New Frontiers in Alzheimer's Disease

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THIS YEAR's American Academy of Neurology (AAN) Annual Meeting, held in Denver, Colorado, USA, from April 13–18, featured an insightful session on Alzheimer's Disease (AD), hosted by Liliana Ramirez-Gomez, Harvard Medical School, Boston, Massachusetts, USA. The session included fascinating insights into the diagnosis, management, and implementation of new therapies in AD, presented by Ramirez-Gomez herself; Julio Rojas-Martinez, University of California, San Francisco, USA; and Jeremy Pruzin, Banner Alzheimer's Institute, Phoenix, Arizona, USA.

THE USE OF BIOMARKERS FOR DIAGNOSIS AND STAGING

The necessity of biomarkers in diagnosing AD is often misunderstood outside of the field of neurology, according to Rojas-Martinez. Despite this, he emphasized as he opened his discussion that they are vital when it comes to increasing diagnostic certainty, which helps both patients and their families; planning for long-term care, especially considering the financial and emotional burden of the disease; and guiding therapeutic decisions. Rojas-Martinez went so far as to advocate for biomarkers to always be used in diagnosing AD, saying that relying on clinical assessment alone is not enough.

> **"The necessity of biomarkers in diagnosing AD is often misunderstood outside of the field."**

He went on to discuss the origin of biomarkers in disease diagnosis, before addressing the current available and approved AD biomarkers, including neuroimaging, cerebrospinal fluid, and blood biomarkers. Delving into the specifics of how β-amyloid plaques (Aβ) and tau tangles are analyzed, he highlighted that many of these can be considered simplistic, limited biomarkers, and, for example, some blood tests involving mass spectrometry, have limited access for patients and practitioners. More analysis methods are constantly being approved, and becoming more relevant as therapies evolve.

Biomarkers are analyzed in those with mild cognitive impairments (MCI) or mild amnestic dementia, as these patients respond to disease-modifying therapies better than those with later stages of the disease. The same goes for patients with early-onset dementia who are suspected to have AD, as well as those with atypical dementia. Biomarkers, Rojas-Martinez explained, are tested once a patient has received a full evaluation and diagnosis. He went on to describe the process of implementing biomarkers, addressing what can be gleaned from positive tests for AD biomarkers; for example, diagnosing not only AD but co-pathologies, as well as how to address non-amnestic MCI compared to amnestic MCI.

Interpreting AD biomarkers is not simple; for cerebrospinal fluid biomarkers, for example, several years of research have gone into figuring out that using $A\beta42_{ELISA}$ and Tau_{ELISA} methods in conjunction yields the highest accuracy. Many other tests will produce equivocal results, which until recently were non-specific, and therefore

not helpful in diagnosing AD. However, newer methods for handling such results have since been developed, and Rojas-Martinez emphasized the importance of relying on ratios in these equivocal situations. The ever-evolving practice of interpreting biomarkers in AD, and the potential for higher accuracy in the future, was underlined as Rojas-Martinez discussed the increasingly important role of blood biomarkers in disease prognosis and staging, along with current and future research, focusing on novel analytical platforms and diverse populations.

EMERGING THERAPIES FOR ALZHEIMER'S DISEASE TREATMENT

Diagnostic methods are not the only area in which AD care and research is progressing. Pruzin's portion of this enlightening session covered several of the new and emerging therapies for treatment of AD. Some of the treatments discussed were treatments already on the market, such as semaglutide, a hormone that activates receptors in the gut, liver, and pancreas, approved for the treatment of diabetes and obesity. Semaglutide is used to lower cardiovascular adverse outcomes in people at risk, and to stimulate insulin release, as well as restore insulin sensitivity. AD is often associated with mixed pathology, commonly with cerebrovascular disease, and evidence has been found for brain insulin resistance in patients. A retrospective study of the treatment of other diseases using semaglutide showed that patients with the disease were significantly less likely to develop dementia. These results inspired the Phase III clinical trials (EVOKE and EVOKE+) currently underway to investigate the effectiveness of this drug in treating cognitive disorders, with results expected in 2026.

Pruzin then gave an overview of several other ongoing trials, all in various stages, from early Phase II to nearly approved. Donanemab, for example, is nearing approval, and though the trial was limited by a lack of diverse participants, the drug shows significant clinical cognitive benefits, slowing rate of decline, and driving down biomarkers.

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However, new treatments for existing patients with AD are not the only exciting development, Pruzin was quick to point out. Preventative treatments are also coming onto the market; drugs which have shown benefit in those with early symptomatic AD, including donanemab, are now being given to individuals with brain Aβ but who are cognitively normal, in the hope that it will prevent, or at least delay, the onset of disease.

Prevention goes beyond drug development; however, modifiable risk factors matter, emphasized Pruzin. A large proportion of dementia cases could be delayed or prevented if clinicians addressed several modifiable risk factors, including depression, obesity, social isolation, smoking, diabetes, and hypertension, among others. Several of these can be addressed early in life, from an

educational standpoint, and others at later stages. The importance of this approach was reinforced in Pruzin's closing statement, as he highlighted the benefits not only of single treatments, but of a combination of treatments, involving pharmacological ones, as well as more lifestyle-based methods, both for symptomatic patients, and as a preventative measure for others.

IMPLEMENTATION OF NEWLY APPROVED DISEASE-MODIFYING THERAPIES

Development of new medications is only one step in the process of treating AD. Ramirez-Gomez rounded up the individual presentations by elaborating on what neurologists are doing in the clinic to implement these new therapies and monitor patients. Lecanemab, the first disease-modifying therapy for AD, approved for those with MCI or mild dementia, is now given to patients with AD by clinicians. Due to the nature of the medication, Ramirez-Gomez underscored the importance of knowing exactly what stage of disease each patient is at, in order to treat them effectively. She also pointed out the need for clinicians to be aware of the costs of the treatment for the patient, and how this may affect them.

In order to address this, at Massachusetts General Hospital, the Alzheimer Therapeutics Program (ATP) has been developed with a protocol for the administration and safety of AD treatment. Patients are referred from several departments, when they show MCI or mild dementia, have had a brief cognitive screening test, a brain MRI, and a continued follow-up plan. The safety of the treatment is monitored, and Ramirez-Gomez emphasized the importance of interdisciplinary work at the program to provide this care for patients. The focus of the program is to provide timely and appropriate treatment for patients with AD, considering the family expectations, costs to the patient, and the effect of treatment on the individual. After the team has confirmed that the patient meets the eligibility criteria and that all their personal factors have been considered, the patient starts lecanemab, and their results are constantly monitored.

Programs such as the ATP demonstrate the rapid development of AD treatment and diagnosis, and as therapies continue to evolve and change, so will the diagnostic tools used in clinical practice, and the approach to treatment taken by clinicians.

Following Ramirez-Gomez's fascinating talk, the three speakers remained to answer questions on emerging therapies in AD, novel methods for interpreting biomarkers, and the various trials taking place today, as well as those still to come. ●