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RESEARCH ARTICLE

ALSUntangled 59: Tamoxifen
THE ALSUNTANGLED GROUP

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Abstract

Here we use the ALSUntangled methodology to review Tamoxifen as an ALS treatment. We show that it has plausible mechanisms, a positive preclinical study, a case report and 2 small trials suggesting benefits. We show that it appears reasonably safe, though there is a small risk of developing cancer with long term use. While we cannot yet endorse this as an ALS treatment, there is enough evidence to warrant another larger ALS trial.

Keywords: *Tamoxifen, ALSUntangled, off-label treatment, trials, ethics, therapy, clinical trials*

ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS). Unlike more traditional reviews (ex. Cochrane), ours are suggested by and written for a nonscientific audience and they are built around a Table of Evidence. This Table includes five categories of interest to patients: mechanistic plausibility, preclinical models, case reports, trials and risks. Within each category, our international team assigns a letter grade ranging from A to F based upon the specific type of information we can find. Our methods are explained in detail in a previous article (1) and on our website (2). The purpose of our reviews is to help PALS make more informed decisions about alternative and off-label treatments. Here, we review Tamoxifen for which we had over 300 requests (3).

Overview

Tamoxifen (scientific name trans-1-(4-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene) is an oral estrogen receptor modulator (4,5). It is sold under many brand names for the treatment of estrogen receptor-positive breast cancer (5). At least one website has argued that tamoxifen should be used to treat ALS (6). This paper reviews the scientific evidence for tamoxifen as an ALS treatment.

Mechanistic plausibility

We have previously reviewed the evidence for a pathogenic role of oxidative stress (7) and neuroinflammation (8) in ALS. Oral tamoxifen crosses the blood brain barrier (9), can reduce oxidative stress and neuroinflammation, and is also neuroprotective.

Oxidative stress

In a human trial of patients with idiopathic oligothenospermia, tamoxifen treatment was associated

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with a reduction in several biomarkers of oxidative stress (10).

Neuroinflammation

In rat models of subarachnoid hemorrhage (11) and spinal cord injury (12), tamoxifen treatment was associated with reduced biomarkers of neuroinflammation.

Neuroprotection

In mice with TDP-43 overexpression, tamoxifen treatment was associated with preservation of motor neuron counts, improved motor performance on a rotarod (13), and improved learning and memory (14). This neuroprotection is believed to have occurred via stimulation of autophagy (13,14).

While all these mechanisms are promising, the fact that tamoxifen treatment can reduce markers of oxidative stress in humans warrants a "Mechanisms" grade of A (Table 1).

Preclinical models

We found mention of tamoxifen treatment being beneficial in a murine retrovirus-induced mouse model of motor neuron disease, and in a mutant SOD1 mouse model of motor neuron disease (15,16); unfortunately we could not find detailed descriptions of these studies. As stated above, in mice with TDP-43 overexpression, tamoxifen treatment was associated with improvements in motor and memory functions (13,14). These studies are flawed due to small sample size (5–10 mice per group), unclear randomization and unclear rater blinding. These studies have not been independently replicated. As a result of these flawed studies in TDP-43 overexpressing mice, ALSUntangled assigns a "Preclinical" grade of C (Table 1).

Cases

On the online forum PatientsLikeMe, 16 patients reported taking tamoxifen for ALS, and 6 competed treatment evaluations (17). In terms of perceived effectiveness, one reported it as "moderate," one "slight," one "none" and the others "can't tell," No more details were available. Dr. Benjamin Brooks reported an improved ALS progression rate associated with tamoxifen treatment in one of his patients with ALS (15,16). This case report does not appear to have been published. Based upon Dr. Brooks' unpublished case, ALSUntangled assigns a "Cases" grade of C (Table 1).

Table 1. Table of evidence for tamoxifen.

	Grade	Explanation
Mechanism	A	Tamoxifen can reduce biomarkers of oxidative stress in humans
Pre-Clinical	C	Flawed studies in TDP-43 overexpressing mice show that tamoxifen treatment was associated with improved motor and memory function
Cases	C	One ALS expert reported an improvement in ALS progression on tamoxifen in his patient
Trials	C	Small trials suggest that tamoxifen treatment at higher doses such as 40mg or 80mg daily is associated with improved survival and ALS progression compared to treatment at lower doses or with creatine or a placebo
Risks	D	While tamoxifen was well-tolerated in small, short duration ALS trials, in other populations it has been linked to the development of cancer

Trials

We found three trials of tamoxifen in PALS. The first of these (NCT00214110) was reported at a meeting and has only been published in abstract form (18). This trial randomly assigned 60 PALS to five different doses of tamoxifen (10 mg weekly; 10 mg, 20 mg, 30 mg, and 40 mg daily) and measured ALS progression and survival over 2 years. Survival was better in patients on the three highest doses of tamoxifen compared the two lowest doses. No significant differences in ALSFRS-R or vital capacity were seen. This trial is flawed due to its small sample size.

The second trial (NCT01257581) was a "selection design" in which 60 PALS were randomly assigned to creatine 30g daily, tamoxifen 40mg daily, or tamoxifen 80mg daily (19). Outcomes including ALSFRS-R, SVC and muscle strength testing were assessed by a blinded observer over 38 weeks of follow up. PALS on the highest dose of tamoxifen had slower declines in ALSFRS-R and muscle strength testing compared to the lower dose or to creatine. This was again a small trial and by design was not able to determine if PALS on any of these treatments did better than they would have on placebo.

Most recently (NCT02166944), a double-blind trial randomized 18 PALS without SOD1 or FUS mutations to receive either tamoxifen 40mg daily or placebo for 1 year (20). The primary endpoint was time to death or permanent assisted ventilation. Secondary endpoints included ALSFRS-R and FVC. There were encouraging trends toward the tamoxifen group being less likely to reach the primary endpoint, and to have slower ALSFRS-R progression (at least for the first 6 months) but these did not reach statistical significance. Again, this trial was flawed due to a very small sample

size which likely made it underpowered to detect statistical significance.

Based on these 3 trials, ALSUntangled assigns a "Trials" grade of B (Table 1). Of additional interest, one large scale study of 10,450 healthy individuals associated tamoxifen with a lower risk of developing ALS using a logistic regression method (21).

Dosing, risk, costs

While no dose of tamoxifen is proven to slow ALS progression, the above-described selection trial suggested that 80 mg daily might be best for future trials (19). At this dose, tamoxifen would cost about $80 per month (22).

In ALS trials, tamoxifen treatment at 40mg and 80mg daily was generally safe and well tolerated with hot flashes being the most commonly reported adverse event (in 24% of PALS, 19). Tamoxifen is carcinogenic in animals, and in patients on tamoxifen for breast cancer, there is a slightly increased risk of developing other cancers (23). Given this small risk of cancer, ALSUntangled assigns a "Risks" grade of D (Table 1).

Conclusion

Tamoxifen is reasonably safe, has plausible mechanisms for treating ALS and has at least one positive preclinical study. One case report and 2 small human trials suggested an association between tamoxifen (at higher doses) and slower ALS progression but this is not enough evidence to recommend this medication as an ALS treatment. Moving forward, we would like to see a larger human ALS clinical trial of tamoxifen at 80mg daily. Interestingly, one study suggests that tamoxifen may decrease a person's risk for getting ALS. We hope to see this independently replicated.

Declaration of interest

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