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RESEARCH ARTICLE

ALSUntangled 48: Perampanel (Fycompa)

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ALSUntangled reviews alternative and off-label therapies on behalf of persons with ALS (PALS). Here we review the use of perampanel (brand-name Fycompa) for ALS, for which we have had over 970 requests (1).

Overview

Perampanel is a drug, taken by mouth, that is approved in the USA, Canada, Europe, and Russia for use in the treatment of seizures. It is thought to work in seizure disorders by blocking the ability of the neurotransmitter glutamate to utilize AMPA receptors to excite neurons (2).

Mechanism

One of the proposed pathologic mechanisms in ALS is glutamate-induced excitotoxicity of motor neurons. This is mediated by several different families of glutamate receptors; however, the AMPA-type glutamate receptor plays the key role in this (3). AMPA receptors appear to be altered in patients with sporadic (4) and certain forms of familial (5–8) ALS and the alteration confers a "gain of function" (9,10). In other words, the AMPA receptors in some PALS can excite motor neurons even more than normally which may contribute to their disease.

Perampanel is a drug designed to inhibit AMPA-type glutamate receptors (11). It inhibits AMPA receptors in primary cultures of rat neurons (12–14) and slices of rat hippocampus (15). It is thought, but not proven, to be highly selective for the AMPA receptor (16). With the currently available scientific methods, it is difficult to directly observe perampanel inhibiting AMPA receptors in humans; however, the demonstrated ability of perampanel to treat most types of seizures, which has been replicated in multiple clinical trials (2), strongly suggests it has an inhibitory effect on neurotransmission. Based on the above evidence, ALSUntangled assigns perampanel a "mechanism" grade of B (Table 1).

It is worth noting that there have been large phase III clinical trials of four other drugs that are thought to act on glutamate neurotransmission. Of these four drugs, riluzole was successful in slowing ALS disease progression modestly (17), but topiramate, ceftriaxone, and talampanel (previously called LY300164) were not (18–20). Riluzole reduces the release of glutamate into synapses but has multiple additional actions (21). Topiramate is a drug approved for seizures that has multiple mechanisms of action including inhibition of AMPA receptors (22). Ceftriaxone is a β-lactam antibiotic that is thought to have the additional biological effect of indirectly decreasing the amount of glutamate in neural synapses, which would decrease glutamate-induced excitotoxicity (23). Talampanel, like perampanel, is an AMPA receptor inhibitor (3).

Pre-clinical models

Drugs that block AMPA-type glutamate receptors, i.e. antagonists, have been tested in several ALS pre-clinical models. The AMPA antagonist drugs talampanel, GYKI-52466, and ZK 187638 are thought to work via the same mechanism as perampanel, i.e. decreasing the AMPA receptor's ability to excite neurons (13,24,25). GYKI-52466 was shown to be protective in a motor neuron cell model of glutamate excitotoxicity (26) and extended survival in a small unpublished study of mutant SOD1 mice (Rothstein cited in 18). ZK

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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.

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187638 was also shown to increase survival time in the mutant SOD1 mouse model (27). Talampanel was shown to have some benefits on the pathology in mutant SOD1 mice (28), but survival testing results have not been published. Other AMPA antagonists, e.g. RPR-1199900 and NBQX, directly inhibit glutamate from binding the AMPA receptor which leads to less neuron excitation (29,30). These two drugs have also been shown to improve survival time in the mutant SOD1 mouse model (29,31).

There has been a pre-clinical study with perampanel in mice that had the gene ADAR2 deleted (ΔADAR2) from their motor neurons. This deletion is associated with a gain of function of the AMPA receptors and an ALS-like disease in the mice (10). Although this model has not been widely used to-date, it may be an adequate model of sporadic ALS given several key similarities including resistance of the motor neurons controlling the muscles that move the eyes (10) and mislocalization of the protein TDP-43 (32,33). In this study, ΔADAR2 mice treated with oral perampanel had a slower decline in motor function than ΔADAR2 mice given a placebo. This functional benefit appeared to coincide with histological improvements in the spinal cord including less motor neuron death and improved localization of TDP-43 (34). Although these results are intriguing, interpretation of the results are limited by several methodological flaws including small experimental groups of mixed gender mice that were not gender-matched between treated and placebo groups (35). Even with these limitations, the functional motor improvement supported by histology strongly suggests that further testing of perampanel in other ALS pre-clinical models is warranted. Based on this single flawed study, ALSUntangled assigns a TOE "pre-clinical" grade of C (Table 1).

Table 1. Table of evidence.

	Grade	Explanation
Mechanism	B	Perampanel non-competitively inhibits AMPA receptors in cell culture and animal brain slices. AMPA receptors undergo a gain of function in ALS which likely contributes to glutamate excitotoxicity of motor neurons. Perampanel could potentially reduce this excitation by blocking AMPA receptors
Pre-Clinical	C	One flawed study in a mouse model of ALS reported perampanel slows motor function loss with corresponding histologic changes in the spinal cord
Cases	D	We found a single person reporting a "slight" benefit in their ALS disease from perampanel. We were unable to verify their diagnosis or reported benefit
Trials	U	We found no published ALS trials of perampanel
Risks	D/F	Given that there is no available data of PALS taking perampanel, our safety analysis is incomplete; however, the risk of falls and serious psychiatric adverse effects warrant a grade of D or lower

Cases

Within the PatientsLikeMe online community, four persons reported taking perampanel for their ALS, one of which completed a more detailed evaluation. This PALS recorded "slight" effectiveness and experienced no side effects (36). We did not have records on this patient to confirm their diagnosis or benefits. A Google search revealed no additional cases of PALS taking perampanel. Based on this single unverified report of benefit, ALSUntangled assigns a TOE "cases" grade of D (Table 1).

Trials

There are three ongoing clinical trials and one biomarker pilot study evaluating perampanel in ALS. These include a 60 patient 9-month placebo-controlled trial at Stony Brook University in New York of 8 mg per day perampanel (37), a 60 patient 11-month placebo-controlled trial in Tokyo of 4 or 8 mg per day perampanel (38), and a 20 patient 3-month open-label trial in Lebanon of 8 mg per day perampanel (39). The biomarker study at Mayo Clinic Jacksonville is testing the effect of a single dose of perampanel on transcranial magnetic stimulation measurements (40). We look forward to the results of these trials; however, they are small and exploratory, which may limit interpretation of the results. The results of these studies have not been published to-date; therefore, ALSUntangled assigns a TOE "trials" grade of U (Table 1).

Of potential interest, another AMPA receptor blocker called talampanel (previously LY300164) was studied in an ALS clinical trial. This was a 9-month randomized placebo-controlled trial of 59 PALS. The results showed there was no statistically significant difference between talampanel- and placebo-treated PALS in disease progression measured by the ALS functional rating scale, respiratory vital capacity, and limb strength. Although the differences between treatment groups were not statistically significant, the functional rating score did decrease 30% more slowly in the talampanel-treated group (41), which prompted a larger 559 patient trial (42). This larger trial was terminated early due to a lack of benefit (20). Some researchers think that even though talampanel failed clinical trials, perampanel could be successful due to perampanel's superior pharmacokinetics (34).

Risks

In patients with seizure disorders (i.e. epilepsy), there are dose-dependent side effects associated with perampanel (43). The side effects with an 8 mg daily dose of perampanel are usually minor and include dizziness (32%), sleepiness (16%), fatigue (8%), irritability (7%), falls (5%), and a problem with balance (5%). The side effects were similar in trials conducted in Parkinson's disease (44). Although in most people, these are minor side effects, the added fall risk and changes in balance could be more significant problems for PALS. In addition, rarely perampanel can cause life-threatening behavioral changes, especially at higher dosages, that may require hospitalization including aggression, thoughts of homicide, and thoughts of suicide. The potential for psychiatric emergencies has merited perampanel a "FDA black box warning" (45,46). The potential for psychiatric side effects in PALS is especially concerning since behavioral and cognitive changes are already very common in ALS (47–49). Our safety review is incomplete because perampanel has not been studied in motor neuron disease patients; however, based on the available data, it is unlikely perampanel would receive higher than a D grade. Therefore, ALSUntangled assigns a TOE "risks" grade of D/F (Table 1).

Dosing and costs

Doses currently being tested in clinical trials are 4 mg once daily (one trial; 38) and 8 mg once daily (all three trials; 37–39). The average retail price for a month supply of perampanel tablets at these doses would be about $1000 (50,51).

Conclusion

Perampanel is a drug currently used to treat seizures which has a mechanism of action that theoretically could be useful in treating patients with ALS. A single flawed study in a mouse model of ALS showed some benefits of perampanel, but data from humans with ALS is quite limited. Due to the lack of data in PALS, the failure of the closely related drug talampanel in ALS clinical trials, and several serious safety concerns, including an increased fall risk and serious psychiatric adverse effects, we cannot recommend off-label use of perampanel for ALS at this time. We look forward to the results of the on-going clinical trials of perampanel in ALS and we will update our TOE grades accordingly when these results become available.

Disclosure statement

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