The Importance of Neuroimaging in Dementia Treatment

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The US Food and Drug Administration (FDA) sparked quite a controversy in June when it bestowed marketing approval on Biogen's Aduhelm (aducanumab) for the treatment of Alzheimer disease. Aduhelm is the first therapy to target the underlying disease process of Alzheimer by reducing amyloid beta plaque in the brain, a hallmark of the disease.

Indeed, many experts remain divided on the drug's efficacy and disagree over whether it should have received FDA approval. There are also issues surrounding insurance coverage for the treatment. (see online sidebar).

At the same time, however, the FDA's decision has shone a spotlight on the important role that neuroradiologists and modalities like positron emission tomography (PET) and magnetic resonance imaging (MRI) play in the diagnosis and treatment of neurodegenerative diseases, as well as in the study of new treatments like aducanumab.

"Aduhelm will increase the need for structural imaging for safety monitoring," says Michael Weiner, MD, a professor in residence of radiology and biomedical imaging, medicine, psychiatry, and neurology at the University of California, San Francisco.

"PET detects amyloid and tau, [and] amyloid PET is often used as an inclusion criterion and to show plaque removal and will likely be needed to identify people for treatment with Aduhelm," explains Dr Weiner, who is also principal investigator of the Alzheimer's Disease Neuroimaging Initiative, the world's largest observational study of patients with Alzheimer disease.

Tina Young Poussaint, MD, FACR, president of the American Society of Neuroradiology (ASNR), and a professor of radiology at Harvard Medical School, agrees.

"Whether it is Alzheimer's disease or other dementias, there will be a change in the number of imaging studies for both PET and MRI," which are used to monitor the impact of treatments with Aduhelm, says Dr Poussaint, who also a neuroradiologist and the Lionel W Young Chair in Radiology at Boston Children's Hospital.

A Need for Standardized Imaging Protocols and Reporting Structure

The expected growth in imaging studies for tracking dementia disease progression and treatment highlights the important need for standards in imaging protocols and reporting structure, Dr Poussaint says. Clinical trials are designed so that patients are imaged at the same facility on the same scanner with the same protocol every time. Changing scanners could lead to changes in interpretation of microhemorrhages and other indicators of safety, which could trigger a change in treatment.

Similarly, patients experiencing side effects, such as dizziness, nausea, confusion, or vision

changes, are instructed to call their healthcare provider or go to the nearest emergency department right away. These may not be the same facilities where their scans are being performed.

"Those are really common symptoms, especially in an elderly population," says Tammie Benzinger, MD, PhD, professor of radiology and neurological surgery at Washington University School of Medicine. "I think we will be facing a situation where patients are going to not only get a lot of MRIs, they also may get them from different ERs or other centers where they are not getting treated.

"Standardization across the field and how we approach these patients is going to be really important," adds Dr Benzinger, who is also director of the Knight Alzheimer Research Imaging Program at the Mallinckrodt Institute of Radiology, as well as course chair of the ASNR's Alzheimer Webinar Series.

While MRI is important to diagnosing and monitoring treatment of Alzheimer disease, PET will be critical to identifying candidates for the new drug, as well as to evaluating its efficacy.

"It is incredibly important for any patient who is considered for this amyloid-reducing antibody therapy to have access to the FDA-approved amyloid PET imaging as a sort of 'gateway test,' to ensure that they have amyloid that could even be removed from the brain," says Richard Wahl, MD, president of the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

"Knowing if amyloid is present or absent in a patient makes a big difference, diagnostically," says Dr Wahl, also the Elizabeth E Mallinckrodt Professor and head of radiology at Washington University School of Medicine, and director of the school's Mallinckrodt Institute of Radiology.

Aducanumab is indicated for early-onset Alzheimer disease, in which the current clinical focus is on identifying structural changes with PET or MRI, Dr Benzinger explains.

"With amyloid PET, we are looking at the actual amyloid deposits in the brain, and with MRI we are looking at brain structure," such as the hippocampus or ventricles, the size of which can help determine the type of neurodegenerative disease or if some other type of pathology is the reason for cognitive impairment, she says.

Dr Benzinger notes that that current MR imaging phenotypes for early Alzheimer disease or vascular dementia, which together may account for 75% of all neurodegenerative diseases, overlap with other diseases such as frontotemporal or Lewy body dementia.

Targeting Unmet Needs in Research

PET can also help researchers better understand the role of TDP-43 in neurodegenerative diseases. TDP-43 is a pathological protein found in amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration with ubiquitin immunoreactive, tau negative inclusions (FTLD-U), and FTLD with motor neuron disease (FTLD-MND).[1]

Dr Weiner calls the development of amyloid and tau PET a game changer in dementia imaging, but he also sees a need for alpha-synuclein and TDP-43 tracers. Abundant in the brain, alpha-synuclein is a neuronal protein that regulates synaptic vesicle trafficking and subsequent neurotransmitter release and is believed to be closely related to Parkinson disease.[2]

"Blood tests for Alzheimer's disease biomarkers are also getting better. Right now, they are screens; however, in the future, blood tests could replace some scans," he adds.

New molecular imaging biomarkers and techniques will be key to more precisely diagnosing neurodegenerative diseases and appropriate treatments for them. Dr Benzinger sees an opportunity to mimic the work done to develop fast imaging protocols and artificial intelligence-based analyses to help clinicians distinguish stroke from other causes of headaches, dizziness, or memory loss.

"There are active areas of research that radiologists can be working on in MRI, and not just in molecular imaging," she adds.

Dr Poussaint would like to see a clinical data repository developed to help further propel research, like those that exist for research into other diseases.

"There is a need for further analysis in (Alzheimer disease) because there are a large number of studies, and this data will have to be mined in a way that can give us even more information than a single (procedure) in radiology or nuclear medicine can provide," Dr Poussaint says.

Although other tests such as lumbar punctures and blood markers are being developed to help diagnose Alzheimer disease, "right now amyloid PET is the only FDA-approved test, and there are several approved amyloid PET agents," Dr Wahl says. "PET

amyloid imaging tells us where within the brain the amyloid is located. These other tests in the blood or cerebrospinal fluid can't tell us that."

Implications for Radiology Practice

Radiologists perform most lumbar puncture procedures,[3] and, therefore, they should be prepared for an increase in imaging requests, Dr Benzinger says, adding that neuroradiologists similarly should also be prepared to perform more MRI scans to monitor dementia patients for, among other issues, amyloid-related imaging abnormalities (ARIA).

"ARIA has two components: edema and hemorrhage. Radiologists are trained to look for these on every single brain MRI," Dr Benzinger says. "But it will require us to think about workflow and how we add capacity, as these patients will require a baseline MRI and then another one every six months for monitoring. There are practice setting implications that radiologists and practice managers need to think about carefully."

Standardized reporting structures will help radiologists manage the increased workload and effectively communicate results to referring physicians, Dr. Poussaint says.

"A reporting structure will also help us mine data from the reports, and that has global implications, including for those countries that don't have the access to imaging that we have," she adds.

One transition that may help develop such a reporting structure is that of molecular imaging and nuclear medicine from qualitative and subjective imaging to quantitative and objective imaging, Dr Wahl says.

"While qualitative readings of the presence or absence of brain amyloid are very important to therapeutic decision making, the quantitative and objective data that amyloid PET imaging can provide may also assist with standardizing imaging protocols and reporting," he says.

Quantitation, Dr Wahl says, could lead to greater consistency among readers across different sites and help reveal more subtle brain changes than qualitative assessment alone.

"I think that we're going to increasingly see amyloid PET used quantitatively. There's a continuum of activity, and that continuum can tell us something about the biological status of an individual patient," he says.

Dr Poussaint believes neuroradiology is uniquely positioned to help forge a new path toward the more accurate diagnosis of neurodegenerative diseases.

"It's a multifaceted approach," she says. "The imaging techniques, education, research, advocacy, and attention to issues of diversity and inclusion that neuroradiology provides is expansive and ultimately will improve our knowledge of neurodegenerative diseases, which will improve the quality of life for patients."

References

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