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Tarenflurbil:

Mechanisms and Myths

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Alzheimer disease (AD), a serious neurodegenerative illness characterized by cognitive impairment and functional in-capacity, is thought to affect more than 26 million people worldwide, a number projected to expand to 106 million over the next several decades. The costs associated with this disease are estimated to be \$25 billion, costs largely associated with the loss of independence and the need for care of these patients. It is no wonder that search for treatments is vigorous, with more than 700 trials registered on clinicaltrials.gov since 1997.

One of the most common targets for treatment for AD is the manipulation of amyloid, which accumulates in the brain of those with the disease. One mechanism for this manipulation is the modulation of the enzyme γ -secretase, which may favor the production of a less toxic form of β -amyloid ($A\beta$). Tarenflurbil has demonstrated such activity in vitro and in in vivo animal studies, and it has shown relative safety in human trials. Hence, it was considered a viable candidate for phase 3 clinical trials in AD. The randomized placebo-controlled trial of tarenflurbil in patients with mild AD reported by Green et al¹ is a well-conducted study of more than 1600 subjects with AD recruited from 133 sites across the United States. These investigators used a rigorous design and a long exposure period of 18 months. During the trial protocol, modifications were made (based on reanalysis of phase 2 data) consisting of shifting from 2 doses to a single high dose and modifying entry criteria to include only very mildly impaired subjects (with Mini-Mental State Examination [MMSE] scores of 20-26 inclusive). In the face of these modifications and the relatively long exposure period, most subjects (97%) were available for the primary analysis and the mean medication compliance rate was higher than 90%. It is therefore quite disappointing to see the dramatic lack of effect in the primary and secondary outcomes, with the exception of the Clinical Dementia Rating sum of boxes scores, which favored placebo. While so many things could go wrong in one of the few long trials that have been published to date, it appears that this cohort was typical of all that we know about patients with AD, with standard use of prescriptive cognitive enhancers, predictable decline in the placebo group in cognition, function, and behavior, no unusual adverse events, and no unreasonable loss to follow-up. We can therefore conclude with conviction that there was no benefit of tarenflurbil in this very typical group of patients with very mild AD.

So why did this fail? Were there any data that should have limited enthusiasm to move to a phase 3 study? Was there false enthusiasm that moved this trial beyond the apparent data? There are several things to consider. The intent-to-treat analysis of the phase 2 study in mild

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to moderate AD demonstrated no significant benefit on the primary outcomes.² Additional analyses that examined subgroups defined by MMSE scores identified a benefit in the group with the highest MMSE scores and a significant negative effect in several outcomes in those with lower MMSE scores. The decision to focus on this subgroup (mild) of a subgroup (mild to moderate) was solidified based on an analysis that demonstrated a differential treatment effect for the subgroup defined by a specific cut point on the MMSE. This approach to defining disease severity ex post facto identified a mild subgroup that demonstrated a benefit and a moderate subgroup that actually worsened. Dramatic differences in the direction of effect in subgroups seem biologically implausible. Should one suspect that at the shift of 1 point in an MMSE score, a patient was at risk for significant adverse effects with the agent that was otherwise beneficial? Could the results of the current trial suggest mathematical regression to the mean? The literature in clinical trials for the treatment of AD has many similar cases of failures in large trials that have based subject selection on a result in a subgroup of previous trials including acetylcarnitine, propentofylline, and most recently bapineuzumab. It would seem that the preliminary studies provided important information that forewarned of questionable effect, and further phase 2 testing might have been advisable before embarking on the “largest phase 3 trial to date.”¹

MECHANISM OF ACTION

Perhaps it was not the clinical data alone that moved this study forward. It is enticing to test a therapeutic agent that may act on the presumed underlying cause of AD. The tarenflurbil project was laced with the hope that the mechanism of action was a safe anti-amyloid approach. Short-term treatment with tarenflurbil in animals resulted in reduced A β 42 levels in the brain, and long-term treatment lowered amyloid deposits and amyloid-associated pathological findings in brains of amyloid precursor protein transgenic mice.³ In studies of healthy (nondemented) humans, tarenflurbil demonstrated dose-dependent blood-brain penetration in the range used in the clinical trials. However, these same studies showed no change in either cerebrospinal fluid (CSF) or plasma levels of A β 42 but demonstrated greater reductions (although not significantly so) in CSF markers in the placebo group than in any of the treated groups.⁴ At best, these results suggest that higher doses might be needed to see effects on the targeted mechanisms; at worst, they suggest that the agent has no effect. The inconsistent direction of effect gives rise to questions about how well transgenic animals model the human condition.

One is left wondering whether there is hope for secretase modulation as a therapeutic mechanism. The development of other agents with similar theoretical mechanisms might do well to take heed of this experience. To date, at least 3 agents are currently under development with purported γ -secretase modulation. Each provides evidence in animal models with varying degrees of supporting human data. For some, small studies demonstrate modifications in plasma markers without modification of the level in CSF^{5,6}; for others, CSF measurements are included but with no evidence of correlation with clinical outcomes.⁷ The work of Bateman et al⁸ using stable-isotope labeling combined with CSF sampling in healthy men permitted direct measurement of A β production during treatment with γ -secretase inhibitor LY450139. Findings suggest reduced production of A β in the central nervous system with no change in clearance of A β . In subjects with AD, this agent has no demonstrated effect on cognitive or clinical outcomes, an observation that may be due to the lack of impact on clearance or to the small sample size. In general, there is a tendency to ignore the need to put the clinical findings together with these markers. Few large-scale clinical trials require the collection of CSF as a necessary outcome in phase 3 trials. Perhaps this is because of the expense or the perceived negative effect this will have on speed of recruitment. However, recent longitudinal collection of CSF biomarkers in the Alzheimer's Disease Neuroimaging Study demonstrates the feasibility of collection of these important

samples from volunteer cohorts, even in studies without the possible benefit of exposure to a therapeutic agent.

While experimental therapeutics in AD continue to focus on anti-amyloid mechanisms, new data suggest that the story may be more complicated. Recent findings indicate that both elevation and reduction in A β levels attenuate synaptic facilitation in the short term. These observations suggest that endogenous A β peptides have a crucial role in activity-dependent regulation of synaptic vesicle release and might be responsible for synapse loss in AD.⁹

THE MYTH OF MECHANISMS

Skepticism is bound to arise over the persistence of anti-amyloid mechanisms in drug development for AD. While there is evidence that amyloid markers are associated with AD and may even predict with some accuracy a future diagnosis, to date no human study has demonstrated that modification of these markers is correlated with modification of clinical measures such as disease incidence, onset, progression, or severity. Convincing clinical outcomes are needed to rise above the myth of mechanisms.

The absence of positive clinical trial outcomes and the growing discrepancies between models of disease and human results must be addressed. It has been suggested that the lack of efficacy may be because treatment approaches have focused too late in the disease process, at a time when it is not possible to observe meaningful effects. However, the tarenflurbil trial used the patients with the mildest impairment in whom change was readily observed in all clinical domains. Trials with newer experimental agents with more limited safety profiles are being proposed in asymptomatic patients. This would ask minimally impaired or unimpaired subjects to expose themselves to the risk of new and possibly toxic agents. Yet, few studies are designed to give thorough answers to questions about mechanisms. If treatment success indeed depends on starting at the earliest stage and our direction is to build treatments based on mechanisms of disease, we must know whether we have the right mechanism and whether the agent has hit its target.

We need well-thought-out approaches to development of potential agents and consistency of findings from smaller studies to larger trials. The field should demand true evidence in smaller studies before embarking on larger ones. While significant results might not be expected from smaller phase 2 studies, clinically meaningful point estimates and a consistent direction of effect across well-established outcomes should be required at a minimum. Post hoc subgroups should be viewed with skepticism until replicated in additional phase 2 work; the substantial cost in time and resources of phase 3 studies is at stake when we go forward with insufficient preparation. The approach to large phase 3 trials cannot be directed simply by the fastest path to market because the failures cost the trust of the patient populations we all seek to serve.

A case can be made for moving forward with an agent based on a suspected mechanistic effect of the approach. However, proof of concept should require evidence of a potential therapeutic action on the mechanism within human trials and should not simply be based on animal and cellular systems as these have not proven to be predictive of the clinical condition or useful in dose selection.

The major impediment to the conduct of clinical trials is recruitment of subjects. As knowledgeable health care practitioners and researchers, we have a responsibility to educate our patients and the public at large about the importance of clinical research, to share the process by which we make the best selection of viable agents that are most likely among so many candidates to lead to positive outcomes, and to explain that even negative results will enlighten us in important ways such as telling us whether we have the right target or that our

agent actually hit the target. To do this with conviction, we must demand that the field use great care in selecting candidate agents for clinical trials. Our earliest trials must be designed to ensure that we have a relevant human mechanism or sound and consistent evidence of a clinical effect before proceeding. To require neither in early-phase studies or to avoid including such measures in larger studies demonstrates a failure to respect the important contribution of human subjects who are also our patients.

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