Review

The Journal of Prevention of Alzheimer's Disease - JPAD©
Volume 5, Number 2, 2018

Development of Azeliragon, an Oral Small Molecule Antagonist of the Receptor for Advanced Glycation Endproducts, for the Potential Slowing of Loss of Cognition in Mild Alzheimer's Disease

A.H. Burstein[1], M. Sabbagh[2], R. Andrews[1], C. Valcarce[1], I. Dunn[1], L. Altstiel[1]

1. vTv Therapeutics Inc., High Point, North Carolina, USA; 2. Barrow Neurological Institute, Phoenix AZ, USA.

Corresponding Author: Larry Altstiel, MD, PhD, vTv Therapeutics LLC, 4170 Mendenhall Oaks Parkway, High Point, NC 27265, Email: laltstiel@vtvtherapeutics.com, Phone: 336-888-0423, Fax: 336-841-0310

J Prev Alz Dis 2018;5(2):149-154
Published online March 22, 2018, http://dx.doi.org/10.14283/jpad.2018.18

Abstract

Increasing evidence supports the role of the Receptor for Advanced Glycation Endproducts (RAGE) in the pathology of Alzheimer's disease. Azeliragon (TTP488) is an orally bioavailable small molecule inhibitor of RAGE in Phase 3 development as a potential treatment to slow disease progression in patients mild AD. Preclinical studies in animal models of AD (tgAPPSwedish/London) have shown azeliragon to decrease Aβ plaque deposition; reduce total Aβ brain concentration while increasing plasma Aβ levels; decreases sAPPβ while increasing sAPPα; reduce levels of inflammatory cytokines; and slow cognitive decline and improve cerebral blood flow. In the Phase 2b study, 18-months treatment in patients with mild-to-moderate AD indicated a baseline to endpoint change in ADAS-cog of 3.1 points in favor of drug. A greater magnitude of effect was evident in the sub-group of patients with mild AD (MMSE 21-26) with a baseline to endpoint change of 4 points on the ADAS-cog in favor of azeliragon and a 1 point change in CDR-sb in favor of drug. Azeliragon 5 mg/day delayed time to cognitive deterioration (7-point change in ADAS-cog from baseline, logrank p=0.0149). Based on promising results from the Phase 2b study, a Phase 3 registration program (STEADFAST) is being conducted under a Special Protocol Assessment from FDA. The ongoing Phase 3 program, if successful may demonstrate azeliragon can slow cognitive decline in mild AD patients.

Key words: Azeliragon, RAGE, Alzheimer's disease.

List of abbreviations: AD: Alzheimer's disease; AGE: advance glycation endproduct; RAGE: receptor for advanced glycation endproducts; LTP: long-term potentiation; FDG-PET: fluro-deoxyglucose positron emission tomography; ADAS-cog: Alzheimer's Disease Assessment Scale cognitive portion; CDR-sb: Clinical Dementia Rating Scale Sum of Boxes; MMSE: mini-mental state examination; ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living; NPI: neuropsychiatric inventory; COWAT: controlled oral word association test; CFT: category fluency test; RUD: Resource Utilization for Dementia; DEMQOL: Dementia Quality of Life.

Introduction

There is a consensus that the pathology underlying Alzheimer's disease (AD) is driven by toxic effects of the Aβ peptide, abnormal phosphorylation of the tau protein and formation of neurofibrillary tangles, and neuroinflammation leading to loss of synapses (1). Nevertheless, therapies directed against production of Aβ, (gamma secretase inhibitors, beta secretase inhibitors), agents that inhibit aggregation of Aβ, and a variety of anti-Aβ monoclonal antibodies designed to promote removal of Aβ from the brain have failed to show significant clinical benefit (2). Likewise, anti-inflammatory agents have not been successful (3). Anti-tau therapies are still in development.

While it is clear that the fundamental pathology of AD is driven by Aβ toxicity, abnormal phosphorylation of tau leading to neurofibrillary tangles, and neuroinflammation, recent clinical results suggest that addressing individual components of AD pathology may not be sufficient to treat the majority of AD, sporadic disease that does not arise from autosomal dominant disease arising from mutations in the amyloid precursor protein (APP) and mutations in components of the gamma secretase complex (PS1/PS2). The lack of success in these areas indicates that it is worthwhile to consider new targets for AD therapy.

One promising target is the receptor for advanced glycation endproducts (RAGE). RAGE, a 35 kDa type 1 membrane protein, is a member of the immunoglobulin super-family of cell surface molecules (4, 5). Its extracellular domain contains three immunoglobulin-like regions, one N-terminal "V"-type domain and two "C"-type domains. There is one transmembrane spanning domain and a short cytoplasmic tail. RAGE binds a variety of ligands including advanced glycation endproducts (AGE) produced by nonenzymatic glycoxidation, β2-integrins, S100/calgranulins, high mobility group box 1 protein (HMGB1), Mac-1, phosphatidylserine and the Aβ peptide (6-11). RAGE is expressed in vascular endothelium, neurons,

Received January 5, 2018
Accepted for publication January 26, 2018

astrocytes and microglia (12) and several RAGE ligands may be involved with AD pathology. HMGB1 serves as a risk factor for memory impairment, chronic neurodegeneration, and progression of neuroinflammation in AD (13). S100 has been associated with neuroinflammation in AD (14). AGEs and RAGE promotes oxidative stress and neurotoxicity via an NADPH oxidase mechanism (15) and AGEs and RAGE regulate Aβ aggregation and amyloid accumulation (16, 17). RAGE also is involved in transport of Aβ from plasma across the vascular endothelium into the CSF (18-20). In addition, ligand binding by RAGE promotes inflammation and oxidative stress and subsequent activation of downstream regulatory pathways including NF-κB, JNK and STAT (11, 21, 22). AGEs induce tau hyperphosphorylation, memory deterioration, decline of synaptic proteins, and impairment of long-term potentiation (LTP) in rats via RAGE activation of GSK-3 (23).

An increasing body of data indicates RAGE is intimately involved in the pathology of AD and that an orally bioavailable small molecule inhibitor of RAGE may have benefit in treatment of AD. A small molecule inhibitor of RAGE, FPS-ZM1, could inhibit RAGE-mediated influx of plasma Aβ 1-40 and Aβ1-42 into the brain and reduce brain levels of Aβ 1-40 and Aβ1-42. In addition, it inhibited beta secretase activity and lowered Aβ production, suppressed microglial activation, normalized cognitive performance and cerebral blood flow in aged APPsw/0 mice (24).

Azeliragon (TTP488, formerly called PF-04494700) is an oral, small molecule inhibitor of RAGE that has similarly demonstrated beneficial effects in animal models and is currently in Phase 3 development for the treatment of patients with mild AD. The clinical development program has been granted Fast Track Designation by the United States Food and Drug Administration (FDA) with the Phase 3 study design being approved by FDA through a Special Protocol Assessment.

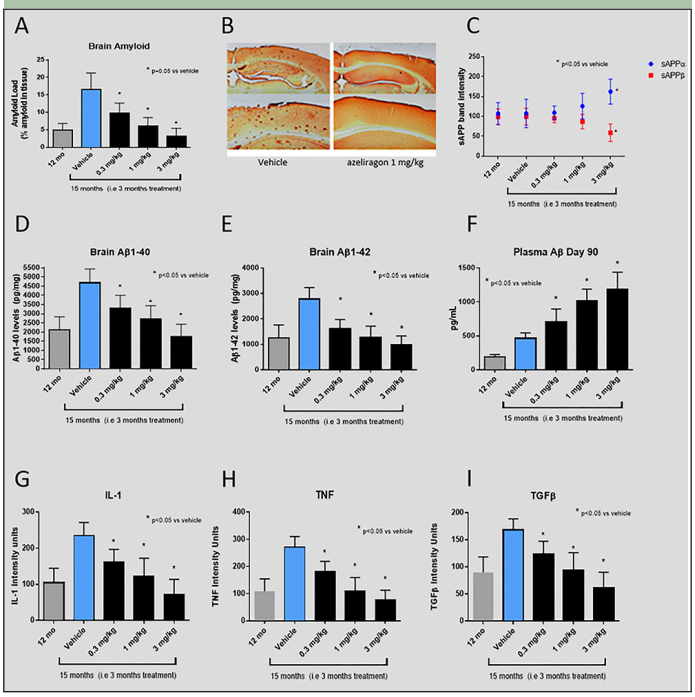
Azeliragon, preclinical results

Azeliragon (3-[4-[2-butyl-1-[4-(4-chlorophenoxy) phenyl]imidazol-4-yl]phenoxy]-N,N-diethylpropan-1-amine) was developed by vTv Therapeutics from compounds identified in a RAGE inhibition screen. It is highly specific for RAGE with a high affinity (Kd for binding to recombinant human sRAGE = 12.7 ± 7.6 nM) with negligible off target binding in a screen of greater than 100 receptors/transporters.

Preclinical Biology

Azeliragon 0.3 mg/kg, 1 mg/kg, 3 mg/kg or vehicle was orally administered once daily to 12-month-old tgAPPSWE/LON transgenic mice for 3 months followed by evaluation of cognition/behavior (Morris Water Maze test), brain amyloid deposition, Aβ peptide and sAPP levels, and inflammatory markers. Plasma was collected for analysis of Aβ peptide levels (25). Azeliragon decreases Aβ deposition in tgAPPSWE/LON transgenic mice. As shown in Figure 1, there was a dose-dependent decrease relative to vehicle in both total Aβ as measured by ELISA and Aβ plaque deposition (Figure 1, A, B). Both Aβ1-40 and Aβ1-42 accumulation in tgAPPSWE/LON mice were prevented in a dose-dependent manner with an accompanying increase in plasma Aβ (Figure 1, D, E, F). These results are consistent with the hypothesis that azeliragon inhibits RAGE mediated transport of circulating Aβ into the brain. Azeliragon also reduced brain concentrations of sAPPβ with a concomitant increase in sAPPα consistent with the hypothesis that inhibition of RAGE by azeliragon decreases β-secretase activity (Figure 1, C).

Figure 1. Amyloid plaque reduction with azelerigon 9 month old tgAPPSWE/LON mice treated with 1 mg/kg azeliragon orally once daily for 3 months (A) and total Aβ reduction with daily po dosing of azeliragon (B). Dose dependent decrease of brain Aβ (D, E) and increase in plasma Aβ (F). Dose dependent increase in brain sAPPα and decrease in sAPPβ (C). Dose dependent reduction of brain IL-1 (G), TNF (H), and TGFβ (I)

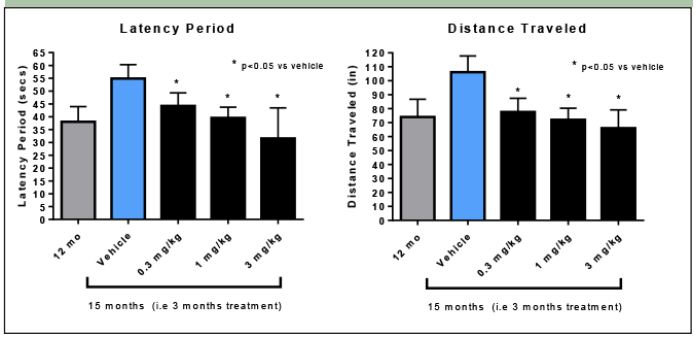


Inhibition of RAGE would be expected to reduce brain inflammation. Treatment with azeliragon decreased brain levels of inflammatory cytokines in brains of tgAPPSWE/LON mice in a dose-dependent fashion. This is consistent with the observation that inhibition of RAGE reduces neuroinflammation (Figure 1, G, H, I).

Azeliragon also slowed decline of cognitive function in 12-month-old tgAPP/SWE/LON mice. Starting at

12 months, mice were treated with vehicle, 0.3 mg/kg, 1 mg/kg, or 3 mg /kg for 3 months and memory was assessed with performance on Morris water maze after 3 months of treatment. As shown in Figure 2, there was a dose-dependent improvement of both latency and distance travelled suggesting that azeliragon slows cognitive decline in in this model.

Figure 2. Azeliragon improvement of latency and distance travelled in Morris water maze in tgAPP/SWE/LON mouse model

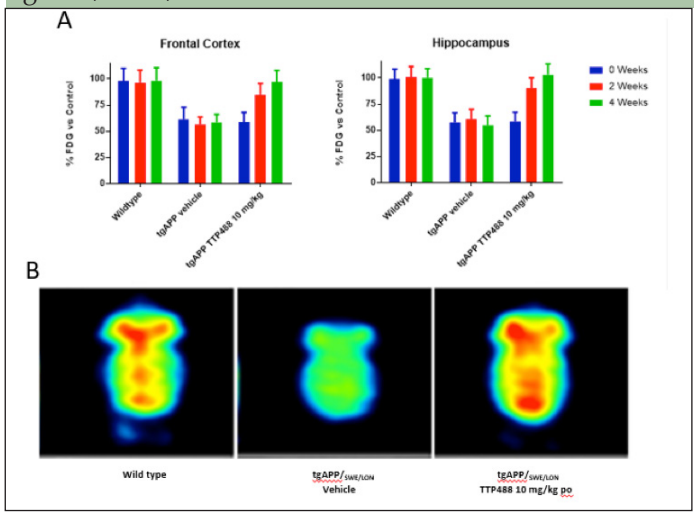


In a separate experiment, azeliragon improved brain glucose utilization in the tgAPP/SWE/LON mouse model, equal numbers of transgenic mice >6 months old (20/group) were treated with either 10 mg/kg azeliragon or vehicle administered subcutaneously for 4 weeks. Cerebral blood flow was measured by laser-doppler flow (LDF) and fluro-deoxyglucose positron emission tomography (FDG-PET) at weeks 0, 2 and 4. Wild type mice were used as controls. Data shown in Figure 3 indicate that treatment with azeliragon increased regional cerebral blood flow in both hippocampus and frontal cortex with values at 4 weeks being similar to that of wildtype animals. These data are consistent with the hypothesis that RAGE mediated inflammation of vascular endothelial cells reduces cerebral blood flow and inhibition of RAGE by azeliragon helps restore blood flow.

Summary of preclinical data

Preclinical studies demonstrate that azeliragon is a selective antagonist of RAGE with subsequent studies in animal models that indicate azeliragon: reduces Aβ plaque deposition; reduces total Aβ brain concentration while increasing plasma Aβ levels suggesting that azeliragon inhibits RAGE-mediated transport of circulating Aβ into brain; decreases aAPPβ while increasing sAPPα indicating azeliragon inhibition of RAGE reduces activity of β-secretase; reduces levels of inflammatory cytokines demonstrating azeliragon inhibition of RAGE reduces neuroinflammation; slows cognitive decline; improves cerebral blood flow. Trough plasma concentrations of azeliragon at the lowest efficacious dose (0.3 mg/kg) were 6 ng/mL thereby providing a proposed target concentration for efficacy in clinical studies. These preclinical results suggesting the potential for azeliragon to modify the underlying disease were the basis for FDA Fast Track Designation.

Figure 3. Regional cerebral blood flow as measured by FDG-PET in tgAPP/SWE/LON mice over four weeks. Bar graph (A) shows %FDG vs control at 0 weeks (blue bar), 2 weeks (red bar) and 4 weeks (green bar). PET images (B) show representative images for wild type control, vehicle treated tgAPP/SWE/LON mice, and azeliragon treated tgAPP/SWE/LON mice after 4 weeks of treatment



Azeliragon clinical experience

Azeliragon has been extensively studied in eight (8) Phase 1 and three (3) Phase 2 studies. Phase 1 studies have evaluated single and multiple-dose pharmacokinetics, safety and tolerability in healthy volunteers, CSF distribution of azeliragon following multiple dose administration, food effect on azeliragon pharmacokinetics, metabolism/disposition, drug-drug interactions with a CYP inducer, CYP3A4 inhibitor and CYP2C8 inhibitor and effect of hepatic impairment on azeliragon pharmacokinetics. Phase 2 studies have evaluated the safety and tolerability following 10 weeks of dosing in patients with mild to moderate AD, safety and efficacy in patients with diabetes and albuminuria, and 18 months dosing to evaluate the efficacy, safety and tolerability following 18 months dosing in patients with mild to moderate AD.

Phase 1

In humans, the pharmacokinetics of azeliragon following a single dose are characterized by rapid absorption over a dose range of 5 to 65 mg and a prolonged PK disposition. Following administration of a single 20 mg dose in healthy subjects, the mean (SD) peak concentration (Cmax) of azeliragon in plasma was 4.0 ± 0.6 ng/mL, with the first peak concentration occurring 12 hours post dose (Tmax-1) and a second nearly comparable peak concentration occurring

approximately 21 hours later (Tmax-2 = 33 hours). [Data on file] There was an approximately 16-20% reduction in exposure (AUC(0-last), AUC(0-72h), Cmax) following administration of azeliragon 5 mg following a high fat meal. At the Phase 3 dose of 5 mg/day, the magnitude of reduction is not anticipated to be clinically meaningful. Consequently, azeliragon may be given without regard to meals.

The average half-life (t½) of azeliragon ranged between 228 and 336 hours (9.5 and 14 days) across doses. Because of its prolonged PK disposition and the length of time it takes to reach steady state, in early studies azeliragon has been administered as a loading dose, at doses of 15 to 60 mg/day for up to 6 days, followed by a maintenance dose, at doses of 5 to 20 mg/day. Under these dosing conditions, steady state is generally achieved within 7-10 days after starting therapy. Following continued QD dosing 5 mg/day the average steady-state peak (Cmax) and trough (Cmin) azeliragon concentrations were 12.4 ± 6.0 ng/mL and 9.9 ± 4.2 ng/mL, respectively. Approximately 10% of free drug in systemic circulation distributes into CSF. (Data on file)

Azeliragon exposure was not significantly changed in the presence of CYP2C8 / 3A4 inhibitors or CYP inducer following co-administration for 14 days in healthy volunteers. Slight changes in exposure, unlikely to be clinically significant, were observed for azeliragon M1 and M2 metabolites, with the non-pharmacologically active M3 metabolite exhibiting a 4-10 fold increase. Together, these data are consistent with the presence of multiple elimination pathways for azeliragon which reduces the magnitude of a clinically relevant drug-drug interaction and supports a recommendation for no requirement for azeliragon dose adjustment when co-administered with CYP3A4 inhibitors or CYP inducers. Co-administration with strong CYP2C8 inhibitors is not supported at this time.

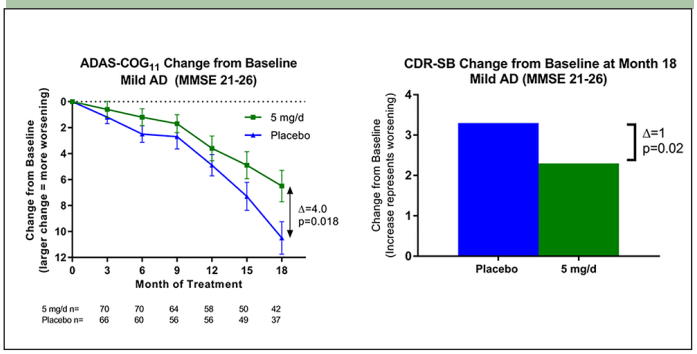
The effects of hepatic impairment on the pharmacokinetics of azeliragon was evaluated in an open-label, single-dose, parallel design trial in which 8 subjects with mild hepatic impairment (Child-Pugh category A), 8 subjects with moderate hepatic impairment (Child-Pugh category B), and 8 healthy subjects received a single 15 mg dose of azeliragon. No clinically important effect of hepatic impairment on Cmax, AUC0-∞ or AUClast was observed in subjects with mild or moderate hepatic impairment. Therefore, it is expected that no dose adjustments will be required when administering azeliragon to patients with mild or moderate hepatic impairment.

The lack of effect of azeliragon on QTc interval was demonstrated in a concentration-driven model-based analysis of the relationship between azeliragon plasma concentration and change in QTc from data collected in 5 Phase 1 studies in healthy volunteers and 2 Phase 2 studies in patients with mild-to-moderate AD and one Phase 2 study in patients with diabetes and persistent albumuria. Model-based analysis showed a small, non-clinically meaningful, positive relationship between azeliragon plasma concentration and QTcF with a slope close to zero. Neither the prediction interval nor the upper bound of the 90% confidence interval reach 10 msec, thus demonstrating no clinically meaningful (i.e. >5 msec prolongation) drug-related effect on QTcF at expected therapeutic and supra-therapeutic doses of azeliragon (33).

Phase 2

The safety and tolerability of azeliragon was initially studied in a 10-week double blind placebo controlled Phase 2a study in 67 patients with mild to moderate Alzheimer's disease (26). Azeliragon doses of 10mg once daily (27 subjects) and 20 mg once daily (28 subjects) were well tolerated following 10 weeks of treatment thereby supporting advancement of the program into 18-months dosing in Phase 2b.

Figure 4. ADAS-COG11 and CDS-sb change from baseline at 18 months in patients taking either 5 mg azeliragon or placebo orally once daily

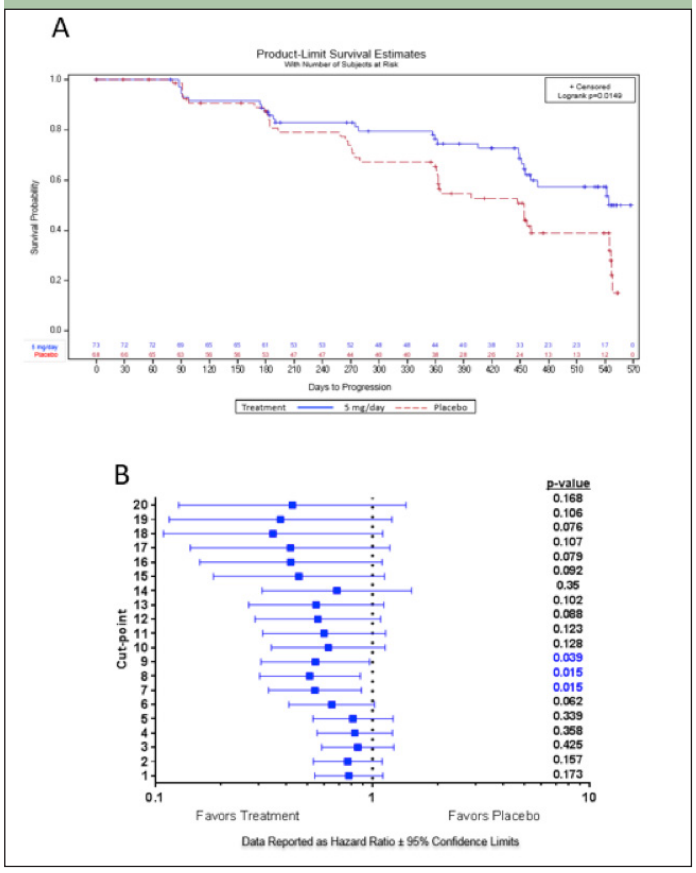


Azeliragon was subsequently studied in an 18 month double blind placebo controlled Phase 2b study in 399 patients with mild to moderate Alzheimer's disease who were taking standard of care medication (cholinesterase inhibitor +/- memantine at stable doses). The primary outcome measure was the Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) (27) with the Clinical Dementia Rating Scale Sum of Boxes (CDR-sb) designated a key secondary measure (28). The results and conduct of the study have been previously described (29, 30). Two doses were initially tested; 5 and 20 mg po qd. The 20 mg dose was poorly tolerated due to falls and confusion and this dosing arm was discontinued. It is important to note that the adverse events were transient and related to plasma concentration of azeliragon. When drug was discontinued and plasma levels fell to those associated with the 5 mg dose, the adverse events abated. The 5 mg dose was well-tolerated and the major drug-related adverse events were mild gastrointestinal distress.

Although this study was terminated early, the 18

month data indicated a baseline to endpoint change in ADAS-cog of 3.1 points in favor of drug for the mild-moderate population (29, 30). The trial had a pre-specified sub-analysis to examine results in patients who entered the study with mild AD based on subjects with a mini-mental state examination (MMSE) score of 21-26. The data shown in Figure 4 indicate that there was a baseline to endpoint change of 4 points on the ADAS-cog in favor of azeliragon and a 1 point change in CDR-sb in favor of drug.

Figure 5. Time to Event Analysis for ADAS-cog11 change from baseline where progression is defined as ADAS-cog11 increase of 7-points. (A) ADAS-cog11 Time to Event Analysis Hazard Ratios using multiple cut-points, across the range of 1 to 20, for defining progression. (B).



Further analyses were performed using time to event analysis for ADAS-cog11 change from baseline where progression was defined as ADAS-cog11 increase of 7-points (32). Azeliragon 5 mg/day delayed time to cognitive deterioration (logrank p=0.0149) (Figure 5a). The results were robust with sensitivity analyses, evaluating all cut-points between a 1 and 20-point worsening in ADAS-cog, demonstrating hazard ratios favoring azeliragon 5 mg/day. (Figure 5b).

Based on the promising results from our Phase 2b study, we initiated a Phase 3 registration program being conducted under a Special Protocol Assessment from FDA. This program, STEADFAST, consists of two 18 month independent identical 400 patient studies in patients with mild Alzheimer's disease as defined by clinical diagnosis of mild AD, MMSE 21-26, CDR-global 0.5 or 1, clinical history consistent with AD, and no exclusionary concomitant illness at time of screening. Patients are on standard of care medication (cholinesterase inhibitor +/- memantine). The primary outcome measures are change from baseline to 18-month endpoint ADAS-COG11 and CDR-sb. Key secondary outcomes include baseline – endpoint change in volumetric MRI. In addition, there are secondary outcomes including FDG-PET, Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), neuropsychiatric inventory (NPI), MMSE, controlled oral word association test (COWAT), category fluency test (CFT), Trail Making Tests A and B, Resource Utilization for Dementia (RUD), Dementia Quality of Life (DEMQOL) and plasma Aβ. Both studies are fully enrolled.

Discussion

RAGE is involved with transport and production of Aβ, neuroinflammation, abnormal tau phosphorylation, and vascular dysfunction in AD. Our preclinical results suggest that the RAGE inhibitor azeliragon effectively addresses many of these disease components. More importantly, clinical data from the Phase 2b study suggest that azeliragon may slow cognitive decline in mild AD patients.

No new drugs for AD have been introduced since the approval of memantine in 2003. Current approved medications offer modest, temporary symptomatic treatment but do not address the fundamental pathologies underlying Alzheimer's disease. The potential reasons for these failures have been reviewed at length (35, 36). In many programs, promising results in animal models of AD, have not been predictive of clinical success (37). It is likely that primary causes of failure have been inadequate target engagement and inappropriate targets for stage of disease. Drugs targeting one aspect of AD pathology, Aβ, have not been successful to date. Several reasons have been given for this including inappropriate patient populations, disease advanced beyond point of meaningful intervention, and safety concerns. Another possible reason could be that treating only one aspect of AD pathology when the disease is established may not be sufficient to provide clinical benefit. In this regard, inhibition of RAGE may have promise in providing clinical benefit. In addition, commonly used testing instrumentation may have limited sensitivity in early disease stages to detect clinically meaningful drug evoked changes. However, lack of effect is more likely due to limited drug activity than sensitivity of testing instrumentation.

It is essential to have a well-grounded clinical program prior to initiating large clinical efficacy studies. Another

reason for failure in Phase 3 programs may be inadequate understanding of dose response with respect to both efficacy and safety outcomes prior to initiation of large pivotal studies. In contrast, the RAGE STEADFAST Phase 3 program is backed by rigorous clinical studies that provided dosing that is both well-tolerated and shows benefit in clinical outcome scales.

We have developed a RAGE inhibitor that has shown promising results in preclinical AD models and more importantly in a Phase2b study. We have embarked on a Phase 3 program that if successful will demonstrate that the RAGE inhibitor azeliragon can slow cognitive decline in patients with mild AD.

Conflict of interest: Drs. Burstein, Andrews, Valcarce, Dunn, and Altstiel are employees of vTv Therapeutics Inc. D.r Sabbagh is a member of the vTv Scientific Advisory Board and has received research grants from Pfizer, Eisai, Lilly, Avid, Bristol-Myers Squibb, Avanir, Janssen, Elan, Bayer, Paramal, Genentech.

Ethical standards: Animal experiments were done in accordance with • U.S. Department of Agriculture's (USDA) Animal Welfare Act (9 CFR Parts 1, 2, and 3) • The Public Health Services Act as amended by the Health Research Extension Act, PL 99-158, November 20, 1985 (42 U.S.C. 289d) • Public Health Service Policy on Humane care and Use of Laboratory Animals, August 2002. Clinical subjects provided informed consent; if they had impaired decisional capacity, caregivers provided consent and subjects assented to participate. The study was conducted under local institutional review board supervision and under an investigational new drug application from the US Food and Drug Administration. It is listed on ClinicalTrials.gov (NCT00566397).

References

1. Lane CA, Hardy J, Schott JM. European J Neurol. Alzheimer's disease. doi: 10.1111/ene.13439
2. Karran E, De Strooper B. The amyloid cascade hypothesis: are we poised for success or failure? J Neurochem. 2016 Oct;139 Suppl 2:237-252.
3. Miguel-Álvarez M, Santos-Lozano A, Sanchis-Gomar F, et al. Non-steroidal anti-inflammatory drugs as a treatment for Alzheimer's disease: a systematic review and meta-analysis of treatment effect. Drugs Aging. 2015;32(2):139-147.
4. Bierhaus A, Humpert PM, Morcos M, et al. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med 2005; 83: 876–886.
5. Schmidt AM, Yan SD, Yan SF, Stern DM. The multi-ligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. J Clin Invest 2001;108:949–955.
6. Hori O, Brett J, Slattery T, et al. The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. J Biol Chem 1995;270:25752–25761.
7. Hofmann MA, Drury S, Fu C, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 1999;97:889–901.
8. Donato R. RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins. Curr Mol Med 2007;7:711–724.
9. Chavakis T, Bierhaus A, Al-Fakhri N, et al. The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. J Exp Med 2003;198:1507–1515.
10. He M, Kubo H, Morimoto K, et al. Receptor for advanced glycation end products binds to phosphatidylserine and assists in the clearance of apoptotic cells. EMBO Rep. 2011;12:358–364.
11. Yan SD, Chen X, Fu J, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature 1996;382:685–691.
12. Ding Q, Keller JN. Evaluation of rage isoforms, ligands, and signaling in the brain. Biochim Biophys Acta 2005; 1746, 18–27.
13. Fang P, Schachner M, Shen YQ HMGB1 in development and diseases of the central nervous system. Mol Neurobiol 2012; 45(3):499-506.
14. Shepherd CE, Goyette J, Utter V, et al. Inflammatory S100A9 and S100A12 proteins in Alzheimer's disease. Neurobiol Aging 2006;27: 1554–1563.
15. Wautier MP, Chappey O, Corda S, Stern DM, Schmidt AM, Wautier JL. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. Am J Physiol Endocrinol Metab 2001; 280:E685–E694.
16. Yan SD, Chen X, Fu J, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature 1996;382:685–691.
17. Yan SF, Yan SD, Ramasamy R, Schmidt AM. Tempering the wrath of RAGE: an emerging therapeutic strategy against diabetic complications, neurodegeneration, and inflammation. Ann Med 2009;41:408–422.
18. Mackic JB, Stins M, McComb JG, et al. Human blood-brain barrier receptors for Alzheimer's amyloid-beta 1-40. Asymmetrical binding, endocytosis, and transcytosis at the apical side of brain microvascular endothelial cell menolayer. J Clin Invest 1998;102(4):734-743.
19. Giri R, Shen Y, Stins M, et al. beta-amyloid-induced migration of monocytes across human brain endothelial cells involves RAGE and PECAM-1. Am J Physiol Cell Physiol 2000;279(6):C1772–C1781.
20. Deane R, Du Yan S, Submamaryan RK, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat Med 2003;9(7):907–913.
21. Mattson MP, Camandola S. NF-kappa-B in neuronal plasticity and neurodegenerative disorders. J Clin Invest 2001;107:247–254.
22. Huang JS, Guh JY, Chen HC, Hung WC, Lai YH, Chuang LY. Role of receptor for advanced glycation end-product (RAGE) and the JAK/STAT-signaling pathway in AGE-induced collagen production in NRK-49F cells. Cell Biochem 2001;81(1):102-13.
23. Li XH, BL Lv, Xie JZ, Liu J, Zhou XW, Wang JZ. AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. Neurobiol Aging 2012 ;33(7):1400-10.
24. Deane R, Singh I, Abhay PS, et al. A multimodal RAGE-specific inhibitor reduces amyloid β–mediated brain disorder in a mouse model of Alzheimer disease. J Clin Invest 2012; 122(4):1377-92.
25. Kostura MJ, Kindy MS, Burstein A, et al. Efficacy of RAGE antagonist in murine model of Alzheimer's disease. Alzheimers Dement 2014;10(4, Suppl):638-639.
26. Sabbagh MN, Agro A, Bell J, Aisen PS, Schweizer E, Galasko D. PF-04494700, an oral inhibitor of receptor for advanced glycation end products (RAGE), in Alzheimer's disease. Alz Dis Assoc Disord 2011;24(30):206-212.
27. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356-64.
28. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull 1988;24:637-9.
29. Galasko D, Bell J, Mancuso JY, et al. Clinical trial of an inhibitor of RAGE-Aβ interacations in Alzheimer disease. Neurology 2014;82(17):1536-42.
30. Burstein AH, Grimes I, Galasko DR, Aisen PS, Sabbagh M, Mjalli AM. Effect of TTP488 in patients with mild to moderate Alzheimer's disease. BMC Neurol 2014;14:1212.doi: 10.1186/1471-2377-14-12.
31. Burstein AH, Lamson MJ, Sale M, Brantley SJ, Gooch A, Dunn I, Altstiel LD. Effect of CYP2C8 and CYP3A4 inhbition and CYP induction on the pharmacokinetics of azeliragon. J Prev Alz Dis 2017;4(4):336.
32. Gooch A. Burstein AH, Brantley SJ, Lamson MJ, Dunn I, Altstiel L. Effect of mild or moderate hepatic impairment on the clearance of azeliragon. J Prev Alz Dis 2017;4(4):335-6.
33. Burstein AH, Brantley SJ, Dunn I, Altstiel LD, Schmith V. Assessment of azeliragon QTc liability through integrated, model-based concentration QTc analysis. Alz Dementia 2017;13(7, supplement): 262-3.
34. Vellas B, Andrieu S, Cantet C, Dartigues JF, Gauthier S. Long-term changes in ADAS-cog: what is clinically relevant for disease modifying trials in Alzheimer? J Nutr Health Aging 2007;11(4):338-41.
35. Mehta D, Jackson R, Gaurav P, Shi J, Sabbagh, M. Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015.Expert Opinion on Investigational Drugs 2017; 6: 735-739.
36. Cummings J, Aisen PS, DuBois B, et al. Drug development in Alzheimer's disease: the path to 2025. Alzheimer's Research & Therapy 2016; 8:39-51.
37. Drummond E, Wisniewski T. Alzheimer's disease: experimental models and reality. Acta Neuropathol 2017;133(2):155-175.