Anticancer Drug Bexarotene Inhibits Build-Up of Toxic Alzheimer's Protein

BY JEFF EVANS

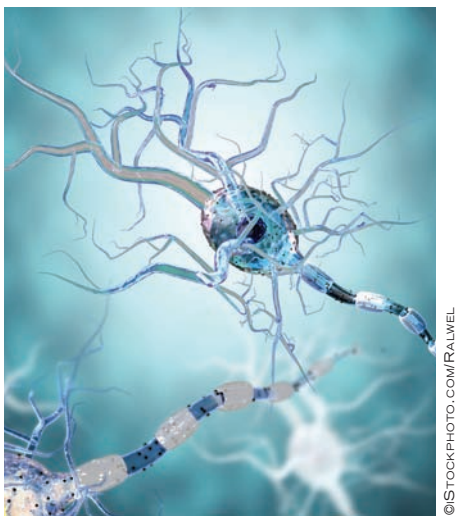
Bexarotene, a drug approved by the Food and Drug Administration to treat skin cancer, stopped the primary nucleation step in the self-assembly of amyloid-beta-42 oligomers and delayed the formation of pathogenic aggregates that are associated with Alzheimer's disease neurodegeneration, according to study results in *Science Advances*.

The researchers, from the University of Cambridge (England), Lund (Sweden) University, and the University of Groningen (the Netherlands), also found that bexarotene (Targretin, Valent Dermatology) blocked the build-up of toxic amyloid-beta-42 (Aβ42) aggregates as well as motility dysfunction in a nematode worm model (*Caenorhabditis elegans*) of Aβ42-mediated toxicity (*Sci Adv* 2016;2[2]:1501244).

The researchers screened a large set of drugs known to interact with amyloid-beta for molecules that could block the primary nucleation of Aβ42 aggregates by analyzing the effects that the drugs had on Aβ42's formation into aggregates. This allowed them to determine potential drug candidates' mechanism for preventing the build-up of toxic Aβ42 aggregates.

Earlier animal studies of bexarotene had suggested that the drug could actually reverse Alzheimer's symptoms by clearing Aβ42 aggregates in the brain. But those earlier results, which were later called into question, were based on a completely different mode of action—the clearance of aggregates—than the one reported in the current study. Bexarotene was tested earlier in an unsuccessful 1-month, randomized, placebo-controlled phase II trial in patients with mild to moderate Alzheimer's, but this new research suggests that the drug may need to be given very early in the disease.

"We anticipate that the strategy that we have described in this paper will enable the identification of further compounds capable of inhibiting Aβ42 aggregation and the definition of the specific microscopic steps affected by each compound (that is, primary or secondary nucleation or elongation)," Johnny Habchi, PhD, and associates wrote. "The results described in the present work indicate that bexarotene and other inhibitors of primary nucleation have the potential to be efficient means of delaying aggregation by reducing the probability that primary nuclei are formed and proliferate, such that our natural protection mechanisms could remain effective to more advanced ages. Indeed, we draw an analogy between the strategy presented here and that of using statins, which reduce the level of cholesterol and thus the risk of heart conditions, and suggest that such molecules could effectively act as 'neurostatins.'"



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Post-TAVR Mortality Lower in Women

BY MARY ANN MOON

Women undergoing transcatheter aortic valve replacement (TAVR) for severe aortic stenosis have lower 1-year mortality than men, even though their 30-day rates of vascular complications and major bleeding are worse, according to a report published in *Annals of Internal Medicine*.

"These findings for TAVR directly contrast with the abundant literature on aortic valve surgery, in which female sex has been shown to be an established risk factor for adverse prognosis," said Susheel Kodali, MD, of Columbia University, NY and New York–Presbyterian Hospital, and his associates.

Previous studies assessing sex-specific differences in outcomes after TAVR, which have been small in size and limited to the experience at only one or two medical centers, have yielded conflicting results. Dr. Kodali and his associates examined sex-specific outcomes in what they described as the largest such study to date—a secondary analysis of data from a large clinical trial, and from a patient registry, involving 2,559 patients treated at 25 sites in the United States, Canada, and Germany. Their analysis involved nearly equal numbers of women (1,220) and men (1,339).

One-year unadjusted all-cause mortality was significantly lower for women (19.0%) than men (25.9). In a further analysis that adjusted for numerous potential confounding factors, female sex remained independently associated with lower 1-year mortality. Women also had a lower rate of rehospitalization at 1 year (15.8% vs. 18.9%). In contrast, stroke incidence did not differ significantly between women and men (5.2% vs. 4.5%).

Mortality was lower for women regardless of access route: 17.4% (vs. 24.0% in men) for the transfemoral approach and 20.8% (vs. 28.8% in men) for the transapical approach, the investigators said (*Ann Intern Med* 2016;164:377–84).

This mortality benefit occurred despite the fact that women had higher rates of vascular complications (17.3% vs. 10.0%) and of major bleeding (10.5% vs. 7.7%) at 30 days.

Although this study was not designed to elucidate why women have lower mortality than men following TAVR, there are several plausible reasons.

In an analysis that adjusted for potential confounding factors, female sex remained independently associated with lower 1-year mortality.

First, men in this study had a greater burden of comorbid conditions than women.

Second, women had smaller annulus sizes and greater ejection fractions than men at baseline, and they also had less aortic regurgitation after undergoing the procedure. "These echocardiographic differences may [represent] better preoperative preservation of contractility and superior hemodynamics in women after the procedure," Dr. Kodali and his associates said.

Third, previous studies have reported that after undergoing surgical aortic valve replacement, women with aortic stenosis have less cardiac fibrosis and more rapid left-ventricular remodeling than men do. "These salutary benefits may extend to women having TAVR" as well, the investigators added.

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