

Antiamyloid Monoclonal Antibody Therapy for Alzheimer Disease

Emerging Issues in Neurology

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Abstract

With recent data demonstrating that lecanemab treatment can slow cognitive and functional decline in early symptomatic Alzheimer disease (AD), it is widely anticipated that this drug and potentially other monoclonal antibody infusions targeting β -amyloid protein will imminently be realistic options for some patients with AD. Given that these new antiamyloid monoclonal antibodies (mAbs) are associated with nontrivial risks and burdens of treatment that are radically different from current mainstays of AD management, effectively and equitably translating their use to real-world clinical care will require systematic and practice-specific modifications to existing workflows and infrastructure. In this Emerging Issues in Neurology article, we provide practical guidance for a wide audience of neurology clinicians on logistic adaptations and decision making around emerging antiamyloid mAbs. Specifically, we briefly summarize the rationale and available evidence supporting antiamyloid mAb use in AD to facilitate appropriate communication with patients and care partners on potential benefits. We also discuss pragmatic approaches to optimizing patient selection and treatment monitoring, with a particular focus on the value of incorporating shared decision making and multidisciplinary collaboration. In addition, we review some of the recognized limitations of current knowledge and highlight areas of future evolution to guide the development of sustainable and flexible models for treatment and follow-up. As the field enters a new era with disease-modifying treatment options for AD, it will be critical for neurology practices to prepare and continually innovate to ensure optimal outcomes for patients.



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Glossary

A β = β -amyloid; **AD** = Alzheimer disease; **ARIA** = amyloid-related imaging abnormalities; **ARIA-E** = ARIA with edema/effusion; **ARIA-H** = ARIA with microhemorrhage/hemosiderosis; **CDR-SB** = Clinical Dementia Rating Sum of Boxes; **EIN** = Emerging Issues in Neurology; **FDA** = US Food and Drug Administration; **mAb** = monoclonal antibody; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **tPA** = tissue plasminogen activator.

Introduction

Additional treatment options are needed for Alzheimer disease (AD), which is simultaneously highly prevalent (acknowledging limitations of precise etiologic diagnosis, it is estimated that more than 6 million individuals in the United States are currently affected),^{1,2} chronic and progressive,³ and devastating to families and society at large.⁴ Recent data on lecanemab⁵ and other monoclonal antibody infusions targeting β -amyloid (A β) protein^{6,7} make clear that new agents are highly likely to be part of the toolkit for clinicians caring for patients with AD. In this new reality, it will be critical for neurology practices to sustainably adapt their workflows and infrastructure to optimize the use of these complex, emerging therapeutics.

Scope and Disclaimers

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This EIN article aims to provide practical guidance on emerging anti-amyloid monoclonal antibodies (mAbs), including (1) briefly summarizing the rationale and available evidence for their use in AD; (2) discussing pragmatic approaches to patient selection and treatment monitoring, with a focus on lecanemab; and (3) highlighting limitations of current knowledge and anticipated future directions.

A Balanced Rationale for Anti-amyloid mAbs as a Component in AD Treatment

Clinically, AD includes a range of syndromic presentations. Biologically, the disease is defined by the presence of A β plaques and neurofibrillary tau deposits.⁸ In addition to being

a hallmark neuropathologic finding, abnormal brain amyloidosis is widely proposed as an early event in the AD cascade based on longitudinal aging studies (showing A β deposition many years before onset of symptoms)⁹ and genetics (identifying alterations in genes central to A β processing in cases of familial AD).¹⁰ This backdrop has formed the basis for therapeutic targeting of A β , with the caveat that the disease's underlying mechanisms are likely multifactorial (e.g., amyloid, tau, inflammation, and other processes).

Numerous earlier drug trials targeting A β failed to convincingly demonstrate clinical efficacy.¹¹ These included aducanumab, an anti-amyloid mAb which in 2021 received accelerated approval from the US Food and Drug Administration (FDA) amidst much controversy.¹² Of note, the FDA approval for aducanumab was based on the drug's ability to lower levels of amyloid plaques measured with PET, on the hypothesis that this would be "reasonably likely to predict a clinical benefit to patients."¹³ However, the FDA approval of aducanumab acknowledged that there remained significant uncertainties about the drug's clinical benefits. In particular, the 2 identically designed phase 3 trials of aducanumab (EMERGE and ENGAGE) were terminated early based on findings from an interim futility study, with subsequent analyses on a larger set of acquired data producing conflicting results. The primary end point of both trials was the score on the Clinical Dementia Rating Sum of Boxes (CDR-SB), a standardized scale (range 0–18) of impairment in 6 domains of cognition and function, with scores assigned by trained clinicians after interviews of the patient and a reliable informant.¹⁴ Although ENGAGE did not meet its primary end point, participants treated with high-dose aducanumab in EMERGE displayed modestly less decline on the CDR-SB (0.39 points) vs placebo.^{12,15} In view of these clinical uncertainties, use of aducanumab in real-world practice has been scant overall.

The phase 3 trial of lecanemab (CLARITY-AD) represented a step forward. Lecanemab lowers brain A β plaque burden through binding to soluble A β protofibrils as well as (to variable extent) other forms of A β .¹⁶ Among 1,800 older adults in CLARITY-AD with biomarker-supported early AD, lecanemab treatment over 18 months led to slowing of cognitive and functional decline based on the CDR-SB.⁵ Although the treatment effect (\sim 0.5-point differential on the CDR-SB) was modest, the approximately 25% reduction in worsening observed would equate to 4–5 months of delay in disease-related clinical progression over 1.5 years. In addition to meeting all

primary and secondary outcomes of cognition and function, lecanemab treatment also yielded differences in AD biomarkers (including CSF, plasma, and PET measures of tau), supporting a downstream pathophysiologic effect of A β plaque removal.⁵ Favorable drug effects were also demonstrated on scores from a care partner questionnaire that assessed daily function as well as exploratory indices of quality of life and caregiver burden.¹⁷

Other than infusion reactions, the most common side effect of lecanemab treatment was the development of amyloid-related imaging abnormalities (ARIA), a known potential complication of anti-amyloid mAbs which is believed to relate to disruptions of vascular integrity.¹⁸ Findings of ARIA in CLARITY-AD consisted of ARIA with edema/effusion (ARIA-E) in 12.6% of treated individuals (vs 1.7% with placebo) and ARIA with microhemorrhage/hemosiderosis (ARIA-H) in 17.3% of treated individuals (vs 9.0% with placebo). The overall incidence of ARIA (either ARIA-E or ARIA-H) with lecanemab treatment was 21.3%, which was lower than rates reported for aducanumab (41% at the highest drug dose) in its phase 3 trials.⁶ Within the confines of the careful patient selection and safety monitoring of CLARITY-AD, nearly 80% of cases with ARIA were asymptomatic, and overall, less than 3% of individuals treated with lecanemab experienced symptomatic ARIA.⁵

In summary, CLARITY-AD demonstrated that lecanemab (1) can slow decline in early symptomatic AD and (2) is associated with risks beyond those of current mainstays of AD management. The drug is currently available under a traditional FDA approval, potentially alongside other within-class agents in the future. With this backdrop, it stands to reason that some patients with AD will be interested in and potentially qualify for treatment. Effectively supporting their neurologic care will require thoughtful translation of trial experience to real-world clinical practice. As such, the balance of this article will focus on discussion of (1) pragmatic approaches for identifying which patients are most likely to benefit from treatment; (2) innovative workflow considerations to optimize risk counseling, safety monitoring, and practice volume sustainability; and (3) novel aspects of ongoing research to contextualize future directions.

Patient Selection: From Overt Indications to Individualized Risk Stratification

The current FDA label specifies that lecanemab is potentially indicated for patients with mild cognitive impairment (MCI) or mild dementia due to AD.¹⁹ Patients with MCI display cognitive impairment that is objectively evident (i.e., not representing subjective concerns only) but is not at a severity to affect functioning in instrumental activities of daily living.²⁰ Patients with mild dementia have cognitive impairment that interferes with the ability to function at work or other usual activities, but is not advanced enough to affect functioning in

basic activities of daily living (e.g., dressing, grooming).²⁰ As these definitions reflect a continuum of cognitive impairment severity, in CLARITY-AD, a Mini-Mental State Examination (MMSE) score of 22–30 was required to ensure that participants fit the target population of early symptomatic AD.⁵ Current safety and efficacy data do not support treatment in presymptomatic AD or in moderate/severe AD dementia.

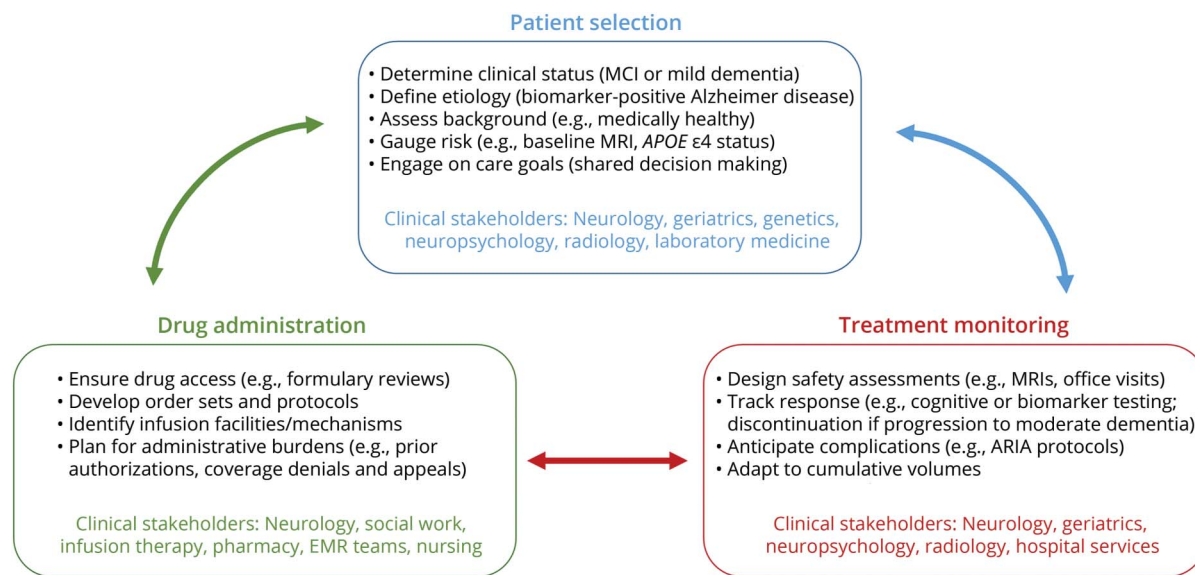
Although the broader inclusion criteria for CLARITY-AD provide additional guideposts for appropriate use, these may not be uniformly applicable toward all clinical contexts. For example, some patients outside of the defined age (50–90 years) or MMSE (22–30) ranges specified in CLARITY-AD could otherwise be considered reasonable candidates for therapy, including younger individuals with sporadic AD who are relatively more likely to have atypical clinical syndromes, which can influence cognitive test performance.²¹ In addition, strict reliance on the CDR-SB or neuropsychological assessment items could necessitate extra training or resources, which may not be practical for all settings. As such, it will be important for clinicians to consider up front how best to systematically identify patients who are most likely to benefit from treatment while ensuring that drug usage generally adheres to the conditions under which CLARITY-AD provides evidence of clinical efficacy.

Evidence of abnormal brain amyloidosis also needs to be demonstrated before initiation of anti-amyloid mAb therapy. In CLARITY-AD, amyloid positivity was determined by either amyloid PET or measurement of CSF biomarkers. Amyloid PET requires specialty scanner and tracer availability as well as neuroradiology expertise and currently is not widely covered by insurance outside of registry-based trials (e.g., the IDEAS study).²² CSF biomarker tests are generally more accessible but require lumbar puncture, proper sample acquisition (including use of special tubes),²³ shipment to a qualified laboratory, and expertise in interpretation.²⁴ Although not yet optimized for clinical use, blood-based biomarkers of AD are being actively studied and may revolutionize screening and treatment monitoring in the future.²⁵ However, it is not yet fully clear whether these blood-based biomarkers will have the sensitivity and specificity necessary for use in decision making on treatment initiation, in comparison with use as screening tools.

There is no indication for anti-amyloid mAb therapy in patients with primary diagnoses other than AD (e.g., Lewy body disease, frontotemporal dementia, or vascular cognitive impairment) or in individuals with suspected multi-etiological cognitive impairment. Particularly given that amyloid positivity is not rare in cognitively unimpaired older adults²⁶ and neurodegenerative copathology is quite common in cognitively impaired individuals,²⁷ comprehensive assessments will remain critical to facilitate individualized counseling on treatment options.

Additional factors influence the risk of side effects from anti-amyloid mAbs. A pretreatment brain MRI is necessary to assess the extent of cerebrovascular disease and other relevant

Figure 1 A Pragmatic Model for Clinical Implementation of Anti-amyloid Monoclonal Antibody Therapies for Alzheimer Disease



Comprehensive advanced planning, multidisciplinary stakeholder engagement, and iterative adaptations are all critical for neurology practices to sustainably incorporate anti-amyloid monoclonal antibody therapies into viable options for qualifying patients with Alzheimer disease. Practice-specific choices on appropriate patient selection, drug administration protocols, and processes for treatment monitoring all have the potential to affect response to treatment for patients and risks of complications from treatment for patients and health systems. This clinical decision making will benefit from remaining dynamic to changes at the practice level (e.g., capacity for safety MRIs), research level (e.g., identification of new risk factors for ARIA), and patient level (e.g., clinical progression or other factors precluding further therapy). ARIA = amyloid-related imaging abnormalities; EMR = electronic medical record; MCI = mild cognitive impairment.

structural abnormalities. Microhemorrhages (particularly in a high number or in a cortical location to suggest underlying cerebral amyloid angiopathy²⁸) and superficial siderosis are associated with higher risk of ARIA.¹⁸ Patients with a history of cerebral macrohemorrhage, large-territory ischemic stroke, multiple lacunar strokes, or MRI signs of severe small vessel ischemic disease affecting the cerebral white matter were excluded from CLARITY-AD and are presumed to be at elevated risk of side effects from anti-amyloid mAb treatment.^{5,29} Patients with barriers to obtaining MRI would also not be candidates for anti-amyloid mAbs because of the need for regular safety monitoring and urgent imaging in case of symptoms.

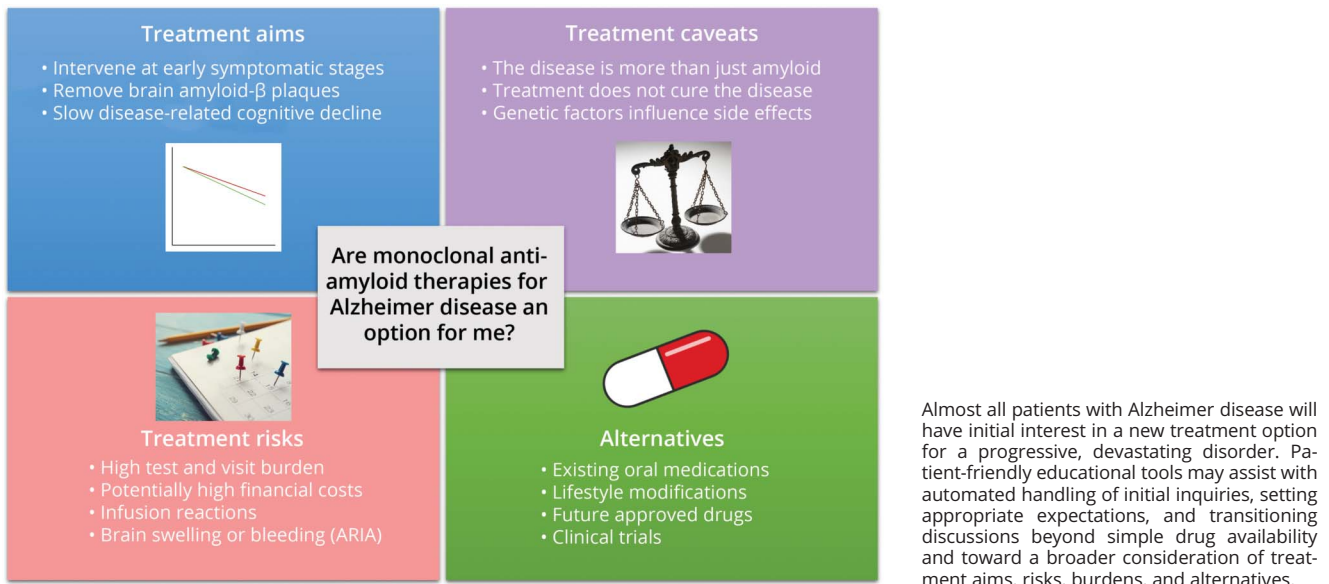
Anticoagulant medications are commonly prescribed in older adults for various indications, but use of these medications with anti-amyloid mAbs is contraindicated because of increased bleeding risk, including the potential for severe macrohemorrhage.^{29,30} A patient who had received 3 doses of lecanemab and subsequently received an intravenous tissue plasminogen activator (tPA) for acute ischemic stroke syndrome died of extensive, multifocal cerebral hemorrhages.³¹ Two additional patient deaths have occurred in the open-label extension phase of CLARITY-AD,³² at least one of which involved exposure to anticoagulant medication.³³ The effect of antiplatelet medications on ARIA risk is less certain. In CLARITY-AD, participants were allowed to take aspirin while receiving treatment, and there was no evidence of increased

risk of ARIA in this setting. Nevertheless, the presence of other possible risk factors of bleeding events in the general population highlights the importance of individualized clinical judgment and counseling regarding the potential for antiplatelet medications to heighten the risk of ARIA-H.

The *APOE* ϵ 4 allele is the strongest known genetic risk factor of sporadic (i.e., nonfamilial) AD,³⁴ and it is associated with higher rates of ARIA with anti-amyloid mAb therapy, particularly among *APOE* ϵ 4 homozygotes.^{5,18} As a result, it is widely felt that *APOE* ϵ 4 allele testing should be offered before anti-amyloid mAb treatment so that risks of ARIA can be appropriately considered.^{29,30} It will be important for clinicians to develop processes for pre-test and post-test genetic counseling regarding the implications of this testing for patients and families, particularly given that there are no other current indications for obtaining *APOE* allele testing in clinical neurology practice.³⁴ Other major neurologic and systemic medical conditions that may influence benefits and risks of therapy (e.g., seizure disorders, cancers, hematologic or immunologic disorders, exposure to other monoclonal antibody therapies) will also require thoughtful decision making at practice and patient levels (Figure 1).

For interested readers, a working group recently composed recommendations on appropriate use of lecanemab.²⁹ In particular, the publication includes a table summarizing key inclusion and exclusion criteria for CLARITY-AD (which

Figure 2 Potential Template for Patient Education on Anti-amyloid Monoclonal Antibody Therapies for Alzheimer Disease



extend to discussion of non-AD neurologic and medical conditions) alongside recommendations from the working group for appropriate clinical use.²⁹ Guidance on clinical use⁶ and appropriate use recommendations³⁰ were also published for aducanumab.

Shared Decision Making: Alignment of Treatment Options to Individualized Care Goals

When treatment with anti-amyloid mAbs may be a viable option, a shared deliberative process among clinicians, patients, and caregivers will be critical to ensure alignment of expectations, benefits, risks, and goals of care.⁶ Given that patients with symptomatic AD may have or develop impairments in a decision-making capacity, it is critical that advanced directives and/or authorizations (e.g., for a designated care partner to make health care decisions on the patient's behalf) are within the medical record before considering treatment. Almost all individuals with AD will have initial interest in a therapy that can potentially slow progression. However, it is important that patients understand that the goal of treatment is slowing of decline rather than stabilization or improvement in cognitive functioning. In addition, some patients may be less enthusiastic when they weigh the possible side effects (e.g., infusion reactions, ARIA) and personal financial costs and logistic burdens associated with treatment. Financial costs of treatment to patients extend beyond medication copays to include recurring infusion center fees, clinic evaluations, and MRI scans and other diagnostic tests. The degree to which insurers will cover these costs is currently unknown. Regular (biweekly or monthly) infusions may also be

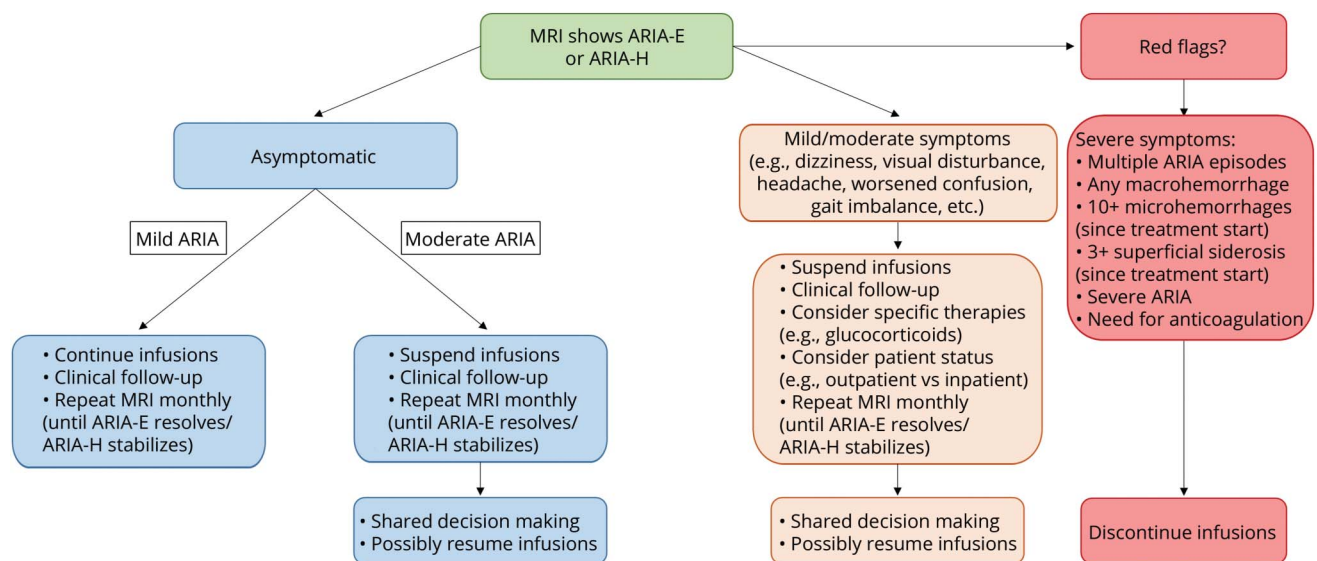
logistically challenging or negatively affect quality of life for some individuals, particularly based on geographic or transportation factors. Here, social work resources could be particularly valuable in navigating paperwork and other needs.

More broadly, shared decision making in this space will need to be individualized and accepting of areas of uncertainty, including risk factors of ARIA and other side effects, limitations of existing trial data (e.g., for minority populations and patients with clinically atypical AD), and ideal treatment duration amidst unknowns about longer term (beyond 18 months) sequelae of drug therapy. Overall, it will be vital for neurology clinicians, patients, and caregivers to engage in nuanced discussions that acknowledge that anti-amyloid mAbs are not a cure for AD but could be a reasonable option for seeking additional slowing of disease progression in some patients with early disease and low likelihood of side effects (Figure 2).

Treatment Administration: Drug Infusions, Safety Monitoring, and Contingencies

Current frameworks of AD care include relatively infrequent use of office visits and advanced diagnostic testing. To adapt these for administration of anti-amyloid mAbs, neurology practices will benefit from multidisciplinary engagement to ensure balanced volumes and access throughout the treatment course (Figure 1). Lecanemab is administered every 2 weeks intravenously over approximately 1 hour.¹⁹ Along with facilitating appropriate patient selection and arranging recurring infusions, clinicians must be prepared to respond to ARIA and other potential complications of treatment. This includes having

Figure 3 Suggested Management Based on ARIA Radiologic Severity and Clinical Condition



A suggested framework for managing imaging findings of ARIA is displayed, with differentiations by clinical and radiologic severity noted. Grading of radiographic ARIA is based on the US Food and Drug Administration prescribing label for lecanemab as follows: (ARIA-E) mild—one site of sulcal or cortical/subcortical FLAIR hyperintensity measuring <5 cm; moderate—one site of FLAIR hyperintensity measuring 5–10 cm or more than 1 site of FLAIR hyperintensity each measuring <10 cm; and severe—any site of FLAIR hyperintensity measuring >10 cm; (ARIA-H) mild—≤4 treatment-emergent microhemorrhages or 1 focal area of superficial siderosis; moderate—5–9 treatment-emergent microhemorrhages or 2 focal areas of superficial siderosis; and severe—10 or more treatment-emergent microhemorrhages or 3 or more focal areas of superficial siderosis. Importantly, practice and provider-specific clinical decision making that is appropriately individualized to the patient will be inherent to optimizing management of complications of therapy with anti-amyloid monoclonal antibodies for Alzheimer disease. ARIA = amyloid-related imaging abnormalities; ARIA-E = ARIA with edema/effusion; ARIA-H = ARIA with microhemorrhage/hemosiderosis; FLAIR = fluid-attenuated inversion recovery.

pathways for urgent evaluation in case of symptoms and liaising with local radiology and emergency medicine teams to ensure awareness around new indications and orders.

Common symptoms of ARIA include dizziness, headache, visual disturbances, and increased confusion.¹⁸ However, most cases of radiologic ARIA in CLARITY-AD were asymptomatic,⁵ which creates a risk of worsening without sufficient monitoring. The FDA label for lecanemab specifies obtaining safety MRI scans before the 5th, 7th, and 14th infusions.¹⁹ This reflects that in CLARITY-AD, ARIA (particularly ARIA-E) were most frequent in the first 4 months of therapy.⁵ However, additional scans may be warranted in individuals at higher risk of ARIA, including in patients with *APOE* ε4 who display initial episodes of ARIA-E beyond this early time window.⁵ Among consensus recommendations,¹⁸ MRI scans for ARIA detection should at minimum include T2–fluid-attenuated inversion recovery, T2* gradient recalled echo, and diffusion-weighted imaging sequences, and benefit from standardization of scanner types and protocols across time points. Given that some ARIA findings can be subtle, with treatment ramifications based on gradation, neuroradiology expertise (through existing local providers or remote partnerships) will be important.

A framework for management based on radiologic severity of ARIA (provided in the FDA label for lecanemab)¹⁹ and clinical symptoms is presented in Figure 3. In CLARITY-AD, most cases of ARIA (more than 80%) resolved within 4

months on discontinuation of lecanemab infusions.⁵ For some patients with symptomatic or radiologically severe ARIA, providers may consider early initiation of high-dose steroids (e.g., intravenous methylprednisolone 1 g daily for 3–5 days, followed by an oral steroid taper over several weeks). Other goal-directed therapies (e.g., antiseizure medications), diagnostic tests, or hospital admission may be required on a patient-specific basis. These contingencies imply that clinical practices offering anti-amyloid mAb treatments will need to ensure that there is sufficient access to general floor and intensive care unit beds, inpatient MRI and EEG, and other hospital resources. Furthermore, patients and clinicians should be aware that treatments indicated for non-AD medical conditions (e.g., intravenous tPA for acute ischemic stroke) could substantially influence the risk of brain macrohemorrhage and, therefore, may be precluded in the setting of anti-amyloid mAb treatment.^{31,35}

Practice Infrastructure: Sustainably Adapting to New Demands

The emergence of anti-amyloid mAbs occurs at a time when communities have variable access to general neurologists, cognitive-subspecialist neurologists, other qualified clinicians, and dementia care resources.^{6,36} In this setting, collaborative care efforts (through formal and informal relationships) and practice-specific adaptations will be critical to ensure

financially and logistically sustainable efforts that meet patients' needs.³⁷ Presumably, it would be most practical for a large proportion of the community-based population to receive initial evaluations by nonspecialist clinicians, for which cognitive screening may be a reimbursable service with appropriate downstream yield (e.g., Medicare annual wellness visit). Training non-dementia-specialist clinicians in improved conceptual awareness and examination skills may help them serve as a dedicated "front line" for communities. Triage models that could identify patients with high risk and/or complexity would likely also have major effects on appointment access and clinician and patient experience.

In addition, heightened requests for information from patients and caregivers, which will vary by demographic and other factors, can be anticipated. Efforts to improve efficiency of request response rates will help to conserve practice resources. One potential strategy to mitigate excess demand involves developing a dedicated website for patient and caregiver education. Phone call or electronic medical record response duration may be improved by providing template responses to frequently asked questions. For some practices, designing a consultation service, through which the specialist communicates with nonspecialist clinicians to support and triage appropriate patients³⁸ and through which the health system addresses any limitations of payer reimbursement for current diagnostic codes, may also mitigate demand.

Ultimately, clinicians offering anti-amyloid mAbs for AD will depend on reimbursements through direct pay, pharmaceutical company support, or a third-party payer. If drug therapy is covered by a payer, policies may vary between traditional Medicare vs Medicare Advantage plans. In addition, within traditional Medicare, coverage determination may be standardized across the United States (i.e., through a national coverage determination) or the coverage decision may be determined on a regional basis (i.e., local coverage determination). Clinicians managing the administration of anti-amyloid mAbs should anticipate and plan for the administrative burden related to drug prior authorization and potential denials and appeals. Overall, neurology practices considering these treatments must be cognizant of the patient's payer and policies, both of which may be dynamic.

Donanemab: A Potential Addition to the Treatment Framework

Donanemab is another high-potency anti-amyloid mAb that is infused intravenously every 4 weeks. Recently, top-line results were announced for the phase 3 trial of donanemab (TRAILBLAZER-ALZ 2). Compared with placebo, donanemab treatment over 18 months resulted in slowing of cognitive and functional decline by approximately 35% in the primary target population studied.³⁹ ARIA-E and ARIA-H occurred in 24.0% and 31.4% of treated individuals, respectively.³⁹ TRAILBLAZER-ALZ 2 included some

unique aspects of study design that limit direct comparisons with CLARITY-AD. Under a "treat-to-clear" model, serial amyloid PET scans were used to determine treatment duration, with 52% of treated participants converting to amyloid PET-negative status by 12 months.³⁹ In addition, tau PET was obtained at baseline to stratify participants, resulting in the study sample being relatively enriched with individuals having intermediate (vs high) levels of tau burden who were hypothesized to be at earlier disease stages with greater likelihood of treatment response. Further details on TRAILBLAZER-ALZ 2 are anticipated to be released later in 2023, and an application for traditional FDA approval is pending a decision over the next year. In the event of donanemab being available clinically in the future, many facets of a framework for implementing lecanemab would be anticipated to translate to donanemab. However, the different trial designs for these in-class agents indicate that additional drug-specific adaptations to workflows will be necessary. In addition, clinicians will need to engage with patients who are eligible for treatment to weigh available options, which may be influenced by differential insurance coverage and copays, infusion and scan frequency, clinical efficacy, and side effect rates. Models for this approach can be adapted from other neurologic subspecialties (such as multiple sclerosis and neuro-oncology), in which frequently there are multiple options for disease-modifying therapy in any individual patient.

Anti-amyloid mAbs in AD: Current Foundation and Future Advances

The collection of late-phase clinical trials of anti-amyloid mAbs represents merely the initial forays of updates to neurologic care for AD in the era ahead. As with other complex diseases for which treatment options have advanced iteratively (e.g., HIV and AIDS), patient selection, clinical decision making, and safety monitoring should all be anticipated to evolve with additional real-world experience and research extensions. In particular, most CLARITY-AD participants had sporadic, clinically typical (i.e., amnesic multidomain dementia syndrome) presentations of AD. There is limited information on how the trial results may extend to clinically atypical AD. Furthermore, individuals with autosomal dominant AD or Down syndrome are currently recommended to be excluded from anti-amyloid mAb treatment because of increased rates of cerebral amyloid angiopathy.²⁹ Additional data may inform changes to these principles. Given the complexity of anti-amyloid mAbs, provider-enrolled patient registries, such as ALZ-NET,⁴⁰ may provide an avenue for modest flexibility on appropriate use at an individual patient level while facilitating data-driven practice changes for the broader field.

Drug-specific characteristics may inform future developments. Existing highly potent anti-amyloid mAbs target various steps in the cascade leading to A β plaque deposition, and it remains possible that subtle mechanistic and pharmacokinetic differences among these agents could influence efficacy, side effects, and

optimal contexts for use,⁴¹ similar to what is observed with newer generation therapies for multiple sclerosis. In particular, the magnitude and rate of A β plaque reduction may differentially regulate downstream pathophysiologic consequences of therapy and resulting clinical outcomes,⁴² which could affect patient candidacy and drug selection. Compared with placebo, treatment with several antiamyloid mAbs has also been associated with lower brain volumes,⁴³ and further research is needed to determine the underlying mechanisms and any longer term implications of these findings. In addition, there is no current consensus on the optimal duration of antiamyloid mAb therapy. The longer term burdens on patients and economic feasibility of treatment may differ widely depending on whether infusions are to continue indefinitely until progression to a moderate dementia, for a defined period (e.g., 18 months), or until reaching amyloid PET-negative status (as with the model used for TRAILBLAZER-ALZ 2).^{7,39}

The timing of therapy, relative to disease stage, may also evolve in the future. Given that high rates of A β deposition largely precede, in some cases by many years, the development of significant clinical impairment,⁴⁴ the value of earlier intervention in preclinical and asymptomatic AD remains of high interest. Unfortunately, results of recent trials of solanezumab, in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study,⁴⁵ and crenzumab, in a cohort of cognitively unimpaired *PSEN1* E280A mutation carriers,⁴⁶ were not positive. However, as lecanemab was the first antiamyloid mAb to convincingly demonstrate a clinical benefit in mildly symptomatic AD and displays higher potency of cerebral A β reduction than previous drugs tested in this setting, results of the AHEAD 3–45 study testing this agent in preclinical AD are eagerly anticipated.⁴⁷

Developments around antiamyloid mAbs are occurring on the backdrop of nuanced debate over what degree and character of clinical change (1) could be reasonably expected within AD trials and (2) would be considered meaningful by patients and care partners. In the early symptomatic stages of AD, it is conceivable that a 0.5-point differential in the CDR-SB could manifest with substantive effects on daily life, for example, if distinctions (e.g., between mild forgetfulness and more moderate memory loss affecting daily activities) affect the ability to maintain employment or remain in a long-standing shared home.¹⁷ Post hoc survival analyses in CLARITY-AD also suggested that by 18 months, a smaller proportion of patients treated with lecanemab (24%) had declined by a global CDR score (0.5 = MCI, 1.0 = mild dementia, 2.0 = moderate dementia) compared with placebo (32%).⁵ However, patients will need to be aware that it is possible that this modest reduction in the rate of decline may not be overtly evident to them or their care partners. Longer term follow-up observations on treated patients from the open-label extension will also be needed to clarify whether nonlinear courses of benefit are a reasonable expectation.⁴⁸ Part of the emphasis on shared decision making around antiamyloid mAbs is

grounded in the idea that there will not be a “one-size-fits-all” formula for judging whether these treatments are right for an individual patient. Here, it will be prudent to draw upon experience from other areas of neurology that routinely weigh evidence-based data and uncertainties among treatment options.

As trials of antiamyloid mAbs in AD continue to develop, steps must also be taken to ensure that these studies include a diverse range of participants reflective of real-world clinical neurology. This lack of diversity has been a clear shortcoming in AD clinical trials to date, which potentially undermines the generalizability of results.⁴⁹ In the phase 3 aducanumab and lecanemab trials,^{5,15} only 0.6% and 2.5%, respectively, of participants were Black and just 1.5% and 12.4%, respectively, were Hispanic. Underrepresentation in clinical trials is particularly problematic when paired with the findings that the incidence and prevalence of dementia is dramatically higher in these populations compared with White populations.^{50,51} Although a detailed consideration of the causes of these disparities is beyond the scope of this article, relevant factors include lack of awareness and access, cultural and language barriers, provider and investigator bias, financial burdens, and distrust sowed through inappropriate medical care and research practices with minoritized persons.⁵² To sustainably diversify clinical trial recruitment for the betterment of patient care, it will be critical for research centers to build infrastructure for effective outreach, develop supportive and long-term relationships with minoritized communities that expand awareness around issues related to cognition and aging, and enhance diversity of personnel involved in AD clinical trials.⁵³

With emerging therapeutics comes the need to close longstanding imbalances between the prevalence of AD and the number of qualified clinicians supporting its care. In comparison with the nearly 7 million people in the United States with AD,¹ fewer than 600 physicians are certified by the United Council for Neurologic Subspecialties in Behavioral Neurology and Neuropsychiatry. Although this figure does not include other clinician colleagues who directly diagnose and treat AD (and thus underestimates the true size of the AD clinician workforce), it, nonetheless, underscores that effectively implementing new treatments will require significantly expanding expertise in and access to those therapies. Collaboration of subspecialists with general neurologists, advanced practice providers, geriatricians, and others will thus be at a premium. In this effort, care must be taken to avoid exacerbating preexisting severe racial and ethnic disparities in diagnosis and treatment.⁵⁴

Conclusions

Recent developments with antiamyloid mAbs include nuance and limitations but represent a step in the right direction for patients with AD. As with developments over time in disease-modifying therapies for other complex disorders (e.g., HIV and AIDS, hypertension, multiple sclerosis), there remains reason for optimism that antiamyloid mAbs may facilitate

slowing of the disease process in some patients with AD and may contribute to precision-based patient selection and combination regimens in the future. In this new era, ensuring a breadth and depth of expertise in these therapeutic options and effective patient selection, administration, and monitoring protocols across neurology practices will be crucial to optimize patient outcomes and enable future advances.

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