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Special Article

Anti-Amyloid Therapies for Alzheimer's Disease: An Alzheimer Europe Position Paper and Call to Action

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Abstract

The growing prevalence and burden of Alzheimer's disease has catalysed huge investments in research on its causes, diagnosis, treatment and care. After many high-profile failures, recent clinical trials of anti-amyloid drugs have marked a turning point for the field, leading to the approval of the first disease-modifying therapies for Alzheimer's disease by the FDA. It is now up to European regulators to determine whether there is sufficient evidence to approve these drugs for patients with mild cognitive impairment or mild dementia due to Alzheimer's disease. Here, we outline Alzheimer Europe's position on anti-amyloid therapies for Alzheimer's disease, which was adopted by the Board of Alzheimer Europe following consultations with our member associations and with the European Working Group of People with Dementia. Beyond questions of drug efficacy, safety and cost, we highlight important issues that must be addressed by industry, regulators, payers, healthcare systems and governments, to ensure that patients have timely, appropriate and equitable access to innovative treatments, regardless of their socio-economic background, insurance status, or place of residence. We also call for continued investment in research on treatments that might benefit people with more advanced Alzheimer's disease – as well as support and care services that can help people live well with dementia at all stages of the disease.

Key words: Alzheimer's disease, drug development, healthcare systems, dementia, policy.

Alzheimer Europe's Call to Action on Anti-Amyloid Therapies for Alzheimer's Disease

Alzheimer Europe emphasises its commitment to a human rights-based approach to dementia, and its firm belief that people with Alzheimer's disease and other forms of dementia have the right to receive an accurate, timely diagnosis, as well as access to patient-centred support, treatment and care.

We call on Industry to:

- Adopt realistic, sustainable pricing policies for anti-amyloid drugs, reflecting the true value of treatment for patients and society, and ensuring affordability for mid- and low-income countries,
- Ensure transparent, timely and accurate communication of results from clinical trials, to trial participants as well as the wider AD community,
- Clearly present the benefits and risks of anti-amyloid drugs in an accessible, inclusive way, providing culturally appropriate information for minority ethnic and other marginalised groups,
- Continue investing in the development of diagnostics and treatments for other causes and stages of dementia, including both symptomatic and disease-modifying therapies.

We call on regulators, HTA and payers to:

- Grant a marketing authorisation for anti-amyloid treatments as soon as the risk-benefit ratio will be shown to be positive
- Ensure that the label for these medicines, as well as any communications and recommendations, clearly address drug eligibility, risk/benefit ratios, and detection, monitoring and management of side effects from anti-amyloid drugs,
- Support the development of patient registries for long-term collection of real-world evidence on the efficacy and safety of anti-amyloid drugs, including data on outcomes that are meaningful for patients and their caregivers,
- Develop clear reimbursement frameworks to ensure equitable coverage for anti-amyloid drugs, as well as the biomarker tests, diagnostics and scans that will be required to identify, treat and monitor eligible patients,
- Ensure that reimbursement of anti-amyloid drugs does not impact the coverage of symptomatic and non-pharmacological treatments that are hugely valued by people with dementia and their carers.

We call on governments and healthcare systems to:

- Commit funding and resources so patients can access diagnosis and treatment in the early stages of Alzheimer's disease, when they are most likely to benefit from treatment with anti-amyloid drugs,
- Invest in infrastructures for diagnosis, drug therapy and side effect monitoring, including tools for biomarker assessment, brain imaging facilities and infusion centres,
- Expand workforce capacity and capability, increasing recruitment and training of dementia specialists, primary care doctors, and other healthcare practitioners to ensure broad access to a timely diagnosis, treatment and care,
- Develop biomarker-guided clinical pathways which support the diagnosis and treatment of Alzheimer's in the early stages of disease, integrated alongside existing pathways focused on managing the symptoms of later-stage dementia,
- Develop clear guidelines on how to identify patients who are most likely to benefit from anti-amyloid drugs, as well as guidance and training on detection, monitoring and management of side effects,
- Ensure that investments in diagnostic tools and infrastructures to support access and delivery of anti-amyloid drugs also benefit the wider dementia community, not just those with Alzheimer's disease.
- Invest in tangible measures to reduce geographic and socioeconomic disparities in access to diagnosis and treatment, to avoid exacerbating existing health inequalities,
- Adopt dementia strategies and health policies that incorporate specific objectives to enable a timely diagnosis and equitable access to anti-amyloid drugs for patients across Europe.

Introduction

In May 2002, the European Medicines Agency (EMA) approved a drug called memantine, which treats some of the symptoms of moderate to severe Alzheimer's disease (AD) dementia. Since then, people affected by AD in Europe have been waiting to gain access to new treatments. Over the last 20 years, however, huge strides have been made in understanding the biological processes which cause AD. As a result, the last decade has seen a rapid expansion in the development of medicines classed as disease-modifying therapies: drugs that target the biological processes thought to drive AD.

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Currently, 79% of AD drugs in clinical trials are classed as disease-modifying therapies (1). Of the 21 disease-modifying therapies being evaluated in Phase 3 clinical trials, 29% target beta-amyloid, a pathological hallmark of AD that can be detected in the brain long before symptoms emerge.

The anti-amyloid drug aducanumab was the first AD disease-modifying therapy to obtain accelerated approval from the US Food and Drug Administration (FDA) in July 2021. Approval of aducanumab was based on its ability to clear amyloid from the brain – a surrogate endpoint deemed "reasonably likely to predict clinical benefit" by the FDA. A marketing authorisation application to the EMA was refused, with the agency citing the lack of evidence for clinical benefits outweighing the risks of aducanumab treatment.

A second anti-amyloid drug, lecanemab, was granted FDA approval in January 2023, via the same accelerated approval pathway as aducanumab. On 6 July this year, however, accelerated approval of lecanemab was converted to full, traditional approval of the drug, based on data from the Phase 3 CLARITY-AD trial. This 18-month, placebo-controlled, randomised clinical trial evaluated the efficacy and safety of lecanemab in people with early AD, showing a 27% slowing of clinical decline on the CDR-SB scale compared to placebo (2). Of note, lecanemab primarily targets soluble amyloid protofibrils, while aducanumab has greater selectivity for amyloid aggregates – differences in binding profile that could partly explain the clinical results observed for these drugs (3).

A third anti-amyloid drug, donanemab (which targets a pyroglutamine modification in amyloid beta species that are enriched in plaques) is currently under review at the FDA, with an anticipated decision on traditional approval at the end of 2023. Meanwhile, a marketing authorisation application for lecanemab is being reviewed by the EMA, which is expected to finalise its assessment in early 2024.

These and other recent developments mean that we may be on the cusp of anti-amyloid treatments being authorised for AD in Europe. In this position paper, we highlight important considerations for the approval, access and availability of anti-amyloid drugs in Europe. We outline specific actions for industry, regulators, Health Technology Assessment (HTA), payers and healthcare systems to ensure timely, safe and equitable access to these innovative treatments for people with early AD (defined as mild cognitive impairment or mild dementia due to AD).

The call to action and position paper was adopted by the Board of Alzheimer Europe, following consultations with our member associations and with the European Working Group of People with Dementia. In it, we highlight three key issues:

- The need for transparent, clear and accurate communications on the benefits and risks of anti-amyloid drugs, allowing people with AD and their carers to make informed choices about treatment
- The importance of equitable access to a timely and accurate AD diagnosis for all, regardless of ethnicity, socio-economic status, language or geographical location, allowing people with AD to access treatments, support and care
- The urgent need for concrete actions and investments in European healthcare systems to prepare for a future where anti-amyloid drugs should be readily accessible for everyone who could benefit from treatment.

The need for transparent, clear and accurate communications on the benefits and risks of anti-amyloid therapies

Anti-amyloid drugs represent a new hope for people with AD. Classed as disease-modifying therapies, drugs such as aducanumab, lecanemab and donanemab have the potential to slow the progression of AD. Meta-analyses of clinical trial data show that anti-amyloid drugs have a modest effect on cognitive and functional abilities after 18 months of treatment, slowing decline by around 20-40% (depending on the assessment scale used) compared to placebo (4, 5). For example, the TRAILBLAZER-ALZ2 trial found a statistically significant, 35% reduction in clinical decline for participants receiving donanemab compared to placebo, using a scale that assesses cognition and activities of daily living (iADRS) (6). In absolute numbers, this reduction in decline corresponds to a 3.25-point difference on the 144-point iADRS scale – a small difference, but one that could give people more time in the earlier, less symptomatic stages of AD, before it progresses to moderate or severe dementia. Of note, post-hoc analyses from TRAILBLAZER-ALZ2 which were presented at CTAD showed a 42% lower risk of progression to moderate dementia over the 76 week trial duration. In terms of patient-reported quality of life measures, data from the CLARITY-AD trial of lecanemab showed that participants receiving lecanemab perceived around 50% less decline than those who received a placebo. Whilst there is ongoing debate on whether these constitute "clinically meaningful benefits" for people with AD, it is clear that anti-amyloid drugs are indeed able to slow cognitive and functional decline, which may be connected with their ability to remove amyloid plaques from the brain, although this has yet to be conclusively demonstrated. Additional studies are currently underway to evaluate the benefits of lecanemab and donanemab in the longer term, and in people in the pre-symptomatic stages of AD (also termed preclinical AD).

However, these potential benefits do not come without risks. Side effects including brain swelling and microbleeds (termed "Amyloid-Related Imaging Abnormalities", or ARIA) are relatively common, occurring in around a third of clinical trial participants receiving anti-amyloid drugs (7). While most ARIA were

asymptomatic or mild, between 2-3% of trial participants experienced severe or life-limiting symptoms such as seizures or stroke (8). Of note, trial participants with two ApoE4 alleles had a much higher incidence of ARIA. A history of seizures, stroke, or treatment with certain anticoagulants may also increase the risk of ARIA (9). As a result, the FDA has included a black box warning of ARIA, and recommends genetic testing prior to initiating treatment with lecanemab. ARIA were most frequently observed during the early months following treatment initiation, so the drug label also states that patients should receive four MRI scans in the first year of treatment, for safety monitoring purposes.

Eligibility for treatment with anti-amyloid drugs is currently restricted to patients with confirmed amyloid pathology in the brain, who therefore need to undergo a PET scan or lumbar puncture tests prior to initiating treatment. While ongoing studies are investigating the safety and efficacy of anti-amyloid drug formulations for subcutaneous administration, patients currently receiving lecanemab treatment have intravenous infusions every two weeks, which last for over an hour – and are required to undergo MRI scans and clinical tests for safety monitoring (1). Patients may also need to undergo genetic testing for ApoE4 status before commencing treatment, the results of which may cause psychological distress, and could also affect family members, employment, and access to health insurance (10). Together, this means that current processes to determine eligibility, administer treatments and monitor safety add a substantial burden of medical intervention.

Alzheimer Europe's position

Alzheimer Europe expects that a positive risk/benefit profile of lecanemab and donanemab would encourage European regulators to grant a marketing authorisation for these anti-amyloid drugs. However, the benefits and risks of initiating treatment with anti-amyloid drugs are multifaceted, and complex, as are the patterns of evidence and effectiveness from clinical trials of anti-amyloid drugs. Consequently, Alzheimer Europe emphasises that accurate communication of these benefits and risks is crucial, as is informed, supported decision-making between patients, their families (including families of choice), and clinicians.

Eligibility (and ineligibility) for treatment must be clearly communicated to patients and their families, who should understand that the goal of treatment is a slowing of clinical decline, rather than stabilisation or improvement of symptoms. Alzheimer Europe believes that patients should receive all the information required to weigh the potential slowing of clinical decline against the side effects, financial costs and logistical burdens of treatment. This should include information on rates of progression from MCI to dementia, highlighting the way it can vary from person to person, with some cases remaining stable for many years, or even returning to normal cognition.

As outlined in our 2020 Ethics Report on legal capacity and decision-making (11), Alzheimer Europe promotes the combined, supported decision-making model as an effective, fair system that provides all possible support and avenues for everyone to exercise their legal capacity. Clinicians should clearly explain the areas of uncertainty and the limitations of trial data, for example the small number of participants from minority ethnic groups. In the eventuality that genetic testing for ApoE4 is recommended by European regulators, patients should also receive counselling on the implications of ApoE4 status, to mitigate the psychological impact of disclosure on patients as well as their biological family members. In all clinical interactions, comprehensive, transparent communication between patients and their doctors, in an environment of mutual trust and respect, should be the norm.

Alzheimer Europe also calls for transparent, timely communication of results from clinical trials of anti-amyloid drugs, both to trial participants as well as the wider AD community, including researchers, healthcare professionals, patients, carers, and the general public. Communications should include plain language materials for wide dissemination, as well as publication of trial data and analyses in scientific journals. Culturally appropriate information for minority ethnic and other marginalised groups should also be developed and shared through appropriate channels.

Additionally, while lecanemab has been approved as a disease-modifying therapy by regulators in the US and Japan, the causes and exact pathophysiological mechanisms driving AD have not yet been definitively established. The scientific evidence points to a complex, multifactorial aetiology for late onset AD, involving a range of different molecular pathways rather than a single causative agent. This should also be communicated to patients and the general public, also emphasising the need for more long-term studies on the efficacy of anti-amyloid drugs to firmly establish disease modification and slowing of clinical decline.

Accurate and understandable communication of risks and benefits by regulators, to clinicians, pharmacists, and other medicines users, is a cornerstone of informed decision-making. As such, Alzheimer Europe emphasizes that European Public Assessment Report (EPAR) summaries, product information sheets, and other benefit-risk communications from European and national regulators should be accessible, clear and consistent, enabling shared and supported decision-making based on what matters most to patients.

As the first in a new class of drugs for AD, rollout of treatments such as lecanemab will necessitate the development of clinical guidelines by national healthcare systems, medical associations and other professional bodies. Alzheimer Europe expects these guidelines to include clear parameters for identifying and prioritising patients who are most likely to benefit from anti-amyloid

drugs (as well as patients who may be at higher risk of side-effects, with relative or absolute contraindications); criteria for initiating and stopping treatment; together with recommendations for effective communications with patients. Finally, Alzheimer Europe calls on governments to take concrete actions to increase health literacy; this will help people to understand the complex information on risks and benefits of anti-amyloid drugs, and further support shared, informed decision-making.

The importance of equitable access to a timely and accurate diagnosis of AD

Eligibility for treatment with aducanumab and lecanemab in the US is restricted to people with mild cognitive impairment (MCI) or mild dementia due to AD, with confirmed amyloid pathology in the brain. It is likely that donanemab, if approved, will have similar eligibility restrictions, as the TRAILBLAZER-ALZ2 trial had similar exclusion criteria to the trials of aducanumab and lecanemab, and was also focused on MCI or mild dementia due to AD.

As such, access to anti-amyloid drugs hinges entirely on a timely and accurate diagnosis of AD, in the MCI or mild dementia stages ("early AD"), with objective confirmation of AD pathology using biomarker measurements. Of note, emerging evidence from clinical trials indicates that anti-amyloid drugs may be less beneficial for individuals who have more advanced cognitive impairment due to AD. In TRAILBLAZER-ALZ2, participants with an MMSE score lower than 22 at baseline experienced a 22% slowing in clinical decline after 18 months of donanemab treatment. In comparison, participants with a baseline MMSE score of 22-30, with less cognitive impairment, experienced a 38% slowing in clinical decline over the same period (6). This underscores the value of a timely diagnosis of AD, not just for treatment eligibility, but also, potentially, for treatment efficacy.

An accurate, timely diagnosis of early AD (defined as MCI or mild dementia due to AD) has a number of benefits beyond eligibility for treatment with anti-amyloid drugs. Early recognition and diagnosis of AD is instrumental in enabling patients and their loved ones to plan for the future. Having a confirmed diagnosis is also the first step towards accessing support services and care pathways, where available. The 2018 Alzheimer Europe report on the carer's experience of diagnosis found that 47% of 1,409 respondents would have preferred an earlier diagnosis of dementia, stating that this would have reduced the negative emotional impact and allowed them to better adjust (12, 13). Health economic studies have also shown that earlier diagnosis is associated with lower health and societal costs (14), as patients who are diagnosed early tend to remain in the community for longer, and are also able to benefit from symptomatic treatments and psychosocial interventions (15).

The 2011 NIA-AA diagnostic guidelines provide clear clinical criteria for diagnosing MCI and mild dementia due to AD – criteria that were used in the enrolment of participants in pivotal clinical trials of anti-amyloid drugs (16). In 2018, the NIA-AA published a research framework based on the 2011 guidelines, defining AD as a biological construct with a biomarker-based classification system (17). Elsewhere, consensus recommendations for MCI diagnosis have also been developed (18). Nevertheless, diagnosing AD in the MCI or mild dementia stages remains challenging in clinical practice. Indeed, almost 60% of older adults with AD never receive a formal diagnosis, or are diagnosed at more advanced stages of dementia – when they would no longer be eligible for treatment with anti-amyloid drugs (19). Moreover, while AD is the most common underlying cause, there are many other diseases that can lead to cognitive impairment and dementia - such as Lewy Body and Parkinson's disease – but have vastly different aetiologies and symptoms. The lack of a specific diagnosis means that many are excluded from accessing patient-centred support, care and treatments.

For those who do receive a diagnosis, the duration between onset of cognitive symptoms to diagnosis currently ranges between 2-3 years in older adults, and up to 5 years or more for people with young onset AD. Moreover, people rarely receive a molecular diagnosis of AD, with confirmation of amyloid pathology in the brain; Amyloid-PET scans are costly and are not widely reimbursed in Europe (20) and there are few evidence-based guidelines on diagnostic disclosure and biomarker counselling (21).

Instead, clinical evaluations, cognitive tests and structural brain scans (MRI or CT) form the mainstay of diagnosis in many countries. As a result, misdiagnosis rates are high; a 2019 study that performed molecular diagnoses with amyloid-PET scans found that 1 in 4 participants had been mistakenly diagnosed with AD (22). In addition, cognitive deterioration due to normal aging can be hard to distinguish from cognitive decline due to AD. This impedes timely diagnosis in the primary care setting, where doctors are often faced with time, resource and training constraints.

Illustrating the scale of this challenge, 76% of respondents to a survey of primary care practitioners in 5 European countries said they had insufficient time to manage patients with early AD, and 39%-59% did not feel confident in the diagnostic procedures (23). There is also a shortage of clinicians specialised in the diagnosis of early AD in Europe; France has an estimated 6.7 specialists per 100,000 people, while Germany has an estimated 24 specialists per 100,000 people (24). People from minority ethnic groups are faced with additional barriers to diagnosis, including a lack of access to culturally-sensitive, validated diagnostic tools, language barriers and structural biases (25).

Alzheimer Europe's position

People with AD have the right to receive an accurate, timely diagnosis, allowing them to access the treatments, support and care they need. However, people with AD are faced with many barriers to diagnosis. Alzheimer Europe emphasises the importance of improving diagnosis rates for people with AD, allowing them to access support, education, information and care - as well as innovative treatments such as anti-amyloid drugs.

Alzheimer Europe calls for concrete measures to ensure equitable access to a timely AD diagnosis for all, regardless of ethnicity, socio-economic status, language or geographical location; as outlined in our 2020 Policy Briefing and report on intercultural care and support for people with dementia and their carers (26). Primary care doctors and AD specialists should have access to culturally-sensitive diagnostic tools, as well as the required time, resources and training to provide individuals with a quality diagnosis. Diagnosis disclosure should always be accompanied by an individualised plan for follow-up and post-diagnostic support. This should including clear information about options for treatment with anti-amyloid drugs, symptomatic therapies and non-pharmaceutical interventions, where relevant. In addition, patients receiving a biomarker-supported diagnosis of MCI due to AD should receive counselling on disease prognosis, so they understand that progression to dementia is not certain, and can be hard to predict.

Currently, there are huge national and regional variations in access to, and availability of diagnostic services in Europe. Alzheimer Europe emphasizes that overstretched and underfunded healthcare systems should receive resources to provide clinical services that are able to diagnose AD in the early stages, when patients are most likely to benefit from treatment with anti-amyloid drugs.

Alzheimer Europe calls on healthcare systems to prepare for diagnostic pathways that include biomarker assessment, by investing in infrastructures for biomarker testing, and expanding workforce capacity and capability. It is likely that access to anti-amyloid drugs for patients with a diagnosis of MCI or mild AD dementia will be dependent on biomarker confirmation of AD pathology; in the future, diagnostic guidelines for AD may also be updated to include a biomarker-based classification of disease. Alzheimer Europe is encouraged by evidence from clinical cohort studies showing that blood-based biomarkers for phosphorylated tau isoforms (e.g. pTau-181, pTau-217) may perform as well as amyloid-PET or CSF biomarker tests (27). To enable implementation in community-based memory clinics and, eventually, in primary care, research efforts should be focused on validation studies in real-world populations.

Finally, while this position paper is focused on early AD, Alzheimer Europe emphasises that the needs of people with more advanced AD, or less common forms of dementia, must not be overlooked. People with diseases such as vascular or other less common forms of dementia are often misdiagnosed, missing out on health, social care and support services that could help them to live well, for longer. Investments in diagnostic tools, tests and infrastructures should also benefit the wider dementia community - not just those with AD dementia.

The need for concrete actions and investments in healthcare systems across Europe

The previous section of this position paper describes some of the healthcare system changes needed to enable a timely diagnosis of AD. However, a diagnosis of MCI or mild dementia due to AD is only a first step on the pathway to access. For people with AD to benefit from anti-amyloid drugs, healthcare systems in Europe will also need to adapt the way they support, treat and care for people with AD (28).

If European regulators impose similar eligibility conditions as the FDA, patients will require biomarker confirmation of amyloid pathology in the brain, currently measured using PET scans or lumbar puncture tests. There may also be a requirement for genetic testing, to establish patient ApoE4 status (29). In addition, European payers may ask that patients are enrolled in a registry to obtain coverage, similar to payers in the US. Treatment with current formulations of anti-amyloid drugs will involve monthly or bi-weekly intravenous infusions in specialist clinics, with regular monitoring involving MRI scans and other medical evaluations (1). If infusion reactions or side-effects such as ARIA occur, hospitals and emergency medicine teams will be required to manage and treat symptoms. Together, these clinical interventions will require a range of specialised personnel and infrastructures, from neurologists, neuroradiologists and genetic counsellors to PET scanners, MRI units and infusion centres. Defined clinical care pathways, standardised ARIA detection, monitoring and management protocols, as well as tools, training and guidelines for healthcare professionals, will also be required to ensure timely and effective treatment.

Currently, European healthcare systems are not resourced, equipped or organised to provide equitable access to anti-amyloid drugs for all people with early AD. Access to approved, symptomatic treatments for Alzheimer's dementia already varies between countries, with only 26% of low- and middle-income countries and 76% of high-income countries including these drugs in national schemes for full reimbursement (30).

The high financial cost of anti-amyloid drugs is the first barrier to equitable access. Lecanemab, the only anti-amyloid drug that is now widely reimbursed in the US, has been priced at USD 26,500 per annum. There are also additional costs linked to administration, genetic testing and safety monitoring, bringing the estimated total annual cost to USD 109,000 per patient. This should be

balanced against the yearly per-patient cost saving from lecanemab treatment, estimated at USD 9,249-35,605 (31). According to a recent study, 216,536 Medicare recipients may be eligible for treatment with lecanemab. The annual cost for treating these people alone would exceed USD 5 billion a year, with individual patients contributing around USD 6,600 per year for out-of-pocket costs (32).

Turning to Europe, recent estimates indicate that around 5.4 million individuals would potentially be eligible for anti-amyloid drugs (33). Treating all eligible patients could cost around EUR 133 billion per year, if a similar lecanemab pricing strategy is adopted in Europe (34). To put this in perspective, the total government expenditure on health across EU27 countries amounted to EUR1,179 billion in 2021, across all indications and ages, and including medical products, hospital, outpatient and public health services (35). Healthcare expenditure per capita also varies widely from country to country. OECD estimates from 2021 indicate that the US spent USD 10,948 on healthcare per capita. In comparison, France, Spain and Hungary spent USD 5,274, USD 3,600 and USD 2,170, respectively. Of note, upfront payment models are used by healthcare systems in many European countries; outside the hospital setting, patients are often asked to co-pay for reimbursable medicines (36). The high price of anti-amyloid drugs may therefore place them out of reach for many patients, further exacerbating health inequalities in Europe.

Anti-amyloid drugs, if approved in Europe, will be deployed within under-resourced and over-stretched healthcare systems. This already has consequences for people with AD, who often have to wait years from onset of symptoms for a diagnosis. Insufficient healthcare systems capacity, a reality for many European countries, will be a major barrier for equitable access to anti-amyloid drugs.

A 2018 analysis estimated that over 1 million patients with MCI in six European countries could progress to Alzheimer's dementia between 2020-2044 while on waiting lists for treatment with anti-amyloid drugs (24). This delay in care was linked to high anticipated waiting times for AD specialists, infusion therapy centres, and PET scanners. For example, in France, there are around 400 memory clinics, and approximately 6.5 dementia specialists (neurologists and geriatricians) per 100,000 population (37). Here, patients could have an initial wait time of 19 months for treatment, due to the lack of dementia specialists; in Italy, where there are an estimated 15.6 dementia specialists per 100,000 population, the primary constraint would be a lack of capacity at infusion centres.

Safety monitoring for ARIA following treatment will require regular MRI scans, for which the US is relatively well-equipped, with 4.4 units per 100,000 population (38). In contrast, Eurostat figures from 2019 indicate that most EU countries have fewer than half that number of MRI units; lowest availability is in Slovakia and Romania (0.4 MRI units per 100,000 population) while Luxembourg, the Netherlands and Estonia have around 1.4 MRI units per 100,000 population (39). It should also be noted that many MRI units and PET scanners are located in more heavily-populated areas, adding a logistical burden for people with AD living in rural areas. Together, these figures underscore the need for substantial investments in healthcare system infrastructures, as well as resources to increase workforce capacity.

Efforts to build capability across healthcare systems will also be required. Currently, European healthcare pathways for people with AD have a strong focus on meeting the needs of people with more advanced, symptomatic dementia. However, anti-amyloid drugs are only likely to benefit people in the earlier stages of AD, when they have MCI or mild dementia. Equitable access to anti-amyloid drugs in Europe will therefore require a paradigm shift in the way healthcare practitioners diagnose, treat and support people with AD (27). As a case in point, the 2011 NIA-AA clinical guidelines for the diagnosis of AD are being updated, incorporating a biological, biomarker-based classification in the current diagnostic framework, which primarily revolves around assessment of cognition and executive function (40). However, many primary care doctors and dementia specialists are not experienced in administering or interpreting molecular, biomarker-based diagnostics for AD. In addition, most neuroradiologists and neurologists will not have experience in assessing MRI scans for ARIA, and will require training on how to detect and effectively manage these potentially severe side effects of anti-amyloid treatment. Similarly, stroke and emergency medicine specialists will need clear guidance on how to manage ischemic stroke in patients receiving anti-amyloid drugs, as there may be contraindications for treatment with thrombolytics or anticoagulants (41).

Alzheimer Europe's position

Anti-amyloid drugs have the potential to change the course of a disease that is one of the leading causes of dependence and disability worldwide. As an organisation that is committed to improving the lives of people affected by dementia, Alzheimer Europe urgently calls on European healthcare systems to prepare for a future where anti-amyloid drugs should be readily accessible for all people with early AD who could benefit from treatment.

To harness the full potential of anti-amyloid drugs, healthcare systems need to incorporate biomarker-guided pathways able to detect AD and intervene at early stages of the disease, alongside pathways that are focused on managing the symptoms of later-stage dementia. As such, Alzheimer Europe calls on national governments and the EU to increase their investment in infrastructures for diagnosis, therapy and ARIA detection, including diagnostic tools, MRI units, PET scanners and infusion

centres. In doing so, governments and healthcare systems should consider the logistical burdens for patients and carers, aiming to reduce geographic and socioeconomic disparities in access that could exacerbate existing health inequalities.

To ensure timely access to diagnosis and treatment for patients, Alzheimer Europe calls on healthcare systems to expand workforce capacity, increasing recruitment and training of primary care doctors, neurologists, geriatricians and neuroradiologists as well as nurses, radiographers and ancillary support staff. Expansion of workforce capacity should be accompanied by an extension in workforce capability; healthcare practitioners should receive clear guidelines on how to identify patients who are most likely to benefit from anti-amyloid drugs (and those with relative and absolute contraindications), as well as guidance and training on ARIA detection, monitoring and management. As indicated previously, these guidelines should support effective patient-doctor communications and informed decision-making. Alzheimer Europe strongly believes that people affected by AD should be meaningfully involved in the design, development and implementation of new clinical care pathways, to ensure they meet the needs, preferences and values of patients and their loved ones.

Alzheimer Europe encourages anti-amyloid drug manufacturers to adopt realistic, sustainable pricing policies that reflect the true value of treatment for patients and society, as well as the capacity for healthcare systems to provide broad coverage. There is a large population of patients in Europe who could potentially be eligible for treatment with anti-amyloid drugs, but many countries are still struggling to manage health budget deficits after the COVID pandemic. Manufacturers should consider fiscal imbalances between different countries in Europe, aiming to price anti-amyloid drugs affordably so they can also be accessed by patients in mid- and low-income countries.

Alzheimer Europe calls on payers to develop clear reimbursement frameworks that will ensure broad coverage for the drugs – as well as the biomarker tests, diagnostics and scans that will be required to identify, treat and monitor eligible patients. Economic evaluations underpinning these reimbursement frameworks should take into account the annual cost of informal care, recently estimated at EUR 27,815 per person with dementia in Europe, amounting to EUR 392 billion overall (29). Importantly, financing access to anti-amyloid drugs should not impact the coverage of symptomatic and non-pharmacological treatments that are hugely valued by people with dementia and their caregivers. As these medicines are being introduced in national health systems, Alzheimer Europe supports the development of patient registries to ensure long-term collection of real-world evidence on their efficacy and safety.

In our 2014 Glasgow Declaration (42) we called for national dementia strategies in every country in Europe, asking that dementia be recognised as a public health priority. Whilst a number of countries have launched dementia plans or strategies, several countries in Europe are lagging behind (43). Finally, Alzheimer Europe re-iterates its call for national governments to adopt dementia strategies, incorporating policy objectives and tangible actions to enable a timely diagnosis and equitable access to anti-amyloid drugs for patients across Europe.

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