Section A-Review paper

REPURPOSING OF BEXAROTENE FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE

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Abstract: There is growing research interest in the relationship between cancer and dementia. The necessity for innovative and efficient drug discovery methods is justified by the variety of the disease and the slow pace of therapeutic advancement in neurodegenerative disease. Drug repurposing is a revolutionary strategy that renews the traditional drug development process by demonstrating novel therapeutic applications for already approved medications. The idea of repurposing anticancer medications as innovative therapies has merit because of the shared molecular foundation and inverse tuning between cancer and neurodegeneration. There are numerous studies in the literature that highlight the success of anticancer medications as repurposed therapies. Among this the nuclear retinoid X receptor agonist bexarotene has coupled the restoration of cognitive ability (AD) by enhancing apoE expression in mice models of Alzheimer's disease. Recent investigations have demonstrated that treatment with bexarotene reduces the number of soluble forms of Aβ, particularly Aβ oligomers. Since then, bexarotene has been the subject of extensive discussion and numerous follow-up studies. Bexarotene is a special substance since the US-FDA has given it approval for use in other conditions, and there is evidence to support its mode of action in Alzheimer's disease. These results and bexarotene's emerging significance in the treatment of Alzheimer's dementia are discussed in this review. In order to create possible repurposed medications with no toxicity for neurodegenerative disorder, This review encourages more research to better understand the possible benefits of anticancer medications.

Key words: Alzheimer's; Neurodegeneration; Retinoid X Receptor Agonist; Bexarotene

1. Introduction

One of the most alarming medical disorders that affecting the brain and neurological function is Neurodegenerative disorders (NDDS). The lack of knowledge about the disease-causing pathways prevents the development of effective treatments (1). By 2025, it's anticipated that there will be 34 million Alzheimer's disease(AD) patients worldwide. According to current estimates, 35.6 million individuals worldwide are thought to be living with dementia. By 2030 and 2050, it is anticipated that this number would have more than doubled (2). Continuous failure of medications that designed for treating NDDS demands to develop new treatment options having maximum success rates. 70% of initiatives fail between phase 2 and phase 3 of clinical trials, making the research and development of innovative medications a time-consuming, expensive process with low success rates (3).

Drug repurposing, also known as drug repositioning, is an effective way to employ already-approved medications for a different condition while the original mechanisms of action remain the same. This repurposing strategy was effective in treating various medical conditions such as cancer, irritable bowel syndrome, Parkinson's disease, cardiovascular disease, and psychosis. Repurposing of drug creates a chance to reinvigorate the lagging drug discovery process by finding new applications for already-approved drugs (4). The fundamental benefit of drug repositioning is that the candidate compounds' pharmacokinetic characteristics and toxicity have already been determined and drugs are commercially available in the market. This hastens the process of drug development and reduces cost factors. There are primarily two approaches for repurposing. The first strategy is to review the medications for novel therapeutic uses within the framework of their approved uses. The second, more cutting-edge strategy is to identify novel therapeutic targets for the current medications. Clinical trials for certain repurposed medications for NDDs specifically for AD have begun. Drugs used as AD treatments include those that are anti-cancer, anti-microbial, antidiabetic, anti-hypertensive, anti-asthmatic, and antipsychotic (5). The greatest risk factor for a variety of illnesses, including cancer and neurological diseases, is ageing. These age-related disorders can be divided into two groups; for instance, diseases characterized by a loss of function, such as neurodegenerative disease, cause cells, tissues, or the loss of ideal physiological activities. Yet, diseases with gain-of-function, like cancer, show an increase in cells and occasionally new cellular functions (6).

Many scientific and clinical processes support the connection between neurodegeneration and oncogenesis. Neurodegeneration and cancer are viewed as two opposing sides of a coin with some common features. Many genes and signaling pathways are affected similarly in both conditions, despite the fact that the general biology of the two diseases is in opposition to one another. Since neurons experience early cell death and cancer cells can proliferate uncontrolled. There is accumulating evidence to suggest a connection between the commonly altered genes in various NDDs and the genes linked to cancer (7). The interesting link between cancer and neurodegenerative disease creates new opportunities for repurposing anticancer medications for neuroprotection, however there are certain limitations. Many are now undergoing clinical testing, and some are in experimental phase (8). Among these an innovative method of treating Alzheimer's disease was presented, that is Bexarotene a retinoid X receptor agonist, in transgenic mice stating familial Alzheimer disease mutations, it was observed to prevent neurodegeneration, enhance cognition, and lower levels of amyloid-β. While the US FDA has approved bexarotene to use in other diseases. Reasonable data are available to support its mode of action in dementia. This review discusses regarding the drug Bexarotene and their emerging role in the clinical field of Alzheimer's diseases (9).

2. Pathophysiology of Alzheimer's diseases

In the past 25 years, an astonishing confluence of seven new facts has occurred, changing our knowledge of this significant disease in fundamental ways. First, Alzheimer's diseases are the leading cause of dementia. Second, buildup of a type of amyloid called Aβ peptide is the disease's primary pathogenic feature. Third, genes for this peptide are positioned on chromosome 21, and it is separated from a larger protein called the amyloid precursor protein. Fourth, people with trisomy 21 (Down's syndrome) have Alzheimer's disease-related degenerative alterations in their brains. Fifth, the prevalence of Alzheimer's disease in many families suggests autosomal dominant inheritance. Sixth, in some of these families, mutations in any one of three genes are sufficient to produce the disease. And finally, in common with the prevalent kind of Alzheimer's disease in the general population, there is a link with the e4 allele of apolipoprotein E (10).

3. Genes associated with Alzheimer's disease

The occurrence of AD patients with an autosomal dominant inheritance pattern in some families has enabled the finding of disease genes. Aggressive forms of early-onset AD are

caused by fully penetrant mutations on three of the causative genes (11). The genes responsible for producing the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PENS2) are located on chromosomes 21q21, 14q24 and 1q42 respectively. These genes' mutations represent approximately 5% of all instances of AD. Other genes, referred to as susceptibility genes, are thought to contribute to the development of AD through complex interactions with environmental factors. Several studies have found a strong correlation between allele polymorphism of one of these susceptibility genes, apolipoprotein E on chromosome 19q13 (APOE), and an elevated risk for late-onset AD. There may be additional AD susceptibility genes, and research is now being done to identify them. In the end, it is likely that a range of genes, each of which is only partially responsible for all cases, will be found to impart risk (10). APP, PSEN1, PSEN2, and APOE are four AD-related gene, all together account for almost half of the inherited vulnerability for AD (12).

Causative genes

Amyloid precursor protein

The secretory or endosomal-lysosomal channels are employed to process the APP known as type I transmembrane glycoprotein. Has a total of 10 isoforms of APP generated by alternative splicing, with amino acid lengths of 304, 639, 677, 695, 696, 714, 733, 751, 752, and 770(13). The three APP isoforms with the most amino acids are those with 695, 751, and 770. The 695 amino-acid genotype is more typically denominated in brain tissue. Despite the fact that the APP's physiological functions are yet unknown, the fact that it is so widely expressed when developing and in a some of adult tissues indicates a fundamental aspect it may play in physiological functions. APP appears to contribute to synaptic plasticity, neurite outgrowth synaptogenesis, static cell-substrate adhesion, and neuronal cell survival (14). In addition, APP regulates the cell migration (15). Caspase-dependent death and neurite degeneration occurs, when APP monoclonal antibodies comes in contact with cortical neurons (16). The soluble component of APP (sAPPα), which is released, exhibits similarities to growth factors and promotes the formation of embryonic neural stem cells (17).

Presenilins

Both presenilin 1 (PS-1) and presenilin 2 (PS-2) are 8-domain transmembrane proteins that catalyse the final step of APP cleavage within the γ-secretase complex and creating the Aβ40 and Aβ42 peptides. There are six different PS-1 splicing variants that have the amino acids

184, 374, 378, 409, 463, and 467. Sequences of PS-2's two isoforms contain 448 and 414 amino acids. Two of the 144 missense mutations of PS-1 that have been found so far are not harmful. There are currently eleven known PS-2 mutations, among one of which is not harmful. The PS-1 mutation causes most serious type of dominant familial AD, with 100% incidence and onset at the earliest 30 years of age (10). Production of Aβ42 increases due to the missense mutation in presenilin PS-1 and PS-2, the very self-aggregating and neurotoxic form of Aβ, according to research done on cell lines expressing human presenilins with mutations, transgenic mice with human presenilins with mutations, and plasma samples and brain sections from patients with presenilin mutations (18). These mutations change the shape of presenilins, increasing the peptide link connecting the threonine and amino acids alanine in APP and the two catalytic aspartates of presenilins, which are located at positions 257 and 385 respectively (19). A typical symptom, including as spastic paraparesis, language difficulties, and frontal behavioural disorders, are linked to specific PS-1 mutations (20). Neurofibrillary tangle disease and frontotemporal dementia (FTD) without amyloidosis both were linked to the PS-1 mutation G183V (21). The idea that all autosomal dominant kinds of AD may be connected to Aβ enlargement in the brain was questioned by the fact that normal levels of Aβ42 were generated by cultured cells transfected with this mutant presenilin (22).

Susceptibility genes

In genetic-association studies, more than 100 additional genes have been examined as risk factors, although none of them are firmly confirmed (23). According to estimates, at least six more susceptible genes affect sporadic AD risk and the age at onset (24).

Apolipoprotein E

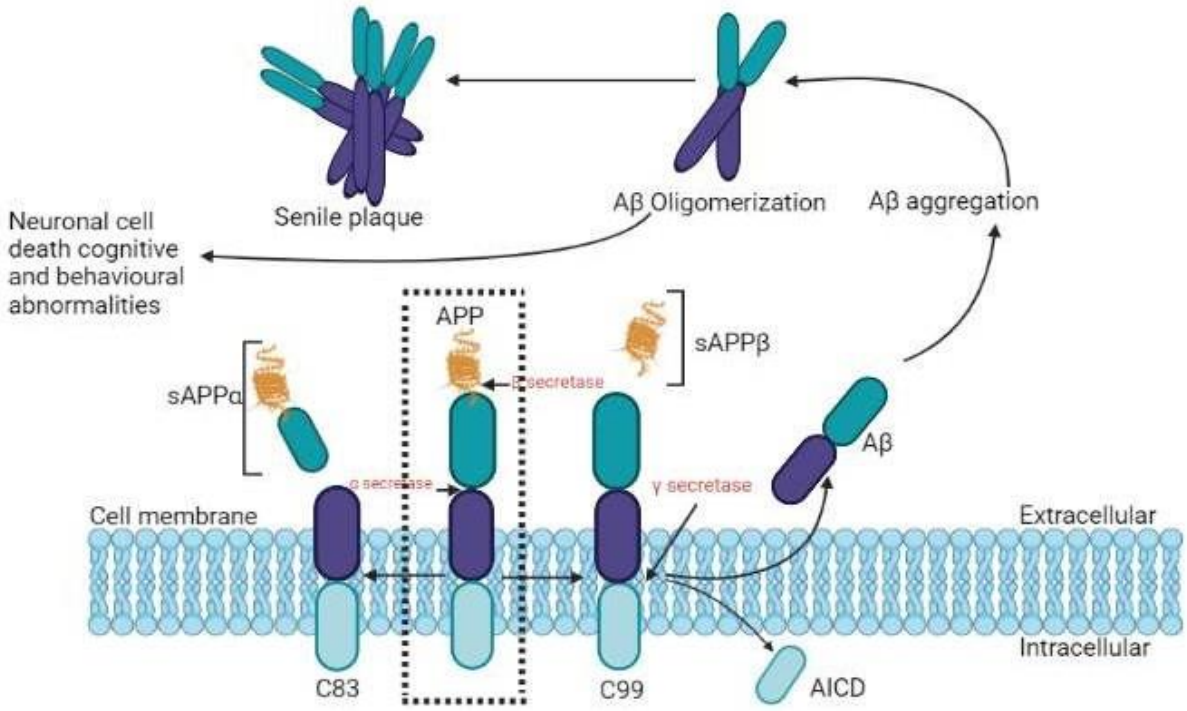
A 299 amino acid protein called apoprotein E (apoE) is responsible for the movement and metabolism of lipids (25). The liver is where 90% of the circulating apoE comes from. ApoE is also produced by other organs such as ovary, spleen, lung, kidney, central nervous system and muscle, in which it is generated via glia, macrophages and neurons. The three major apoE isoforms (apoE2, apoE3, and apoE4) are recognized and expressed by the three natural allelic apoEs, e2 [APOE*E2], e3 [APOE*E3], and e4 [APOE*E4]. Little fundamental variations exist between various apoE isoforms. Cysteine is found in position 112 while arginine is found in position 158 of apoE3. Arginine takes the place of cysteine in position 112 of apoE4. Position 158 of apoE2 has cysteine in place of arginine. APOE*E3, which is

present in 40% to 90% of the total population, is the most prevalent APOE allele. 10% to 15% of the general population has the APOE*E3 gene, which is more common in northern than southern European regions (26). The least common allele is APOE*E2 (around 10%). The most important and well-founded inherited risk factor in the late-onset AD was the APOE gene polymorphism (10). Relatively the noncarriers, people with the APOE*E4 gene are at greater danger of getting Alzheimer's disease (AD), with a three to four times greater risk for heterozygotes and a nine to ten times the increased risk for homozygotes (27). Around 45% of APOE alleles in the population of AD patients are of type e4(28). On the other hand, APOE*E2 appears to protect against AD (27). It's interesting to note that just a small percentage of people with mutant APP and APOE*E2 do not get dementia (29). Many genetic epidemiology studies conclusively show that people with one or more of the genetic conditions with the APOE*E4 gene who are in their sixth or seventh decade of life. However, the outcome varies with age-specific and sex, with its highest impact being reported at about 70(30). There are elderly people with two APOE*E4s who appear to be immune to the APOE*E4 impact. According to reports, the purified apoE4 isoform has a greater affinity for Ab than apoE3 does (31), indicating that it might serve as a pathogenic chaperone to stabilise the b-sheet structure of Ab fibrils (32) and damaging Ab clearance (33). Recent studies in APOE transgenic and knockout mouse models reveal that apoE4 significantly increases the quantity of fibrillar Ab accumulation in the brain as compared to apoE3's effects (34). Therefore, having the APOE*E3 genotype is not required nor adequate on development of AD. Hence, additional genetic or environmental influences exist, that can alter the risk for AD either by itself or in combination with APOE*E4(35).

4. The generation of β Amyloid

Neuritic plaques, the recognisable lesions detected in the brains of AD patients, are mostly consisting of accumulation of a peptide containing 40 or 42 amino acid residues known as Ab. The metabolic digestion of the complex transmembrane glycoprotein known as APP gives rise to Ab peptide. APP can be metabolised via two distinct metabolic pathways. The a-secretase enzyme cleaves APP within the Ab sequence in the so-called "nonamyloidogenic pathway," releasing its transmembrane fragment, sAPPα, which seems to have neuroprotective properties. In the amyloidogenic process, the b-secretase enzyme generates sAPPβ together with a 12-kd protein fragment (C99), that often subsequently cleaved by the g-secretase complex to create Aβ (Figure;1). Presenilin act as a precursor for g-secretase

complex and anterior pharynx deficient 1, presenilin enhancer 2 (Pen-2), nicastrin serves as cofactors (36).



Figure;1: Generation of Beta amyloid plaques

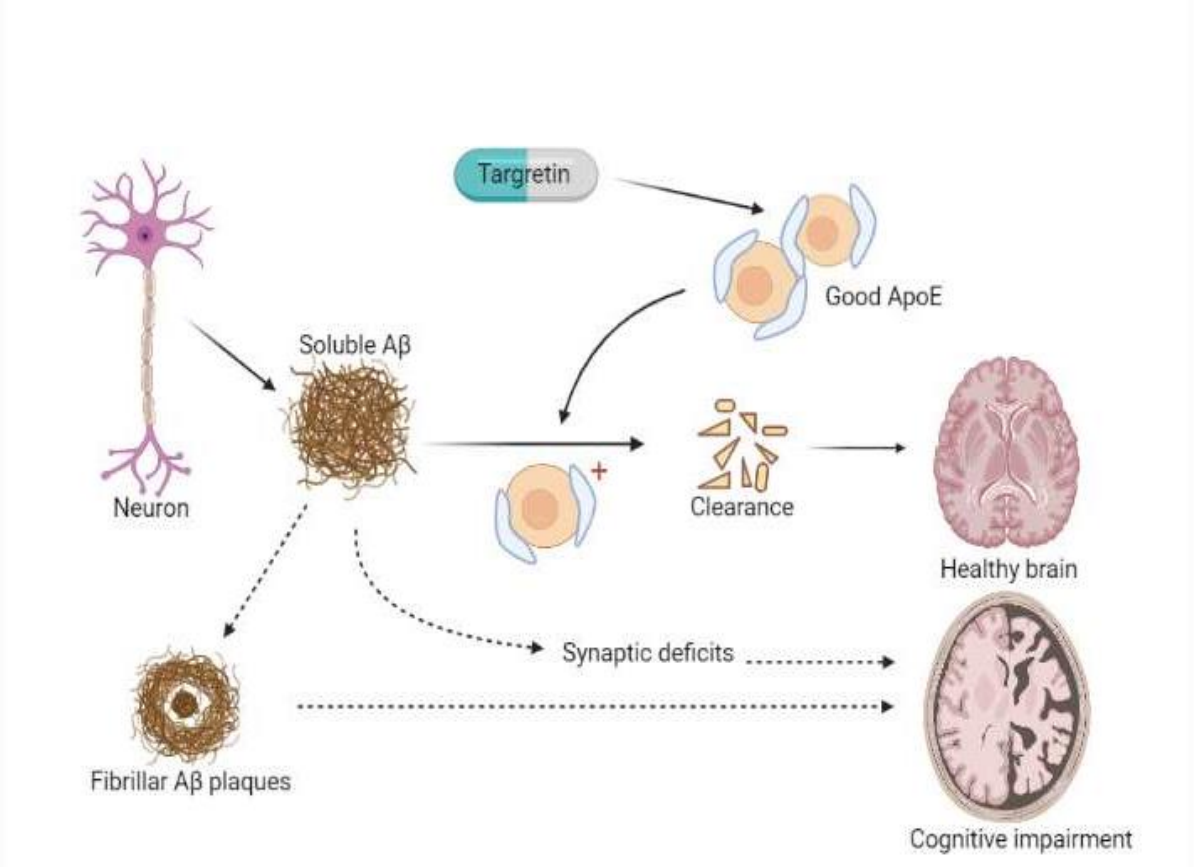
5. Bexarotene: APO E directed therapeutics for the treatment for Alzheimer's diseases

Bexarotene: APO E directed therapeutics rapidly clear β Amyloid

Allelic variation in the apolipoprotein E (APOE) gene is the genetic risk factor for sporadic AD that has the greatest genetic impact. Possessing an APOE4 allele significantly raises illness risk(37). ApoE produces high-density lipoprotein (HDL) particles, that encourage the proteolytic breakdown of soluble forms of Ab (38)(39).

The ligand-activated nuclear receptors (LARs), peroxisome proliferator-activated receptor gamma (PPARg), and liver X receptors (LXRs) control the transcription of apoE(40), which, along with retinoid X receptors, form obligatory heterodimers (RXRs). Ligation of either component of the pair controls transcriptional activity(41). To promote the production of apoE, its lipid transporters ABCA1 and ABCG1, and the nuclear receptors themselves, PPARg: RXR and LXR: RXR operate in a feed-forward approach(40). Agonists of these receptors generate "alternative" activation states in macrophages and microglia, which enhances phagocytosis(9)(10). In animal models of AD, chronic treatment of LXR and

PPARg agonists lowers Aβ levels and enhances cognitive performance(10). They hypothesised that activating PPARg: RXR and LXR: RXR, generating apoE expression, facilitating Aβ clearance, and encouraging microglial phagocytosis would boost natural Aβ clearance pathways. The U.S. Food and Drug Administration (FDA) has approved bexarotene (Targretin), a highly selective, blood-brain barrier-permeant RXR agonist with a good safety profile(11)(12). Bexarotene treatment of primary microglia or astrocytes increased ABCA1, apoE and ABCG1 expression and secretion of highly lipidated HDL particles. In a PPARg-, LXR-, and apoE-dependent manner, bexarotene administration of primary microglia and astrocytes promoted degradation of soluble Aβ42(Figure:2). During bexarotene treatment, the levels of Aβ proteases, insulin-degrading enzyme, and neprilysin were stable.



Figure; 2: Mechanism for clearance of β Amyloid by APOE directed therapeutics

Bexarotene: preclinical studies

Landreth and Cramer et al reported that the drug bexarotene, which initiates the RXRs has the ability to enhance the synthesis of ABCA1 and APO E. In their study bexarotene was found to quickly remove soluble Aβ from the brain, lessen the amount of neuritic plaques, restore behavioural impairments, and enhance cognition in mice that had been genetically modified to express a mutant version of the APP gene(9). Hippocampal in vivo micro dialysis was used in their work to check the levels of brain interstitial fluid (ISF) Ab in 2-month-old APPswe/PS1De9(APP/PS1) mice. Aβ42 and ISFAβ40 concentrations were instantly reduced by bexarotene within 6 hours of medication, and by 24 hours, there had been a 25% reduction. Bexarotene significantly reduced ISFAβ40 and Aβ42 levels by 25% after a single dose for more than 70 hours, returning to baseline after 84 hours. Because of enhanced clearance there is a suppression of ISFAβ, as a reduced Ab40 half-life from 1.4 to 10.7 hours. Similar to APP/PS1 mice, bexarotene decreased murine Ab levels in C57Bl/6 mice. Nevertheless, it did not have any impact on Ab levels in apoE-null mice, proving that apoE was necessary for the increased clearance of soluble ISFAβ(42).

Bexarotene in clinical trials

With its strong blood-brain barrier permeability and effective safety profile, bexarotene is a promising choice for future therapeutic development in the treatment of Alzheimer's disease. The pharmaceutical industry, however, is perhaps less eager to create a medicine that would soon be made available in generic form. Bexarotene has only been produced by Eisai Pharmaceutical, and Targretin's patent was expected to expire in 2016(43). Release of its generic version was expected by Mylan Inc., in 2015(44). After the initial 2012 study, bexarotene was used off-label in dementia patients, however these cases have not always been documented. The medicine was relatively well tolerated in one clinical case of usage of bexarotene in an APO E4-positive patient with AD, without the cognitive advantage was observed after three months of 150 mg daily medication. Most common negative effect was hypercholesterolemia, which was treated with statin therapy(45).

Currently, two clinical trials involving human patients are being conducted in various stages. First one is Dr. Cummings, who implemented BEAT-AD (Bexarotene Anti-Amyloid Treatment for Alzheimer's Disease) at the Cleveland clinic. It has completed recruiting and the results were released in the year February 2016. Nuclear receptors known as retinoid X receptors (RXR) have been connected to a number of metabolic activities associated with the generation and elimination of A (harmful protein) and Alzheimer's disease (AD). FDA

approval for the study drug "bexarotene" as an anti-tumour agent excludes its use in Alzheimer's disease. In an experimental model of Alzheimer's disease, bexarotene reduces A (harmful protein) in the brain by acting as an RXR agonist. This study compares the effects of 300 mg of "bexarotene" given for 30 days versus a placebo (control substance) on abnormal proteins detected in the brain (based on brain scans). It was randomized double blind interventional study involving 20 participants with mild to moderate Alzheimer's disease. Primary purpose of the trial is to estimate the safety and efficacy of Bexarotene in the patients with AD. The active arm and the comparator used are Bexarotene and Placebo. The primary outcome measures of the study were transformed from zero to week 4 on treatment in Amyloid burden was compared to placebo among the individuals with ApoE4 genotypes, where ApoE4 carriers were compared to Non ApoE4 carriers and homozygote ApoE4 carriers were compared to heterozygote ApoE4 carriers. There were many secondary outcome measures in which MMSE (Mini metal state examinations) and ADAS-Cog (Alzheimer's disease assessment scale-cognitive subscale) were clinically significant. The complete grouping and interventions are shown in the table 1. Subjects were randomized 4:1 to get 4 weeks of double-blind medication of either Bexarotene or placebo. The endpoint of the study for all the subjects was measured by standardized uptake value ratio (SUVr) on amyloid brain imaging acquired through 18F-AV-45 PET.

Sl no	NCT number	Phase	Active arm	Comparator arm	Total no of participants		Status of the study	
			75 mg of Bex BID (150 mg) for 1 week	1 placebo capsule BID for 1 week	20		Active	Comparator
					No of participants receive active arm	No of participants receive comparator	Completed 15	Completed 4
			150 mg of Bex BID (300 mg) from 2-4 weeks	2 placebo capsule BID from 2-4 weeks			Withdrawn	Withdrawn
1	NCT01782742	2	Open label phase from week 5	Open label phase from week 5-8	16	4	1	0

Table:1 Dr. Cummings' clinical trial for BEAT-AD (Bexarotene Anti-Amyloid Therapy for Alzheimer's Disease)

When all patients were considered in the study, neither the composite nor regional amyloid burden changed. ApoE4 noncarriers had a substantial decrease in brain amyloid in five of six regional measures on the composite measure. The amyloid load in ApoE4 carriers remained unchanged. Among ApoE4 noncarriers, there was a statistically significant correlation between higher blood Aβ1-42 levels and lower levels of brain amyloid (not in carriers). Patients receiving bexarotene showed substantial increases in blood triglycerides. No clinical measure consistently changed over time. Conclusions: The main outcome of this study was unfavourable. The evidence suggests that in ApoE4 noncarriers, bexarotene boosted serum Aβ1-42 and decreased brain amyloid. Bexarotene shouldn't be used in any other research setting since high triglycerides may cause a cardiovascular risk. More research into RXR agonists as AD treatments is necessary(46)(47)

Second one is research to determine how bexarotene affects the metabolism of apolipoprotein E and beta amyloid in healthy individuals. A total Aβ clearance and apoE production in the human brain of healthy, young people with the APOE3/3 genotype are the two outcomes being measured in this double-blind, exploratory medication trial. From the time of the first subject recruitment until the publication of the study's final report entire study interval expected was 6 to 10 months. Following eligibility verification, all subject was randomly assigned to receive either oral bexarotene or a placebo as shown in (table;2). The research may show the pharmacodynamic characteristics of a brand-new Alzheimer's disease treatment strategy. The main biomarker assessments by this investigation are thought to be very dynamic and can give quick information about the biological activity of the candidate treatment being investigated. Additionally, exploratory research will use a proteomics-based screen to find blood and CSF proteins that are triggered by the Test Article. This could lead to the discovery of new biomarkers that can be used in the upcoming clinical trials to show the activity and target engagement of bexarotene (48)(49).

Sl no	NCT number	Phase	Active arm	Comparator arm	Total no of participants	Status of the study
1	NCT02061878	1	Subjects will be given 3 Targretin capsules (75 mg) twice in a day (450 mg/day) for 5 days	Subjects will be given 3 capsules of Avicel pH (75 mg) twice in a day (450 mg/day) for	12	Completed but has no results

				5 days		

Table: 2 Bexarotene, an RXR antagonist, and the Metabolism of Beta-Amyloid and Apolipoprotein E in Healthy Subjects: A Randomized Controlled Study

6. Conclusion:

Genes and proteins involved in several signalling pathways are exclusively associated with neurodegeneration. This review focuses on the similar signalling pathways and genes of the most dangerous forms of Alzheimer's. The common processes of multiple signalling pathways suggest the potential relationship between cancer and AD. Anticancer medications are now more appealing for therapeutic repurposing for NDDS. Based on the research that is currently accessible, we discovered that anticancer medications have neuroprotective properties in a variety of ways, including eliminating harmful protein aggregation, preventing neuroinflammation, and immunomodulation. Kinase inhibitors, antimetabolites, alkylating agents, and antibodies are just a few of the pharmacological families that are shown encouraging repurposing outcomes. Among those retinoid x receptor agonist bexarotene is the one having potential feature that can reduce the risk of Alzheimer's by reducing the amyloid burden in the brain. The finding that bexarotene could be useful in lowering the pathology and cognitive deficits of Tg mice with Aβ pathology recommends that evaluation of bexarotene as a repurposed therapy for AD is necessary. While bexarotene has significant toxicity, there is debate concerning its off-label usage in AD based upon the findings in Tg animal systems/body. Often raising cholesterol and triglyceride levels, as well as raising the chance of developing hypothyroidism. According to one case study, bexarotene treatment for AD may be beneficial. The best way to learn more about bexarotene's medicinal potential is to rigorously assess its potential benefits and risks in controlled trials. This review suggests that RXR agonists can be useful in treating AD and its precursor stages because of bexarotene's capacity to quickly improve a wide spectrum of impairments.

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