Bexarotene in Context: A Look at the Exciting Results

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In February 2012, the journal Science published findings of a research team, led by Gary Landreth out of Case Western Reserve University, regarding the FDA approved cancer drug bexarotene and its ability to rapidly remove beta-amyloid from the brains of animal models of Alzheimer’s Disease (AD), and even reverses some symptoms of dementia. The results were heralded throughout the mainstream and web-based media.

The researchers looked at the drug Bexarotene (Targretin), approved in 1999 for cutaneous T cell lymphomas. Landreth and colleagues fed bexarotene to demented mice, and with just a single dose it lowered the most toxic form of beta-amyloid in the brain by 25 percent within six hours, an effect that lasted for up to three days; after two weeks, there was a 75 percent decline in the amount of amyloid plaques. The drug did its job with unprecedented speed. Mice that were cognitively impaired resumed normal behaviors after 72 hours of treatment: They began to crinkle toilet paper placed nearby to make nests, a skill lost as amyloid increased in their brains.

The drug also restored some of the animals’ other normal behaviors. After treatment, the mice could identify a smell and perform better on water maze tests requiring them to remember how to find a submerged platform. They were also better able to remember a cage in which they had been shocked, all behaviors that are lost with the progression of the illness.

Bexarotene activates retinoid receptors on brain cells that increases the production of apolipoprotein E, which readers of this blog will recall, is known to remove excess beta-amyloid from the brain. It also appears to enhance another cleanup process, called phagocytosis. Bexarotene functions differently than the amyloid-clearance approach using monoclonal antibodies, which are further down the drug development pipeline. Those antibodies bind directly to amyloid and then remove it. Bexarotene activates the ApoE clearance mechanism of beta-amyloid.
One reason the field is buzzing about this finding is that bexarotene is an oral medication while monoclonal antibodies must be delivered intravenously. This makes Bexarotene appealing on many fronts; it is already FDA-approved, it can be taken orally, and it has an unprecedented speed by which it reduces beta-amyloid and improves cognition in mice.

In humans, the gene for apolipoprotein E comes in three versions, one of which, the E4 variant, confers a significantly higher risk of getting Alzheimer’s disease—a roughly 60 percent chance at age 80 for those who carry a copy from both their mother and father, as against a less than 10 percent overall risk at that age in the general population. About 20 percent of the U.S. population has at least one copy. The E4 carriers are thought to be vulnerable to Alzheimer’s because they have a diminished ability to clear beta-amyloid from the brain.

The science behind this set of experiments looks very good. That is, it is well designed and well controlled, but the results are still limited to the context of mouse models of Alzheimer’s disease, which are not exact replicas of the human form of the disease. Early-stage human clinical trials are set to begin within months to examine the possibility of similar benefits in humans.

Prevention and Impact of MCI in Latin America, China and India: Results from the 10/66 Study

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Here are some sobering statistics from the World Health Organization:

1. Of the 35 million people currently living with dementia worldwide, 58 percent are estimated to live in low-and middle-income countries, with this number approaching 71 percent by 2050.
2. Both Eastern and Southern Asia will see dementia growth rates more than double in the coming 20 years.
3. Increased dementia growth rates are also expected for Latin America (134 percent to 146 percent) and North Africa and the Middle East (125 percent increase). Along with these increased rates of dementia, comes a daunting economic burden to these countries.

Keeping these statistics in mind, the review of an article from Sosa et al, was especially interesting as it sought to examine amnestic Mild Cognitive Impairment (aMCI) – the prodromal stage before dementia – in these countries and characterize the impact of aMCI on the population.

The 10/66 study consists of a series of cross sectional geographic catchment areas surveyed between January 2003 and 2007. The target sample size was 2000 persons from each country, and all community residents aged 65 and older were eligible for participation. Each participant completed the standard protocol, with all testing done either in Spanish, Tamil, or Mandarin. Interviews included questions regarding socio-demographic status, education, childhood environment, social networks and support, self report lifestyle measures (diet, smoking, exercise). Participants also underwent physical function tests that included, resting blood pressure, anthropometric measures, and a structured neurological examination.

The battery of cognitive assessments included a screening instrument for dementia, and used the Mayo Clinic definition of amnestic MCI (aMCI). Assessing the “impact of amnestic MCI” was quantified by investigating the associations of aMCI with disability and neuropsychiatric symptoms. Disability scales used were the World Health Organization disability assessment
schedule (WHODAS-12) which assesses physical mobility, communication, self care, life and social activities and interpersonal interactions. Neuropsychiatric symptoms were assessed by the Neuropsychiatric Index (NPI) and categories were grouped by: depression, anxiety, apathy and irritability.

Data were obtained from over 15,000 non-demented participants (aged 65yrs+) across the different countries. In the total sample, women participated more than men, and younger ages (65-69yrs) for participation were noted in China, India and Venezuela. Disability was significantly higher in aMCI cases, however there were differences noted in these associations between countries (China being the lowest). After adjustment, aMCI cases were more likely to have informant rated anxiety, irritability, and apathy symptoms with no significant “between-country” differences. The prevalence of aMCI ranged from 0.8 percent in China to 4.3 percent in India and changed very little after controlling for age, gender, and education level.

This study examined the prevalence estimates and impact of aMCI, across a diverse group of countries and the impact of aMCI with regard to physical and behavioral functioning. Rates of prevalent aMCI appeared to be lower than those previously reported from some community samples (i.e. Korea, Italy, Japan, US and Finland) however, were comparable to rates reported by others (Germany, France and Great Britain). The authors rightly conclude that the variability of aMCI prevalence rates across world regions, most likely reflects diagnostic issues arising from a lack of specific operational criteria of aMCI as well as differences and cultural variations relevant to some of the diagnostic components.

The specific issue raised, and one that is subject to cultural influences is the necessity of having a “subjective memory complaint” as part of the diagnostic criteria. This specific diagnostic criteria is highly subject to cultural influences (i.e. Is the memory issue “enough” to warrant a formal complaint?). Another interesting finding was that aMCI associations with disability were relatively more consistent across all regions, thus supporting the use of this measure in cross cultural studies. Lastly, this study did not find an association between aMCI and depressive symptoms, but did find associations between anxiety, irritability and apathy, a finding consistent with other larger studies.

The major limitation of this study as suggested by the authors was that samples drawn were from specific geographic catchment areas and therefore, cannot be assumed to be representative of the entire nation. Lastly, this was a cross sectional study, and further longitudinal analyses on this data set are needed to clarify the predictive validity of the aMCI diagnosis in this sample. Nevertheless, this study is one of the first to investigate the prevalence of aMCI in low and middle income global communities, and as such could be particularly useful to any initiative that seeks to provide community level interventions to prevent the progression to dementia.

Here are three articles you can refer to:


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**ADCS Trials Enrolling...**

![Nerve Growth Factor Study (NGF)](http://adcs.org/Studies/NGF.aspx)

The NGF is a Phase II clinical study of Ceregene's CERE-110, a gene therapy product designed to deliver nerve growth factor (NGF) to the brain for the treatment of Alzheimer’s disease (AD) is currently underway. This study is a randomized, double-blind, placebo-controlled trial and employs gene therapy to deliver nerve growth factor (NGF) directly into the brain.

http://adcs.org/Studies/NGF.aspx
The goal of the Alzheimer’s Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer’s disease in future generations. Information from the study might, in the future, lead to new treatments.

http://adcs.org/Studies/ImagineADNI2.aspx