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REVIEW

The emerging role of bexarotene in the treatment of Alzheimer's disease: current evidence

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Abstract: In 2012, a novel approach to the treatment of Alzheimer's disease was introduced, heralding a wave of excitement in the field of dementia. Bexarotene, a retinoid X receptor agonist, was shown to reverse neurodegeneration, improve cognition, and decrease levels of amyloid-β in transgenic mice expressing familial Alzheimer disease mutations. Since then, there has been widespread discussion about bexarotene, as well as a number of follow-up studies. Bexarotene is a unique compound, as it is approved by the US Food and Drug Administration for other purposes and there are reasonable data to justify its mechanism of action in dementia. This review discusses these studies and the emerging role of bexarotene in the clinical field of Alzheimer's dementia.

Keywords: repurposing, ApoE-targeted mice, amyloid, therapy, dementia

Introduction

Our knowledge about the pathogenesis of Alzheimer's dementia (AD) has expanded dramatically over the last decade. Unfortunately, these findings have not been successfully translated into new therapies for AD. These attempts by the pharmaceutical industry to find new treatments have not been successful during the last decade, with an overall failure rate of 99.6%[1] and only one newly approved therapy since 2004 in the United States.

The pharmaceutical industry has scaled down the search for new Alzheimer's treatments after the failure of several high-profile expensive trials. This, however, might have initiated a trend of investigating drugs that have already been approved by the US Food and Drug Administration for other indications, but that may interact with AD pathophysiology through mechanisms unrelated to their original therapeutic indication. Because these medications have already gone through Phase I and Phase II trials, their chances of passing through additional trials, if necessary, are very good. That by itself facilitates progression through the clinical trial pipeline,[1] which can save years of work and millions of dollars.

A landmark paper by Landreth and Cramer et al published in *Science* on bexarotene, a compound currently approved to treat cutaneous T-cell lymphomas, created potential new hope for the treatment of AD.[2] This review describes and discusses the literature addressing the effects of bexarotene in an Alzheimer's model of mice and the potential clinical implications.

Background

Disease-modifying therapies can be classified mainly as amyloid-related, tau-related, and neuroprotective. The therapies that target amyloid processing in Alzheimer's

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disease rely on different mechanisms of action: inhibition of beta secretase or gamma secretase, enhancement of alpha secretase or amyloid-β (Aβ) metabolism, and even amyloid removal by monoclonal antibodies or plasma exchange.[3,4]

Increased production and/or decreased clearance of Aβ from the brain can contribute to Alzheimer's disease. Therapeutic strategies to promote Aβ clearance, such as the use of apolipoprotein E (APO E), hold promise for the treatment of AD.

APO E and Alzheimer's disease

APO E is a lipid transport protein that promotes Aβ degradation and protects against atherosclerosis. APO E exists in three isoforms: E2, E3, and E4. Most humans are homozygous for APO E3. APO E4 is considered a risk factor for late-onset AD, and APO E2 is considered protective.[5]

Expression of APO E and the lipid transporter genes *ABCA1* and *ABCG1* facilitate the formation of APO E-associated lipoprotein particles.[6] This is regulated by ligation of either member of the following pair of nuclear receptors: retinoid X receptor (RXR) and peroxisome proliferator-activated receptors[7] and RXR and liver X receptor.[8]

Activation of either pair induces the expression of APO E, which promotes Aβ degradation. Agonists of these receptors also promote phagocytosis in microglia and macrophages.[9,10]

Bexarotene in animal models of AD

Landreth and Cramer et al reported that a drug that activates RXRs, such as bexarotene, has the potential to increase APO E and ABCA1 production. In their study, bexarotene rapidly cleared soluble Aβ from the brain, reduced neuritic plaque burden, reversed behavioral deficits, and improved cognition in mice genetically engineered to express a mutant form of the *APP* gene.[2]

Their impressive results captured worldwide attention and led to additional research. Four studies in particular[11–14] attempted to replicate and validate Landreth and Cramer's observations that bexarotene stimulates the clearance of soluble Aβ peptides and reverses behavioral deficits in mouse models of Alzheimer's disease. *Science* published these four follow-up studies as commentary to the original study in a single issue.

Fitz et al found that oral administration of bexarotene reversed cognition in two different tasks to the level of non-transgenic controls.[11] They also confirmed that soluble Aβ is present in the interstitial fluid. Veeraraghavalu et al also found that oral bexarotene given over the course of 7 days

reduced Aβ40 levels.[14] Both the Fitz et al and Veeraraghavalu et al studies failed to replicate the effect of amyloid deposition in the brain.[11,14]

Tesseur et al found improvement in social recognition and another memory task, but no change in soluble Aβ40 levels or amyloid deposition after 19 days of treatment.[13] Price et al were unable to show any reduction in soluble Aβ40 or amyloid deposition. However, the last two studies reported significant upregulation of ABCA1 levels.[12]

In responding to these four follow-up studies, Landreth et al[15] emphasized that the additional research validated their main conclusion: bexarotene stimulates clearance of soluble Aβ. Only two of the studies, however, replicated most of the original findings. Landreth also emphasized that bexarotene was less efficient in older mice or in more aggressive amyloidogenic models of mice, which might have explained why these follow-up studies failed to find any reductions in amyloid plaques. They concluded, "the behavioral improvements were poorly correlated with the microglial-mediated removal of insoluble, deposited forms of Aβ."[15] In addition, they pointed out that the Price et al,[12] Tesseur et al[13] and Veeraraghavalu et al[14] studies used unconventional formulations of bexarotene, which alter its pharmacokinetics and bioavailability, a critical difference from the original 2012 study.[15]

Another study, published in an open-access journal, assessed the effects of bexarotene in mutant APP/PS1 mice, which were acutely dosed with the compound. Although ABCA1 was upregulated in the treated mice, there was no attenuation of Aβ plaques or cognitive deficits.[16]

In the latest in vivo study, Boehm-Cagan and Michaelson investigated the effects of bexarotene on messenger RNA and protein levels of APO E, ABCA1, and ABCG1 in young mice and assessed the extent to which this reversed the APO E4-driven pathological phenotype.[17] This investigation showed that bexarotene increased messenger RNA and protein levels of ABCA1 and ABCG1 in hippocampal neurons. The compound also reversed APO E4-induced cognitive and neuronal impairments. The authors suggested that "RXR activation and increased levels of ABCA1 and ABCG1 could be useful in the treatment of human apoE4 carriers."[17]

In a more recent study, Tai et al[18] studied the role of the RXR agonist (bexarotene) in EFAD transgenic mice (transgenic mice expressing 5× familial AD mutations and human APO E3 or APO E4), which have the highest levels of soluble Aβ in E4FAD hippocampus. In E4FAD hippocampus, short-term (6 months) bexarotene treatment increased ABCA1, APO E4 lipoprotein-association/lipidation, and APO E4/Aβ complex

and decreased soluble Aβ levels. The authors conclude that RXR agonists address the loss of function associated with APO E4 and exacerbated by Aβ pathology.

The above studies may support one of the possible mechanisms of bexarotene's action via amyloid cascade, but there may be other potential mechanisms as well. In vitro studies suggest that APO E4 may affect tau hyperphosphorylation via direct interaction with either tau or other pathways.[19,20]

Further research is required to determine which one of these possible mechanisms underlies the effects of APO E4 on tau hyperphosphorylation in targeted replacement (TR) mice, and its reversal by bexarotene treatment.

Bexarotene in current clinical practice

Bexarotene is a retinoid approved by the US Food and Drug Administration in 1999 for use as a treatment for cutaneous T-cell lymphoma (CTCL).[21] Bexarotene is convenient because the capsules can be taken orally once daily with meals. When used to treat cutaneous T-cell lymphoma, the drug can cause adverse effects including hypertriglyceridemia, hypercholesterolemia, and hypothyroidism; these require monitoring but can be managed with concomitant medication.[22–24]

Hypothyroidism caused by bexarotene use was associated with marked reductions in serum concentrations of thyroid-stimulating hormone and thyroxine. Bexarotene may suppress thyroid-stimulating hormone production and increase thyroid hormone metabolic clearance.[23] Treatment of patients with bexarotene-induced hypothyroidism commonly requires high doses of thyroid hormone for replacement therapy, often at twice the typical dose used to treat more common hypothyroidism.[22]

Hypertriglyceridemia developed in 79% of patients who took bexarotene in a study of early-stage cutaneous T-cell lymphoma, whereas hypercholesterolemia occurred in 48% of patients, and hypothyroidism in 40%.[24]

Associated hypertriglyceridemia secondary to bexarotene treatment can be managed with medication such as Fenofibrate. There are case series showing that concomitant use of omega-3 fatty acids may adequately manage hypertriglyceridemia in these patients.[25]

Bexarotene in human clinical trials

Bexarotene is a good candidate for further drug development in AD treatment, given its high blood–brain barrier permeability and current safety profile. However, the pharmaceutical industry might be less enthusiastic in developing a drug that will soon be available generically. Eisai Pharmaceutical has manufactured bexarotene exclusively, and its patent on

Targretin is estimated to expire in 2016.[26] A generic version may be released by Mylan Inc., in 2015.[27]

Bexarotene has been used off-label in dementia patients since the initial 2012 report, but these cases have not been consistently published. In a single case report of bexarotene use in an APO E4-positive patient with AD, the drug was tolerated relatively well (the most common adverse effect was hypercholesterolemia, which responded to statin therapy), but no cognitive benefit was noted after 3 months of 150 mg daily treatment.[28]

There are currently two clinical studies on human subjects in different phases. The first one, Bexarotene Anti-Amyloid Therapy for Alzheimer's Disease (BEAT-AD), which is being conducted by Dr. Cummings at the Cleveland Clinic, has completed recruiting, and the results are expected to be released this year (Jeffrey Cummings, Cleveland Clinic, 2014). The purpose of this study is to determine the safety and effect of 300 mg bexarotene administered daily for 1 month compared with placebo. The primary study endpoint is the change from baseline to week 4 in amyloid burden, as measured by standard uptake units regional on amyloid brain imaging obtained through 18F-AV-45 positron emission tomography. Secondary outcome measures include Alzheimer's Disease Assessment Scale–Cognition change from baseline to week 4 and to week 8, biomarker changes, magnetic resonance imaging changes, Clinical Dementia Rating–Sum of Boxes, Neuropsychiatric Inventory, and Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory.[29]

Landreth and his laboratory have also developed a trial of bexarotene in healthy people to establish how the medication works in normal subjects. Landreth and Cramer have formed a spinoff company, ReXceptor, to perform the testing. Their primary objective is to determine whether bexarotene enhances the clearance of newly generated Aβ. The researchers will also assess whether the drug elevates levels of APO E and APO E-based high density lipoproteins (HDLs) in cerebrospinal fluid (personal communication).[30]

ReXceptor is working in collaboration with C2N diagnostics (St Louis, Missouri), which produces a proprietary stable isotope labeling platform, to measure the metabolism of both brain-derived Aβ and APO E (personal communication).

Discussion

Since the publication of the four follow-up studies on bexarotene, there has been much controversy surrounding the drug's effects on AD. On one hand, the follow-up studies failed to replicate the plaque-clearing finding, which raises

the concern that it may be too soon to test the drug in patients with Alzheimer's disease. On the other hand, the most important result of the 2012 study, cognitive improvement, has been independently validated. That triggers a new thought process, in that it may be irrelevant if the drug actually clears the plaques and that perhaps our focus needs to shift toward the effects of soluble Aβ. Landreth also emphasized that different formulations of bexarotene were used in the validating studies, which may explain the discrepancies between the initial and follow-up study results.[15]

A number of questions remain, however, and these must be addressed in future research. First, how does bexarotene improve cognition? It may do so through an additional mechanism not fully known yet. A French study showed that cholesterol and bexarotene compete for the same binding site in the C-terminal region of Alzheimer's Aβ1-42. Bexarotene competed with cholesterol for binding to Aβ and prevented neurotoxic oligomeric channel formation.[31] In a recent study, bexarotene was shown to counteract both Aβ-induced and Aβ-independent increases in cortical network hyperexcitability.[32]

Next, how much reduction in Aβ synthesis needs to occur to produce a cognitive benefit?

Third, what is the peripheral effect of bexarotene? We know it noticeably changes the metabolism of lipids in the peripheral blood. Cumming's study at the Cleveland Clinic may shed further light on the effect of bexarotene in Alzheimer's patients. The study has enrolled 20 subjects (10 patients in each group), but whether the study is sufficiently powered to detect efficacy remains to be seen, especially if changes are not as dramatic as those reported in the Landreth mouse model.

Fourth, what is the appropriate dosage for use in a clinical trial of AD? When used to treat cutaneous lymphoma, bexarotene is calculated per milligram per square meter. The dose, however, may be different for the treatment of AD, as the medication must pass through the blood–brain barrier. In addition, it is not clear at what stage of the disease the drug should be given to maximize the effect. If given too late in the disease process, it may not produce the same effects.

What is bexarotene's risk–benefit ratio when used as an Alzheimer's drug? The relatively common adverse effects observed with bexarotene use in cancer patients, such as hyperlipidemia, might add an unjustifiable toxicity burden to a frail patient. Adding other medications (ie, statins) to manage these symptoms might add unexpected pharmacodynamic interactions that obscure any functional effect on cognition. Adverse effects, however, may be overcome by designing an improved analog.

Will the results of the studies of bexarotene treatment using mouse models translate to humans? It is important to emphasize that most published studies have tested bexarotene in transgenic mice expressing mouse APO E,[2,12–14] which is structurally and functionally distinct from any of the human isoforms. Also, these mouse models failed to develop tauopathy, which is a hallmark finding of the disease in humans.

Will increasing APO E4 produce positive or negative effects? Because bexarotene was shown to increase levels of mouse APO E and ABCA1/ABCG1-induced APO E lipoprotein association/lipidation, it is expected that its effects will depend on the APO E genotype. Accordingly, in the case of APO E3 or mouse APO E, the effects could be beneficial either because of increased levels of APO E and/or because of increased lipidation. However, in the case of APO E4, the effects of increasing APO E4 could be either "good" or "bad," depending on whether APO E4 functions via a toxic gain of function or loss of function.

Finally, we know that bexarotene can address a loss of function associated with APO E4, but is this pathway relevant for APO E3 carriers? Also, is bexarotene an APO E4-specific AD therapy?

Much research remains to be done, but even if bexarotene is found to be ineffective as a treatment for Alzheimer's disease in humans, it has opened the door to finding a new treatment approach to the pathology of this disease and, in fact, may one day represent a new class of AD therapies.

Acknowledgment

Disclosure

The author reports no conflicts of interest in this work.

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