


RESEARCH ARTICLE

Potential eligibility for Aducanumab therapy in an Irish specialist cognitive service—Utilising cerebrospinal fluid biomarkers and appropriate use criteria

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Abstract

Objectives: Aducanumab is a monoclonal antibody which has recently been licenced for use by the food and drug administration for treatment of patients with mild cognitive impairment due to Alzheimer's disease (AD) or mild AD dementia. Appropriate use criteria (AUC) for Aducanumab in clinical practice are available. We look to review patients in our specialist interdisciplinary cognitive service with positive cerebrospinal fluid (CSF) biomarkers for AD for their hypothetical eligibility for Aducanumab, or a similar anti-amyloid agent.

Methods: Retrospective analysis was undertaken of patients with positive AD-biomarker CSF analysis. Data available at time of CSF analysis was reviewed to determine hypothetical eligibility for Aducanumab.

Results: Seventy patients had positive AD-CSF biomarkers. Forty nine of these were seen in the Gerontology-led service, with 21 in the neurology cohort. Average patient age was 70 years old. Forty patients (57%) met eligibility criteria for Aducanumab therapy by AUC guidelines.

Conclusion: We highlight the patients within our service who would be appropriate for Aducanumab or similar anti-amyloid agents should licencing be granted in the European Union, and the need to develop the resources and capacity to deliver this or other emerging disease modifying AD therapies.

Clinical Trial Registration: All patients in the combined cognitive clinic provide consent re willingness to be contacted re research.

KEYWORDS

Aducanumab, Alzheimer's, anti-amyloid therapy, cognition, memory

Key points

- This paper highlights the patients within an Irish specialist cognitive service who would be appropriate for Aducanumab or similar anti-amyloid agents should licensing be granted in the European Union.

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- Within this cohort forty out of seventy potentially suitable patients (57%) met eligibility criteria for Aducanumab therapy by AUC guidelines.
- Barriers to systemic readiness for anti-amyloid therapy include physician training in and access to lumbar puncture, and access to MRI scanning.
- Emergence of these therapies has led to an increasing awareness of potential serious adverse effects of side effects of anti-amyloid therapies, including amyloid-related imaging abnormalities (ARIA)

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with progressive impairment in multiple cognitive domains including memory, comprehension, language, attention, reasoning and judgement.¹ It is the most common cause for dementia worldwide, and predominantly affects older adults.² Whilst previously considered a clinical diagnosis, in the last number of years, development and increasing availability of in-vivo AD biomarkers has led to it being considered more a clinico-biological diagnosis, based on both biomarkers and clinical phenotype.³

While an exact aetiopathogenesis remains unknown, the neuropathological features of the disease include the presence of amyloid plaques and neurofibrillary tangles.^{4,5}

Hitherto, there had been no disease modifying treatment (DMT) available for AD. Treatment has focused on symptomatic management, however in the absence of a DMT, the disease inevitably progresses. In June 2021 Aducanumab (a monoclonal antibody against amyloid beta) was approved for use by the United States Food and Drug Administration for the treatment of patients with mild AD dementia, or mild cognitive impairment due to AD, making it the first disease modifying therapy approved for the treatment of this disease.⁶ It is delivered by monthly intravenous infusion. Alternative anti-amyloid therapies are quickly emerging, including lecanemab⁷ and donanemab,⁸ heralding the arrival of further novel DMTs in the treatment of AD.

Suggested 'Appropriate Use Criteria' (AUC) for Aducanumab were derived by an expert panel and are based on the original trials, updated prescribing information and expert consensus.⁹ The AUC as taken from these recommendations are summarised in Table 1. It is mandated by these criteria that all patients considered for treatment with Aducanumab must have the diagnosis confirmed by clinically validated amyloid studies. These include amyloid Positron Emission Spectrometry (PET) or cerebrospinal fluid (CSF) analysis. Given that anti-amyloid therapy AUC are only available at present for Aducanumab we felt this would help assess our systemic 'real world' readiness for anti-amyloid therapies.

In our tertiary hospital a specialist cognitive service has been established which is jointly run by the neurology and gerontology services. This centre focuses on early clinicobiological phenotyping of patients, with routine assessment of CSF biomarkers. Clinical diagnosis following investigations is ascribed on the basis of specialist multi-disciplinary consensus review.

We reviewed the patients within this specialist service to assess their hypothetical eligibility for Aducanumab therapy as per the AUC.

2 | METHODS

Retrospective database analysis was undertaken of patients with positive AD-biomarker CSF analysis over a 4 year period (2017–2021). This was defined as low amyloid-beta 42 and high phosphorylated tau (p-tau).

Demographic, neuropsychological performance, neuro-radiological, laboratory, and clinical phenotype diagnosis data were reviewed at time of CSF analysis to determine hypothetical eligibility for Aducanumab.

3 | RESULTS

Two hundred seventeen patients had CSF taken for AD-biomarker analysis. Among these, 70 patients were identified within our cognitive service who had positive AD-CSF biomarkers. Forty nine patients were identified from the gerontology cohort and 21 patients from the neurology cohort. Within the gerontology cohort, the mean age of patients with biomarker positivity was 71.2 years (+/– 5.9 years). 57% of patients were male. Within the neurology cohort, the mean age with biomarker positivity was 66.6 years (+/– 8.1 years). 47% of patients were male.

Forty patients (57%) met eligibility criteria for Aducanumab therapy by AUC guidelines. This comprised 63.2% of the gerontology cohort (31/49) and 42.8% of the neurology cohort (9/21). Of note, 33% of patients in the neurology cohort presented with an amnesic phenotype as opposed to 80% of the gerontology cohort.

The most common reason for being unsuitable (14%; 10/70 patients) was a cognitive score below threshold (Mini Mental State Examination [MMSE] score <21, Montreal cognitive assessment score <17, Addenbrooke's Cognitive Examination-III [ACE-III] <60). Following this, 9% (6/70 patients) would have been excluded due to laboratory abnormalities and a further 9% (6/70) due to imaging abnormalities. A full outline of why patients would have been unsuitable for Aducanumab therapy is available in Figure 1.

In total within our cognitive clinic we identified 70 patients with positive AD-CSF biomarkers, 40 (57%) of whom met eligibility

TABLE 1 Appropriate use criteria (AUC) for Aducanumab as reproduced from J Cummings et al.

Participant feature	Clinical trial enrolment criteria	Appropriate use in clinical practice
Age	50–85	Younger or older patients meeting all other criteria for treatment could be considered candidates for Aducanumab
Diagnosis	Clinical criteria for MCI due to AD or mild AD dementia	Clinical criteria for MCI due to AD or mild AD dementia
Scale scores at baseline	CDR global score 0.5; MMSE 24–30; RBANS delayed memory score of 85 or less	MMSE 21–30 or equivalent such as MoCA 17–30
Amyloid status	Amyloid positive PET (visual read)	Amyloid positive PET (visual read) or CSF findings consistent with AD
Genetic testing	Consent for APOE genotyping	Genotyping should be discussed with the patient/care partner. ARIA risk should be described, and the patient's preferences assessed
Neurological evaluation	Non-AD neurological disorders, stroke and TIA excluded	Non-AD neurological disorders excluded
Cardiovascular history	Angina; myocardial infarction; congestive heart failure excluded	Stable cardiovascular conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Medical history	Excluded: clinically significant systemic illness; diabetes that cannot be managed; uncontrolled hypertension (systolic >160; diastolic >100); history of cancer unless in remission for 5 years or localised to skin or prostate; impaired liver function; hepatitis; HIV infection	Stable medical conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Psychiatric history	Unstable psychiatric illness in the past 6 months; alcohol or substance abuse in the past year; use of cannabinoids; positive urine tests for excluded substances	Must be stable psychiatrically; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen
Reproductive status	Female subjects who are pregnant or breast feeding excluded; female subjects who are of child bearing age must be practicing contraception	Female subjects who are pregnant or breast feeding excluded; female subjects who are of child bearing age must be practicing contraception
Clotting status	Bleeding disorders, anticoagulants excluded	Patients on anticoagulants are excluded
Concomitant medications	Cholinesterase inhibitors and memantine allowed	Patients can be on standard of care with cholinesterase inhibitors and memantine
Baseline MRI	Baseline MRI finding that excluded participation: acute or subacute haemorrhage, macrohaemorrhage, greater than 4 microhaemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (>1.5 cm), superficial siderosis, or diffuse white matter disease	Patients should be excluded if there is evidence of acute or subacute haemorrhage, macrohaemorrhage, greater than 4 microhaemorrhages, cortical infarction (>1.5 cm), 1 lacunar infarction (>1.5 cm), superficial siderosis, or diffuse white matter disease
Care support	Reliable informant or care partner	May be living independently or with care partner
Informed consent	Must be signed by participant and care partner	Patient and care partner must understand the nature and requirements of therapy (e.g. monthly infusions to be performed indefinitely) and the expected outcome of therapy (slowing of decline of clinical features)

Abbreviations: AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini mental state Examination; PET, Positron Emission Spectrometry; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; TIA, transient ischaemic attack.

criteria when the AUC were utilised.⁷ However if we re-examined our data using the clinical trial inclusion criteria⁹ a further 21 patients would have been deemed unsuitable due to cognitive scores below threshold, leaving only 19 suitable patients (27%, 19/70 patients).

4 | DISCUSSION

Cerebrospinal fluid biomarkers are increasingly being used to aid diagnosis of Alzheimer's and other neurodegenerative conditions. As stated our centre aims to be a leading unit in deep clinicobiological

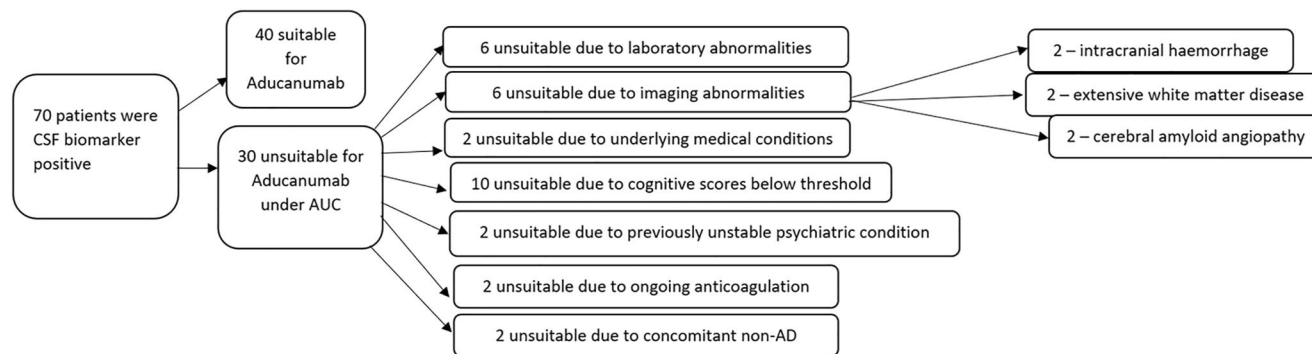


FIGURE 1 Full outcomes of those unsuitable for Aducanumab therapy

phenotyping of patients presenting with cognitive symptoms, of which CSF analysis plays an ever increasing role. As per the AUC for Aducanumab, amyloid PET or cerebrospinal fluid (CSF) analysis are a requirement prior to consideration for treatment. This is likely to be similar for other anti-amyloid therapies. The extent to which CSF or other biomarkers are routinely used in the work up of cognitive patient in other Irish centres, and even those outside of Ireland, seem variable. This may be a barrier to system readiness when identifying patients who would be suitable for anti-amyloid treatment.

Another consideration given the potential necessity for CSF analysis in order to qualify for anti-amyloid therapies would be physician training in diagnostic lumbar puncture. There are a variety of specialities depending on region or country which may predominantly lead care in dementia, including psychiatry, neurology or gerontology. While lumbar punctures are one of the most commonly performed invasive tests in clinical medicine, in some speciality schemes there may not be training provided. There are also other resource implications to consider including beds available for day case procedures and nursing support for these. This would need to be addressed as anti-amyloid therapies emerge.

As mentioned, 40 patients (57%) were deemed suitable for Aducanumab when assessed using the AUC, however if we re-examined our cohort using the clinical trial criteria this reduced to 27%. Recent Italian data agrees with this variability and likely increase in numbers when addressing 'real world' eligibility of Aducanumab when compared previous epidemiological estimates of eligibility.¹⁰ This is a wide range and underscores the need for consensus around fair selection criteria in the event of European licencing of any future anti-amyloid therapy.

The emergence of anti-amyloid therapies has also brought increasing awareness of potential serious adverse effects. Of particular concern are amyloid-related imaging abnormalities (ARIA).¹³ ARIA can be divided into ARIA-E and ARIA-H. ARIA-E refers to changes felt to represent vasogenic oedema and ARIA-H attributed to changes secondary to microhaemorrhages.¹³ ARIA (both E and H subtypes) were found to occur in 35.2% of patients on high dose Aducanumab when compared to 2.7% in the placebo group.¹⁴ The AUC recommend MRI prior to commencement of Aducanumab, in order to exclude patients who have evidence of substantial cerebrovascular disease at baseline.¹¹ This should be

obtained no more than 1 year prior to treatment. It is then recommended that MRI should be obtained prior to the fifth infusion, prior to the seventh infusion and prior to the 12th infusion (infusions are given monthly, with doses gradually increasing in increments to a target dose of 10 mg/kg by the seventh infusion). However if ARIA is detected on MRI, imaging should be repeated within 1 month, and potentially monthly thereafter.¹² This may lead to challenges in the safe delivery of anti-amyloid therapy, with significant imaging demands being added to already stretched MRI waiting lists, which may make this degree of monitoring untenable. We believe this would challenge our systemic readiness to deliver anti-amyloid treatment if licenced for use in Europe. Furthermore, as risk-stratification for ARIA can be guided by APOE genotype, it may become a standard requirement to genotype patients prior to commencing anti-amyloid therapy, with the inherent ethical and clinical resource implications of adding this step to standard practice.

A limitation of this study is the retrospective nature of the data collection. Due to historical routine CSF analysis in our cohort, amyloid biomarker positivity was used as an initial screening for selecting patients who would have been suitable for Aducanumab. In 'real world' use of amyloid therapies it is important to note there will be many patients potentially felt to be of initial suitability for treatment in which CSF biomarkers may not turn out to be positive, adding to the numbers who may access the service for potential work-up and diagnosis. In data from an Italian centre it was estimated that one third of patients with MCI or AD did not exhibit a CSF amyloid positive status.¹⁵ Comparatively, in our study, approximately two thirds of patients (147/217 patients) who underwent CSF analysis did not exhibit amyloid positivity, however this was not exclusively performed in MCI or AD settings. As our unit is a referral centre for potentially more complex cases we therefore may see a higher proportion of less common dementia causes, for instance, frontotemporal dementia or tauopathies.

In conclusion, this report highlights the presence of Irish patients eligible for anti-amyloid therapy should a European licence be granted, and the need to develop a system readiness and capacity to deliver this and other emerging disease-modifying AD therapies.

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CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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