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What is the Safety and Efficacy of Tarenflurbil (R-flurbiprofen) in Mild to Moderate Alzheimer's Disease?

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What is the safety and efficacy of Tarenflurbil (R-flurbiprofen) in mild to moderate Alzheimer's Disease?

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OBJECTIVE: The objective of this systematic review is to determine what is the safety and efficacy of Tarenflurbil (R-flubiprofen) in mild to moderate Alzheimer's Disease.

STUDY DESIGN: Review of three English language primary studies published in 2007, 2008, and 2009.

DATA SOURCES: Randomized, double-blind, placebo-controlled clinical trials comparing Tarenflurbil 800 mg BID to placebo were found using Ovid MEDLINE, PubMed, and Cochrane databases.

OUTCOMES(S) MEASURED: Cognition was assessed by the Alzherimer's Disease (AD) assessment scale cognitive subscale (ADAS-Cog). Functional ability was assessed by the AD cooperative study activities of daily living scale (ADCS-ADL). Global function was assessed by the clinician interview based impression of change plus caregiver input (CIBIC+) and by the clinical dementia rating sum of boxes (CDR-sb). Adverse effects were assessed by patient reports. The combined most common adverse effects reported include any adverse effect, diarrhea, nausea, adverse GI events, dizziness, urinary tract infection, and other renal/urinary disorders.

RESULTS: Green et al found that the Tarenflurbil and placebo groups did not differ in the change from baseline to 18 months. Wilcock et al found that for mild AD, treatment with 800 mg of Tarenflurbil was associated with a significantly lower rate of decline than was treatment with placebo in activities of daily living and global function. The difference between 800 mg Tarenflurbil and placebo group in cognitive decline was not significant. For moderate AD, treatment with placebo was associated with a significantly lower rate of decline in global function than 800 mg of Tarenflurbil. Non-significant effects were recorded for activities of daily living and cognition. All three trials found Tarenflurbil to be safe and tolerable.

CONCLUSIONS: The studies reviewed demonstrate that Tarenflurbil is safe and well tolerated, but did not slow cognitive decline. Analysis of functional ability showed differences between mild and moderate AD. In mild AD, Tarenflurbil had lower rates of decline in activities of daily living, however, had no significant effects in moderate AD. Tarenflurbil showed improvement and/or maintenance in global function for both mild to moderate AD.

KEY WORDS: Alzheimer's Disease, Tarenflurbil, R-flubiprofen

INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of chronic dementia[1], accounting for 60-80% of all dementia[2]. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) characterizes AD by the development of multiple cognitive deficits manifested by both memory impairment and one or more of the following: aphasia, apraxia, agnosia, and disturbances in executive functioning[3]. The cognitive deficits cause significant impairment in social and/or occupational functioning[3]. The course is characterized by gradual onset and continuing cognitive decline[3]. The effects do not occur exclusively during the course of delirium, during substance-induced or systemic conditions, or are due to other central nervous system conditions that cause progressive deficits in memory and cognition[3].

The exact etiology of AD is unknown, but it is thought to be due to an imbalance between neuronal injury and repair[1]. Factors such as free radical formation, vascular insufficiency, inflammation, head trauma, hypoglycemia, and aggregated beta amyloid protein may cause neuronal injury[1]. Factors contributing to ineffective repair may include the presence of the apolipoprotein E gene, altered synthesis of amyloid precursor protein, and hypothyroidism[1]. Characteristic intracellular tau-containing neurofibrillary tangles and extracellular beta amyloid plaques are found in the brain. Also, deficits in key neurotransmitters, particularly acetylcholine, are linked to the cognitive symptoms. The greatest risk factor is advancing age (>65 years old). Other risk factors include female gender, family history, and head trauma.

Alzheimer's Disease affects 5.3 million Americans[2] making it a prominent concern for health care practitioners. Patients with AD have more than three times as many hospital stays compared to other older adults[2]. Cost of care also increases with coexisting AD; the total Medicare costs and Medicare costs for hospital care are almost three times higher for AD

patients than for other Medicare beneficiaries[2]. The estimated annual total cost of caring for a single AD patient in an advanced stage is more than $50,000[4].

As of yet, no treatment is available to prevent, cure, or cease the deterioration of brain cells in AD. Current approved therapies offer minimal effects and variable success. Existing regimens include the use of three approved cholinesterase inhibitors (Donezepil hydrochloride, Galantamine, and Rivastigmine tartrate) and one N-methyl-D-aspartate receptor blocker (Memantine). Tarenflurbil offers a different mechanism of action than the current approved regimens. Leading theories on the pathophysiology of AD implicate overproduction of amyloid beta peptide[5,6]. Tarenflurbil is a selective amyloid beta peptide-lowering agent; therefore, Tarenflurbil may provide a safe and effective treatment option as mono or adjuvant therapy for patients with mild to moderate AD. This paper evaluates three randomized controlled trials comparing the administration of Tarenfluribil to placebo group as treatment in mild to moderate AD.

OBJECTIVE

The objective of this systematic review is to determine "what is the safety and efficacy of Tarenflurbil (R-flurbiprofen) in mild to moderate Alzherimer's Disease?".

METHODS

A detailed literature search was conducted using Ovid MEDLINE, PubMed, and the Cochrane Database of Randomized Controlled Trials and Systematic Reviews. The key words used were "Alzheimer's Disease", "Tarenflurbil", and "R-flubiprofen". All articles selected were published in peer review journals. The articles were selected based on relevance and the outcomes mattered to the patients (Patient Oriented Evidence that Matters, or POEMS). The studies included were randomized, controlled, double-blind, placebo controlled trials with a

patient oriented outcome. The studies excluded were articles published prior to year 2006. The statistics reported or used included p-value, mean change from baseline, 95% Confidence Interval (CI), Relative Risk Increase (RRI), Absolute Risk Increase (ARI), Numbers Needed to Harm (NNH), Absolute Risk Reduction (ARR), and Numbers Needed to Treat (NNT).

Three randomized, controlled, double-blind, placebo controlled trials were chosen for this review. The criteria for selection of studies included the following: The population were patients aged 55 years or older who had a Mini-Mental State Examination (MMSE) score of 15-26. The intervention was the administration of Tarenflurbil. Comparisons included the treatment group receiving 800 mg of Tarenflurbil two times per day compared to a placebo group. Table 1 includes the demographics of the included studies.

Table 1. Demographics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
[7]Galasko, 2007	RCT, specifically a randomized double-blind, placebo-controlled clinical trial	16	55-80	MMSE score >27 with no sig medical illness; willing to restrict use of ASA to <100 mg/d	CI to LP; use of NSAIDs w/in 3 mo; insulin use; h/o peptic ulcer, EtOH abuse, head injury w/ LOC >1h, epilepsy; CA w/in 2 yrs; abnormal ECG, renal/hepatic function	0	Tarenflurbil 800 mg BID vs. placebo group for 3 weeks
[5]Green, 2009	RCT, specifically a multicenter, randomized, double-blind, placebo-controlled trial	1642	>55	MMSE of 15-26; Hachinski score <4; no h/o MR; adequate vision/hearing; caregiver visits ≥ 4 d/wk who can also accompany clinic visits	Evidence of epilepsy, focal brain lesion, psych/ renal/hepatic disorders; h/o head injury w/ LOC >1h, NSAID hyper-sensitivity, peptic ulcers; recent chronic NSAID use; CA w/in 2 yrs; uncontrolled cardiac conditions; anticoag use w/in 12 wks; Memantine w/in 30d	603	Tarenflurbil 800 mg BID vs. placebo group for 18 months
[6]Wilcock, 2008	RCT, specifically a Phase II, multicenter, randomized, double-blind, placbo-controlled, parallel group study	141	>55	MMSE of 15-26; Hachinski score <4; no h/o MR; adequate vision/hearing; caregiver visits ≥ 4 d/wk who can also accompany clinic visits	Evidence of epilepsy, focal brain lesion, psych/ renal/hepatic disorders; h/o head injury w/ LOC >1h, NSAID hyper-sensitivity, peptic ulcers; recent chronic NSAID use; CA w/in 2 yrs; uncontrolled cardiac conditions; anticoag use w/in 12 wks; Memantine w/in 30d	28	Tarenflurbil 800 mg BID vs. placebo group for 12 months

OUTCOMES MEASURED

All outcomes measured were based on relevance to Patient Oriented Evidence that Matters (POEMS). The primary outcomes measured were cognition, functional ability, and global function. Secondary outcomes measured were adverse effects. Cognition was assessed by the AD assessment scale cognitive subscale (ADAS-Cog). Functional ability was assessed by the AD cooperative study activities of daily living scale (ADCS-ADL). Global function was assessed by the clinician interview based impression of change plus caregiver input (CIBIC+) measured by improvement or no change and by the clinical dementia rating sum of boxes (CDR-sb). Adverse effects were assessed by patient reports and by detailed questioned asked at clinic visits or by telephone.

RESULTS

Green et al assessed cognition and functional ability as continuous data. The primary analysis was performed on changes from baseline to month 18 in total score for ADAS-Cog and ADCS-ADL. The statistics included were mean change from baseline, 95% confidence interval (CI), and p-values. Treatment comparisons were made by slope analysis of the ADAS-Cog and ADCS-ADL. All efficacy analyses were performed using the intent-to-treat (ITT) population consisting of all participants who were randomized, had mild AD at screening, and received at least 1 dose of study medication. The statistical analysis found that the Tarenflurbil and placebo groups did not differ in the change from baseline to 18 months. The mean treatment difference for the ADAS-Cog score was 0.1 (95% CI -0.9 to 1.1; p=.86) (Table 2). The mean treatment difference for the ADCS-ADL score was -0.5 (95% CI -1.9 to 0.9; p=0.48) (Table 3).

Wilcock et at assessed cognition, functional ability, and global function as continuous data. The primary analysis was based on interaction between baseline score to month 12 and

treatment group for ADAS-Cog and ADCS-ADL. The secondary analysis was made for CDR-sb. The statistics included were mean rate of change in points per year, 95% CI, effect size, defined as mean percentage difference in slopes, and p-vaue. The ITT population was defined as all patients randomly assigned to treatment who received at least one dose of Tarenflurbil and who had at least one post-baseline efficacy measurement, or who discontinued the study because of adverse event before an efficacy assessment. A positive result in analysis of the data required a statistically significant change in one measure of cognition (ADAS-Cog) and one measure of function (ADCS-ADL or CDR-sb). For mild AD, treatment with 800 mg of Tarenflurbil was associated with a significantly lower rate of decline than was treatment with placebo in actives of daily living (ADCS-ADL 95% CI 0.33 to 7.62, effect size of 46.4%, p-value = 0.033) (Table 3) and global function (CDR-sb 95% CI -1.57 to -0.03, effect size of 33.7%, p-value = 0.042) (Table 4). The difference between 800 mg Tarenflurbil and placebo group in cognitive decline was not significant (ADAS-Cog 95% CI -4.07 to 1.36, effect size of 33.7%, p-value = 0.327) (Table 2). For moderate AD, treatment with placebo was associated with a significantly lower rate of decline in global function than was 800 mg of Tarenflurbil (CDR-sb 95% CI 0.82 to 4.03, effect size of -52%, p-value = 0.003) (Table 4). Non-significant effects were recorded for activities of daily living and cognition (ADCS-ADL 95% CI -13.44 to 3.17, effect size of -38.2%, p-value = 0.223 and ADAS-Cog 95% CI -4.13 to 5.67, effect size of -10.1%, p-value = 0.756) (Table 2 and 3, respectively). Effect sizes were not consistent across measures.

Table 2. Rate of change from baseline in primary efficacy outcome and comparison of 800 mg Tarenflurbil with placebo measured by the ADAS-Cog scale.

		95% CI	Effect size	p-value
Green	Mild to moderate	-0.9 to 1.1	NR	.86
Wilcock	Mild	-4.07 to 1.36	33.7%	.327
	Moderate	-4.13 to 5.67	-10.1%	.756

NR = not reported in study

Table 3. Rate of change from baseline in primary efficacy outcome and comparison of 800 mg Tarenflurbil with placebo measured by the ADCS-ADL scale.

		95% CI	Effect size	p-value
Green	Mild to moderate	-1.9 to 0.9	NR	.48
Wilcock	Mild	.33 to 7.62	46.4%	0.033
	Moderate	-13.44 to 3.17	-38.2%	.223

NR = not reported in study

Wilcock et al also assessed global function with dichotomous data using the CIBIC+ scale. With the CIBIC+ scale, effects were measured as improvement or had no change. The relative risk reduction (RRR) was calculated to be 63% and the absolute risk reduction (ARR) was calculated to be 12%. The number needed to treat (NNT) was 9 (Table 4).

Table 4. Summary of analysis of global function based on outcomes and NNT (CIBIT+) and rate of change from baseline over 12 months.

		RRR	ARR	NNT	95%CI	Effect size	p-value
CIBIC+	Mild	63%	12%	9	NR	15%	0.208
	Moderate	-100%	-0.21	-5*	NR	NR	0.070
CDR-sb	Mild	NR	NR	NR	-1.57 to -0.03	33.7%	0.042
	Moderate	NR	NR	NR	0.82 to 4.03	-52%	0.003

NR = not reported in study

*The negative value for NNT indicates that for every 5 participants taking the 800 mg Tarenflurbil there was one fewer patient who declined from the participant's normal level of global function.

Adverse effects of all three studies were converted to dichotomous data. The number of adverse events that occurred in the 800 mg Tarenflurbil treatment group determined the experimental event rate (EER). The number of adverse events that occurred in the placebo-controlled group determined the control event rate (CER). The EER and CER were used to determine the relative risk increase (RRI) and absolute risk increase (ARI). The numbers needed

to harm (NNH) was then calculated by taking the inverse of the ARI (1/ARI). NNH represents the number of patients that would need to take 800 mg of Tarenflurbil in order to cause one adverse event.

Adverse effects included, but are not limited to, diarrhea, constipation, nausea, vomiting, dizziness, urinary tract infection, agitation, confused state, upper respiratory tract infection, headache, depression, and rash. Table 5 describes the outcomes measured and NNH for the combined most common adverse events reported, which includes any adverse effect, diarrhea, nausea, any GI effect, dizziness, urinary tract infections, and renal/urinary disorders.

For any adverse effect, Green et al found that 87.2% taking Tarenflurbil vs. 85% receiving placebo reported any adverse event, with a RRI of 2.4%, ARI of 2%, and NNH of 50; Wilcock et al found that 90% taking Tarenflurbil vs. 85% receiving placebo reported any adverse event, with a RRI of 5.8%, ARI of 5%, and NNH of 20. Galasko et al found 66% of both the Tarenflurbil and placebo group reported any adverse event, therefore the RRI and ARI were found to be zero, and the NNH was therefore undetermined. For diarrhea, Green et al found that 8.3% taking Tarenflurbil vs. 7.3% receiving placebo reported diarrhea, with a RRI of 14%, ARI of 1%, and NNH of 100; Wilcock found that 10% of participants taking Tarenflurbil vs. 8% receiving placebo reported diarrhea, with a RRI of 25%, ARI of 2%, and NNH of 50. For nausea, Green et al reported that 4.7% taking Tarenfluril vs. 5.8% taking placebo reported nausea, with a RRI of -19%, ARI of -1.1% and NNH of -91; Wilcock et al found that 10% taking Tarenflurbil vs. 6% receiving placebo reported nausea, with a RRI 67%, ARI of 4%, and NNH of 25. Galasko et al reported on all adverse gastrointestinal (GI) events finding that 33% taking Tarenflurbil vs. 42% taking placebo reported any GI event, with a RRI of -19.5%, ARI of -0.08%, and NNH of -2.5. For urinary tract infection (UTI), Green et al found that 12.9% taking

Tarenflurbil vs. 13.3% receiving placebo reported a UTI, with a RRI of -3%, ARI of -0.4%, and NNH of -250; Wilcock found that 7% taking Tarenflurbil vs. 8% receiving placebo reported a UTI, with a RRI of -13%, ARI of -1%, and NNH of -100. Galasko et al reported on all renal/urinary disorders finding that no participants taking Tarenflurbil vs. 8% receiving placebo reported renal/urinary disorders, with a RRI of -100%, ARI of -8.3%, and NNH of 12.

Table 5. Summery of outcomes measured and NNH for the combined most common adverse events of all studies presented.

Adverse Event	Study	RRI	ARI	NNH
Any adverse effect	Green	2.4%	2%	50
	Wilcock	5.8%	5%	20
	Galasko	0%	0%	0
Diarrhea	Green	14%	1%	100
	Wilcock	25%	2%	50
Adverse GI events	Galasko	-20%	-8.2%	-13%
Nausea	Green	-19%	-1.1%	-91
	Wilcock	67%	4%	25
Dizziness	Green	49%	2.8%	36
	Wilcock	17%	1%	100
Renal/urinary disorders	Galasko	-100%	-8.3%	12
Urinary tract infection	Green	-3%	-0.4%	-250
	Wilcock	-13%	-1%	-100

*The negative value for NNH represents that for every number of participants taking 800 mg of Tarenflurbil there is one fewer adverse event.

Green et al found that of the participants that discontinued, 95 in the placebo group vs. 158 in the Tarenflurbil group discontinued due to adverse events. Wilcock et al reported that the most common types of adverse events leading to discontinuation were GI disorders, metabolism and nutritional disorders, and psychiatric disorders. Galasko et al reported that no serious adverse events were found and that no significant differences in the number or nature of adverse events were reported across groups. No subjects discontinued participation in the study because of adverse events.

DISCUSSION

The studies chosen for this review encountered certain limitations. There were a high proportion of study participants taking co-medications, which may have had implications on outcomes. The studies were also limited by a high discontinuation rate. Green et al reported that 269 participants (33%) discontinued from the placebo group, while 334 participants (40%) discontinued from the 800 mg Tarenflurbil group ($p=0.006$). Wilcock et al reported that an equal number of participants discontinued from both the placebo and Tarenflurbil group ($n=13$ and $n=13$, respectively).

Green et al reported that the 800 mg Tarenflurbil dose might have been too low for a therapeutically relevant effect in humans. Plasma concentrations of Tarenflurbil indicated that the compound was absorbed as expected, however, data indicated that a dose-dependent penetration of drug from plasma to cerebrospinal fluid was only 0.5% to 1%, indicating low brain penetration.

CONCLUSIONS

The studies reviewed demonstrate that Tarenflurbil is safe and well tolerated, but did not slow cognitive decline. Analysis of functional ability showed differences between mild and moderate AD. In mild AD, Tarenflurbil had lower rates of decline in activities of daily living, however, had no significant effects in moderate AD. Tarenflurbil showed improvement and/or maintenance in global function for both mild to moderate AD.

Baseline differences in disease severity (MMSE score of 15-26) and differences co-medication use may have impacted the disease-modifying effect. There is a clear distinction between effects of 800 mg Tarenflurbil on mild AD compared to moderate AD. Future research should be aimed at controlling both baseline MMSE score and co-medication use. In addition to

regards with co-medication use, further research should focus on differentiating Tarenflurbil as mono or adjunct therapy.

An ongoing study performed by Wilcock et al included a follow-on phase of an additional effect from 12-24 months of treatment with 800 mg Tarenflurbil. Results indicated that patients with mild AD who were in the 800 mg Tarenflurbil group for 24 months had lower rates of decline for all three primary outcomes compared to patients who were in the placebo group and compared to patients in the 800 mg Tarenflurbil group for months 12-24 (all $p < 0.001$). Further research should be focused on lengthening duration of treatment with 800 mg Tarenflurbil in mild AD.

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