New impetus for Amyloid PET imaging following the FDA approval of a new Alzheimer's Disease treatment

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Word Count: ~~781~~ 961

For the UK, where approximately 4% of the population over the age of 65 are diagnosed with Dementia, a disease-modifying treatment option for Alzheimer's Disease (AD), the most common form of dementia, would be revolutionary (1). The FDA has currently approved 2 new monoclonal antibody-based treatments and we expect similar recommendations for the United Kingdom soon (2,3)

The latest drug, Lecanemab, also known as BAN2401, is a humanized IgG1 monoclonal antibody that has shown a dose-dependent reduction in the rate of cognitive decline in early Alzheimer's Disease in both the phase 2 dose-setting study and the phase 3 CLARITY study when measured by clinical dementia rating/scoring systems (3–5). A subset of both studies also identified a dose-dependent reduction in the amyloid burden

as visualised by PET imaging providing evidence that Amyloid-PET tracers were able to give non-invasive correlative measurements that accompanied the slowing (or improvement) in cognitive decline in those patients on the treatment arms. If these promising trial results are confirmed, then there are implications for clinical practice, including functional neuroimaging, in AD.

There are currently three fluorinated Amyloid-PET tracers approved by the European Medicines Agency (EMA) and the UK Medicine and Healthcare products Regulatory Agency (MHRA), but only ^{18}F-Florbetaben is available for use in the UK, and even so, it is currently only utilised in specialist centres (6). Although supply is currently limited, there is some evidence that Amyloid-PET may be cost-effective in establishing the diagnosis of AD (7,8), but as yet, there has been little work to study the benefits of using this imaging to monitor treatment response outside of the trial setting.

In 2016, the SNMMI (Society of Nuclear Medicine and Molecular Imaging) and the EANM (European Association of Nuclear Medicine) recommended the use of Amyloid-PET in patients with an unknown cause of cognitive impairment, where AD is considered in the differential (9). However, national guidelines in the UK have not yet been updated, with NICE currently only recommending the use of FDG-PET for differentiating dementia subtypes in a specialist clinical setting (10). There are no national guidelines for the use or incorporation of Amyloid-PET imaging in the diagnosis or management of AD in the UK.

The mounting evidence in support of Amyloid-PET imaging, in conjunction with the advent of these monoclonal antibodies, suggests there will be an influx of demand for Florbetaben-PET and other Amyloid-tracer imaging in the UK. The AMYPAD consortium, a European collaborative effort, has conducted many studies into the clinical use of Amyloid-PET, with Flutemetamol and Florbetaben tracers (11). The diagnostic and patient management study arm of this joint work is centred on clinical management and has recognised the need for quantitative measurement of brain amyloid by PET imaging. Visual assessment alone poses challenges such as reader and tracer variability. There has been progress in quantitative analysis methods using standard uptake value ratios (SUVr), Centiloid scales (CL) and reference-based Z-scores (11,12), which will reduce inter-reader variability and aid the comparison of data between centres, including the use of different tracers and PET scanners (13,14). Ultimately this will allow for more robust diagnosis and detection of disease progression from prodromal to sub-clinical and indeed clinical states. The next step is therefore for UK guidelines to incorporate the use of Amyloid-PET for diagnostic purposes as a means of increasing use and availability. Meanwhile, further research into the use of Amyloid-PET to monitor treatment response, in larger and longer clinical trials could happen simultaneously.

The practicality of introducing Lecanemab in the UK needs careful and financial consideration. There is a need for MRI/CT surveillance to monitor for relatively common Amyloid Related Imaging Abnormalities (ARIA) alongside the use of Amyloid PET imaging to detect treatment response (3,4). Furthermore, this will need to happen alongside an expansion in biochemical and genetic testing so those at the highest risk of

potentially serious side effects of severe brain inflammation and haemorrhage, namely ApoE4 carriers, are either advised against the treatment or undergo further testing. Amyloid-PET may be useful in this setting to first establish the diagnosis before the commencement of therapy and then allow for dose setting due to its ability to monitor response to treatment, potentially reducing the risk of the most severe adverse events.

A publication by Wittenberg et. al in 2019 estimated the economic burden the UK may face in the event of widespread Amyloid-PET use (15). The review calculated the costs for 100,000 or 250,000 additional PET scans per year as approximately £113 million and £285 million respectively. These sums included changes to infrastructure in terms of new scanner requirements and workforce costs, as well as the cost of radiotracers. The review also cautioned that there would be elevated initial costs whilst Amyloid-tracer production attempts to meet the new demand. The statistics used in these calculations are not excessive; NICE summaries estimate 885,000 people over the age of 65 were living with Dementia in 2019, with approximately 200,000 diagnosed annually. Secondary to increasing life expectancy and demographic changes, we expect to see 1.6 million people suffering with Dementia by 2040 (15,16).

The FDA approval of Lecanemab, and indeed Aducanamab, are landmarks that highlight an area of clinical management and neuroimaging that will require close attention. These steps should prompt the UK to increase its preparedness both for the demand for Amyloid-tracers and for clinical guidelines to support the utilisation of Amyloid-PET alongside drug therapy. The routine prescribing of Lecanamab in the UK will not be

immediate, as the monoclonal antibody has only undergone limited evaluation to date, and the safety profile may warrant further evaluation by the regulatory bodies (e.g., MHRA in the UK or EMA in the European Union). Nevertheless, these exciting developments should prompt the UK to increase its preparedness both for the demand for Amyloid-tracers and for clinical guidelines to support the utilisation of Amyloid-PET alongside drug therapy.

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