxidant response element) and increase the expression of more than 200 antioxidant and anti-inflammatory genes (4).

Mechanism(s)

Oxidative stress is believed to be important in the pathophysiology of ALS (5). While most trials attempting to manipulate oxidative stress in PALS have thus far been unsuccessful (5), none of these trials targeted it via Nrf2. Few of these trials utilized biomarkers, so it is unclear if the agents and doses used were successful even in reducing oxidative stress. Nrf2 expression is reduced in the spinal cords of patients who died from ALS (6), and PALS with endogenous overexpression of Nrf2 have a delayed ALS onset (7), supporting a potential role for agents like Protandim that act through this pathway. Protandim can activate Nrf2 in human coronary epithelial cells (8); it has not been shown to activate Nrf2 in motor neurons, nor in any cells in living patients even though an in vivo assay exists (9). One study showed that Protandim can up-regulate antioxidant biomarkers and decrease markers of lipid peroxidation in humans (2). This study had a small sample size (29 patients). One of the authors on this study, J. McCord, was associated with LifeVantage (the company that sells Protandim) at the time this article was published (10). This creates a potential conflict of interest. The study has never been replicated by an independent group, and has never been carried out in PALS. ALSUntangled assigns a TOE 'Mechanism' grade of A based on this information (Table I).

Preclinical data

We found no studies of Protandim in preclinical ALS models. ALSUntangled assigns a TOE 'Pre-Clinical' grade of U based on this information (Table I).

The ALSUntangled Group Currently Consists of the following members: Richard Bedlack, Colin Quinn, Chafic Karam, Alex Sherman, Lyle Ostrow, Orla Hardiman, Terry Heiman-Patterson, Laurie Gutmann, Mark Bromberg, Gregory Carter, Edor Kabashi, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, L. P. Rowland, Erik Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Maragakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula, Gleb Levitsky, Mieko Ogino, Jeffrey Rosenfeld, Efrat Carmi, Merit Cudkowicz, Christina Fournier, Paul Barkhaus, Brett Morrison, Lorne Zinman, Craig Oster, Eric Valor, Neta Zach, Ahmad Ghavanini, Yvonne Baker, Kristiana Salmon

Note: this paper represents a consensus of those weighing in. Every investigator in this group does not necessarily share the opinions expressed in this paper.

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Table I. TOE grades for Protandim as an ALS treatment.

	Grade	Explanation
Mechanism	A	Protandim can increase antioxidant levels and decrease markers of lipid peroxidation in humans
Preclinical	U	No known studies of Protandim in preclinical ALS models
Cases	C	One unpublished report of Protandim benefit with a validated ALS diagnosis and benefits in ALSFRS-R score
Trials	U	No known trials of Protandim or any other Nfr2 activators in ALS
Risks	B	More than 0% but less than 10% of exposed patients in human trials experienced adverse events related to Protandim (but no serious adverse events)

Other manipulations of Nrf2 have been studied. Several different Nrf2 activating compounds were able to preserve motor performance and prolong survival in G93A mutant SOD1 mouse models of ALS (11–13), and knocking out Nrf2 resulted in a modest reduction in survival in this model (14). Interestingly, Nrf2 activation may need to occur in specific cell types in order to help these animals: genetic overexpression of Nrf2 in G93A mutant SOD1 mouse astrocytes delayed disease onset and prolonged survival (15), but overexpression of Nrf2 in neurons and muscle did not (16). These studies all have flaws according to published guidelines (17).

Data in PALS

Within the online community PatientsLikeMe, eight PALS reported taking Protandim (18). Of the five with evaluations, one perceived 'moderate' effectiveness and the others reported either no effectiveness or that 'they can't tell' any effectiveness. Google Search of 'ALS and Protandim' led us to the website of S. Bishop, who reported improvements in his ALS from Protandim (19). We were able to connect with Bishop via e-mail (20). He sent us records confirming a history of slowly progressive weakness without pain or sensory loss, exams by multiple neurologists showing upper and lower motor neuron signs in the arms and legs, EMG showing denervation and reinnervation in the arms and legs, and unremarkable C-spine imaging; based on this we agree that he likely meets revised El Escorial criteria for 'clinically probable ALS' (21). Between 1 January 2000 and 1 November 2009 his ALSFRS-R score declined from 48 to 37. In November 2009 he started Protandim at 1 tablet per day (20). On 28 July 2015 his ALSFRS-R score was 44. Bishop's website referred us to a N. Marvin, a Family Practice Physician who has his own website (22) and has led international teleconferences about Protandim. In a telephone interview Marvin reported being aware of 18,000 people taking Protandim for various reasons, including eight PALS (23). He stated that four of these eight PALS have regained motor functions they had lost (23); records were not available to validate these diagnoses or improvements. It should be noted that Bishop's report has been criticized for two reasons (24). First, his progression rate was said to be very slow even before he started Protandim. This is true, but he was nonetheless slowly getting worse with a decrease in his ALSFRS-R score of 11 points. Since starting Protandim his ALSFRS-R score improved by 6 points. 'Reversals' in ALS progression such as this can occur spontaneously (25,26), but are very rare. A second critique is that his wife is a distributor for LifeVantage, the multi-level marketing company that sells Protandim (27). This creates a potential conflict of interest. N. Marvin is also a distributor for this company (22). ALSUntangled assigns a TOE 'Cases' grade of C based on this information (Table I).

There are no trials of Protandim or any other Nrf2 activators in ALS. ALSUntangled assigns a TOE 'Trials' grade of U based on this information (Table I).

Dosing, risks and costs

Protandim is most commonly taken at a dose of 1 tablet (675 mg) per day, although some studies use more (28). It is not clear to us that the optimal dose for increasing Nrf2 or antioxidant levels has been established in humans yet. No adverse events were seen in two small human trials of Protandim for non-neurological conditions (2,28). N. Marvin estimated that 8% of the 18,000 people he knows of on Protandim have had side-effects (23); these include loose stools and rash. ALSUntangled found no evidence of deaths or hospitalizations due to Protandim. Since at least one type of ALS is caused by a toxic 'gain of function' in SOD1 (29), agents that increase SOD levels such as Protandim (2) could theoretically accelerate ALS progression. This does not appear to be happening in mSOD1 mice exposed to other Nrf2 activators (11–13). ALSUntangled assigns a TOE 'Risks' grade of B based on this information (Table I).

The cost for a one-month supply of Protandim at 1 tablet daily is around $50 (27).

Conclusions

Protandim appears reasonably safe and inexpensive, has a promising mechanism by which it could help ALS, and there is a patient with a validated ALS diagnosis whose ALSFRS-R score improved on it. There are significant problems with the data described, including small study sample sizes, failure to demonstrate that Protandim increases Nrf2 in humans, failure to establish an optimal dose, and potential conflicts of interest among several of the

key individuals involved. Nonetheless, in our opinion, further study of Protandim in ALS appears warranted.

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