Anti-Amyloid Therapies for Alzheimer's Disease and Amyloid-Related Imaging Abnormalities: Implications for the Emergency Medicine Clinician

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Alzheimer's disease is the neurodegenerative disorder responsible for approximately 60% to 70% of all cases of dementia and is expected to affect 152 million by 2050. Recently, anti-amyloid therapies have been developed and approved by the Food and Drug Administration as disease-modifying treatments given as infusions every 2 to 5 weeks for Alzheimer's disease. Although this is an important milestone in mitigating Alzheimer's disease progression, it is critical for emergency medicine clinicians to understand what anti-amyloid therapies are and how they work to recognize, treat, and mitigate their adverse effects. Anti-amyloid therapies may be underrecognized contributors to emergency department visits because they carry the risk of adverse effects, namely amyloid-related imaging abnormalities. Amyloid-related imaging abnormalities are observed as abnormalities on magnetic resonance imaging as computed tomography is not sensitive enough to detect the microvasculature abnormalities causing vasogenic edema (amyloid-related imaging abnormalities-E) microhemorrhages and hemosiderin deposits (amyloid-related imaging abnormalities-H). Patients presenting with amyloid-related imaging abnormalities may have nonspecific neurologic symptoms, including headache, lethargy, confusion, and seizures. Anti-amyloid therapies may increase risk of hemorrhagic conversion of ischemic stroke patients receiving thrombolytics and complicate the initiation of anticoagulation. Given the novelty of anti-amyloid therapies and limited real-world data pertaining to amyloid-related imaging abnormalities, it is important for emergency medicine clinicians to be aware of these agents. [Ann Emerg Med. 2025;85:526-536.]

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INTRODUCTION

Alzheimer's disease is a neurodegenerative disorder responsible for approximately 60% to 70% of dementia. It affects more than 55 million people worldwide and is predicted to reach 152 million by 2050.[1] This increase is largely attributable to an aging and growing population.[2] Alzheimer's disease occurs over the age of 65 years in 95% of cases and can be either sporadic or familial in nature.[3] In the United States, Alzheimer's disease affects 6.7 million and is the sixth leading cause of death.[4] Given the increasing prevalence of Alzheimer's disease, understanding the pathologic processes leading to its development and the potential adverse effect of emerging disease-modifying therapy is of utmost importance for emergency medicine. Emergency departments (EDs) worldwide are increasingly providing care for persons living with dementia, with a multitude of challenges associated with detection, communication, decisionmaking, best practices, and care transitions.[5-7]

As the main neuropathological features of Alzheimer's disease are represented by extracellular deposits of β-amyloid plaques, anti-amyloid therapies have been an area of intense research focus in the last several decades.[8] The first anti-amyloid therapy, aducanumab, was approved by the Food and Drug Administration (FDA) in 2021 and was recently voluntarily removed from the market by the manufacturer in 2024 after Medicare declined to cover it.[9] Lecanemab followed in approval in the United States in 2023, and a third anti-amyloid therapy, donanemab, was approved in the early summer of 2024.[8]

Although these medications are the first disease-modifying agents of their kind, potentially slowing the progression of Alzheimer's disease, they carry the risk of adverse effects, namely in the form of amyloid-related imaging abnormalities.[10] These adverse effects are observed as abnormalities on magnetic resonance imaging (MRI), with presentations ranging from asymptomatic MRI findings to severe neurologic symptoms such as lethargy, confusion, falls, and seizures as a result of encephalitis and microhemorrhages.[11,12] Given the novelty of anti-amyloid therapies and limited real-world data pertaining to adverse effects, it is important for emergency medicine clinicians to be aware of these medications and how to approach patients on anti-amyloid therapies. The purpose of this

narrative review is to introduce emergency medicine clinicians to the anti-amyloid therapies and the risk of adverse effects as they may precipitate ED visits and influence the diagnostic and therapeutic management of disease states, including acute ischemic stroke, seizures, headache, and venous thromboembolism.

Pathophysiology of Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder characterized by 2 hallmark pathologies: extracellular β-amyloid plaques and intracellular neurofibrillary tangles.[13] β-amyloid accumulation occurs over years and results in many cellular effects at the neurons, leading to neurodegeneration and cognitive deficits in a defined chronological order.[8] Although there are other genetic and cellular factors at play contributing to the development of Alzheimer's disease, and not every patient with a high burden of β-amyloid accumulation will develop it, it is a key factor in the pathology of Alzheimer's disease.[8] The β-amyloid accumulation initiates a neurodegeneration cascade, which includes inflammation, gliosis, neuronal damage, synaptic loss, and eventual neural death. β-amyloid exists in monomers, oligomers, fibrils, protofibrils, and aggregated plaques, providing a number of targets for Alzheimer's disease pharmacotherapies.[14] Thus, a number of anti-amyloid therapies have been tested that target β-amyloid accumulation, each with a unique binding profile.[15] Plaque β-amyloid, the only type of amyloid visualized on positron emission tomography, is markedly reduced by all anti-amyloid therapies.[16]

ANTI-AMYLOID THERAPIES

Anti-amyloid therapies are the first disease-modifying treatments for Alzheimer's disease. They include active immunotherapies, passive immunotherapies with anti–β-amyloid antibodies, and monoclonal antibody therapy.[8] See Figure 1 for unique binding sites of anti-amyloid therapies.[17] Although each anti-amyloid therapies has a different target, the main mechanism of β-amyloid reduction is likely through microglia activation and subsequent phagocytosis and cell degradation.[16]

The first anti-amyloid therapy was aducanumab, a human monoclonal antibody selectively targeting different forms of both aggregated soluble and insoluble β-amyloid (Table 1).[11] The accelerated FDA approval of aducanumab was based on its ability to clear amyloid from the brain despite not showing meaningful clinical improvement.[9,18] It was denied approval in Europe, and when Medicare

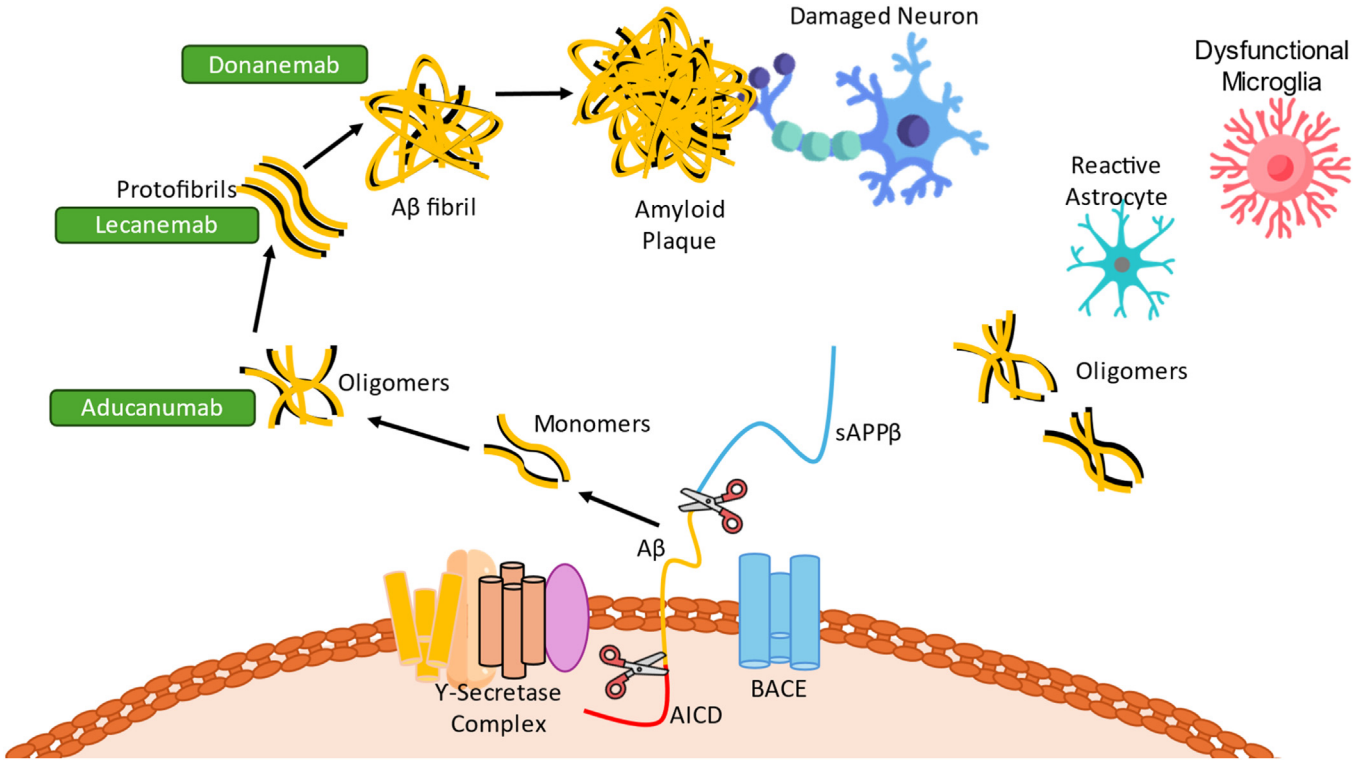

Figure 1. Molecular targets of anti-amyloid treatments. Mechanism of action of anti-amyloid therapies for treatment of Alzheimer's disease targets extracellular amyloid. AICD, amyloid precursor protein intracellular domain; BACE, β-secretase; sAPPβ, soluble amyloid precursor protein-β; Aβ, amyloid-beta.

Table 1. Anti-amyloid therapies.[8,9,13,15]

Agent	Mechanism	Dose	Efficacy	Adverse Effects	Comment
Aducanumab	Human monoclonal antibody selectively targeting different forms of aggregated soluble and insoluble β-amyloid	1 mg/kg intravenous infusion every 4 weeks titrated to a dose of up to 10 mg/kg over a 6-mo period	Cognitive decline slowed in high-dose aducanumab group of the EMERGE study only; no difference in ENGAGE study	Amyloid-related imaging abnormalities-E: 26% of low dose groups; 35%-36% of high-dose groups Amyloid-related imaging abnormalities-H: 16% of low dose groups; 19%-20% of high-dose groups	**Withdrawn from US market** after Medicare denied reimbursement
Lecanemab (Leqembi)	Humanized IgG1 antibody targeting soluble β-amyloid oligomers	10 mg/kg intravenous infusion every 2 wk	CLARITY-Alzheimer's disease study showed modest, statistically significant improvement in cognitive decline at 18 mo	Infusion reactions: 26.4% vs 7.4% placebo Amyloid-related imaging abnormalities-E: 12.6% vs 1.7% placebo Amyloid-related imaging abnormalities-H: 14% vs 7.7% placebo	High participant/family burden Annual cost $26,500 Medicare covers 80% cost
Donanemab (Kisunla)	Targets pyroglutamine modification present only in brain β-amyloid plaques	700 mg for the first 3 doses and 1,400 mg thereafter every 4 wk	Significant improvement in cognitive decline at 18 mo, particularly for patients with a low/medium tau population	Amyloid-related imaging abnormalities-E: 24% vs 1.9% placebo Amyloid-related imaging abnormalities-H: 19.4% vs 7.4% placebo	Potential to stop therapy when amyloid is removed Lower participant/family burden due to monthly infusions Annual Cost and Medicare coverage not yet available

Amyloid-related imaging abnormalities-E, amyloid-related imaging abnormality (edema); amyloid-related imaging abnormalities-H, amyloid-related imaging abnormality (hemosiderosis)

declined to cover its treatment, it was withdrawn from the market in 2023.[8,9,18]

Lecanemab is a humanized IgG1 antibody targeting soluble β-amyloid protofibrils.[15] In addition to its anti–β-amyloid effects, it blocks fibrinogen's ability to bind to β-amyloid, which may also play a role in disease progression (Table 1).[19] It was FDA-approved through an accelerated pathway in January 2023 based on its ability to clear amyloid, then traditionally approved in July 2023 based on the results from the CLARITY-Alzheimer's disease trial.[20] This 18-month, multicenter, double-blind, randomized trial of 1,795 patients with early Alzheimer's disease found that there was a 27% reduction in cognitive decline with lecanemab compared with placebo, measured using the Clinical Dementia Rating–Sum of Boxes from baseline to 18 months.[20] Of note, women enrolled in the study experienced less response to lecanemab.[21] Neuroimaging changes noted as amyloid-related imaging abnormalities with cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis (collectively known as amyloid-related imaging abnormalities-H) occurred in 26.4% of patients, whereas amyloid-related imaging abnormality with edema or effusions (known as amyloid-related imaging abnormalities-E) occurring in 12.6% of patients.[20] Treatment is covered by Medicare, although it is mandatory that the prescribing physician enters each patient into a federal registry given risk of adverse effects.[22] Although lecanemab offers promise in that it demonstrated a slowing in cognitive decline, some experts advocate for a minimal clinically important difference of 0.74 points on Clinical Dementia Rating – Sum of Boxes for anti-amyloid therapies relative to placebo

in order to justify the risk of amyloid-related imaging abnormalities.[23,24] This was not met as the difference in Clinical Dementia Rating–Sum of Boxes was 0.45, suggesting that adverse effects should be carefully weighed against the potential slowing of cognitive decline.

A third anti-amyloid therapy, donanemab, approved by the FDA in June 2024, is a humanized monoclonal antibody (Table 1). It was not granted an accelerated approval pathway and thus was traditionally approved. Unlike previous anti-amyloid therapies, it targets a pyroglutamine modification present only in brain β-amyloid plaques (Figure 1).[13] The TRAILBLAZER-ALZ 2 trial was a multicenter, randomized, double-blind, placebo-controlled, 18-month study that enrolled 1,736 patients with early Alzheimer's disease.[12] The primary endpoint of change was measured by another clinical trial centric scale—the integrated Alzheimer Disease Rating Scale score—that showed a slowing of cognitive decline in the donanemab group, particularly for patients with a low/medium tau (thought to correlate with less advanced Alzheimer's disease).[12] Similar to lecanemab, amyloid-related imaging abnormalities were common, with amyloid-related imaging abnormalities-E occurring in 24% of patients and amyloid-related imaging abnormalities-H in 19.7%.[12] Most of the amyloid-related imaging abnormalities (combined) were asymptomatic. Donanemab is easier to administer relative to lecanemab (once monthly instead of twice monthly infusions), and therapy may potentially be stopped once a substantial amount of amyloid is removed. Of note, the 1-year minimal clinically important difference for the integrated Alzheimer Disease Rating Scale is 5 points for Alzheimer's disease and 9 points for Alzheimer's disease with mild dementia.[25] Based on these cutoffs, donanemab met the minimal clinically important difference, suggesting that the benefits may exceed the risk of adverse effects and cost of therapy.[12,25]

Many questions remain regarding which patients should be initiated on anti-amyloid therapies. There are no comparative studies between lecanemab and donanemab. The number needed to be treated to demonstrate a benefit for all anti-amyloid therapies was calculated between 14 and 18 patients with Alzheimer's disease.[24] Number needed to harm is more difficult to assess given the heterogenous nature of amyloid-related imaging abnormalities. Thus, we are currently at the forefront of disease-modifying therapeutic development for Alzheimer's disease, and given the risk in an anticipated number of patients likely to develop Alzheimer's disease in the next few decades, ED clinicians will increasingly see patients on anti-amyloid therapies.[1]

Adverse Effects

Adverse effects of anti-amyloid therapies include a combination of vague signs and symptoms such as headache, dizziness, confusion, gait disturbance, and seizures, which may present as amyloid-related imaging abnormalities on MRI findings.[11,12,20] Neither the sensitivity and specificity nor the reliability of these components of the history and physical examination findings are known because diagnostic accuracy studies are nonexistent for anti-amyloid therapy adverse effects.

Amyloid-Related Imaging Abnormalities. Amyloid-related imaging abnormalities occur in 20% to 40% of patients.[11,12,20] The pathophysiology of amyloid-related imaging abnormalities is yet to be fully determined but is thought to be related to antibody-mediated breakdown of β-amyloid plaques, which results in the release of β-amyloid deposited in vessel walls.[10,26] This leads to increased cerebral amyloid angiopathy, alterations in perivascular clearance, and inflammation.[10] Cerebral amyloid angiopathy itself results partially from β-amyloid accumulation, although in Alzheimer's disease, deposits tend to be in the vessel walls, whereas in cerebral amyloid angiopathy, β-amyloid tend to be in the brain parenchyma.[27] In turn, this process causes edema and sulcal effusions. Amyloid-related imaging abnormalities-E is associated with vasogenic edema or sulcal effusion, whereas amyloid-related imaging abnormalities-H is named for hemosiderin deposition resulting from hemorrhage (Figure 2).[10] There appears to be an anti-amyloid therapy dose-dependent relationship to the development of amyloid-related imaging abnormalities-E, which in turn is a risk factor for incident amyloid-related imaging abnormalities-H.[27,28] Anti-amyloid therapies bind accessible β-amyloid in the vasculature, which disrupts the integrity of the vessel wall.[26] Furthermore, displacement of β-amyloid from the plaques to the vessel walls can worsen the severity of preexisting cerebral amyloid angiopathy. This results in subsequent extravasation and leakage of blood products through damaged vessel walls.[26]

Few risk factors for amyloid-related imaging abnormalities have been elucidated. Risk of amyloid-related imaging abnormalities-E increases with the number of apolipoprotein gene e4 alleles, suggesting a genetic predisposition to both Alzheimer's disease and amyloid-related imaging abnormalities development.[29] Apolipoprotein gene-e4 expression is the strongest and most common genetic risk factor for late-onset Alzheimer's disease.[29-31] In a systematic review including more than 15,000 patients, apolipoprotein gene-e4 expression was the main risk factor for both amyloid-related imaging abnormalities-E and amyloid-related imaging

abnormalities-H.[32] Additionally, in nearly half of amyloid-related imaging abnormalities-E occurrences, there is concomitant amyloid-related imaging abnormalities-H, suggesting common pathophysiology.[33] Another risk factor for amyloid-related imaging abnormalities is cerebral amyloid angiopathy at baseline, which is present in approximately 50% of patients with Alzheimer's disease.[34] Cerebral amyloid angiopathy is a leading cause of lobar intracerebral hemorrhage (ICH), compounding the risk of amyloid-related imaging abnormalities.[35] Finally, amyloid-related imaging abnormalities is more common at initiation and titration of anti-amyloid therapies, with enhanced clinical vigilance recommended within 14 and 24 weeks of initiation of lecanemab and donanemab, respectively.[12,20]

Although amyloid-related imaging abnormalities is mostly asymptomatic or results in transient symptoms (eg, headache), it can result in severe morbidity, including lethargy, confusion, neuropsychiatric symptoms, and, in rare cases, seizures.[27] Amyloid-related imaging abnormalities tends to occur within the first 6 months of anti-amyloid therapy, requiring frequent MRI monitoring by the prescribing physicians during this period (eg, at 4 and 12 weeks, then less frequently).[12,20] Any patient with amyloid-related imaging abnormalities signs should have MRI monitoring every 4 to 6 weeks, and anti-amyloid therapy should be held until resolution. Both amyloid-related imaging abnormalities and clinical symptom severity are classified as mild, moderate, and severe and inform the decision to continue or suspend anti-amyloid therapies.[36] For severe amyloid-related imaging abnormalities (eg, amyloid-related imaging abnormalities-H with macrohemorrhage) and symptoms (eg, incapacitating symptoms), the anti-amyloid therapy may be discontinued indefinitely.[12,20] Artificial intelligence

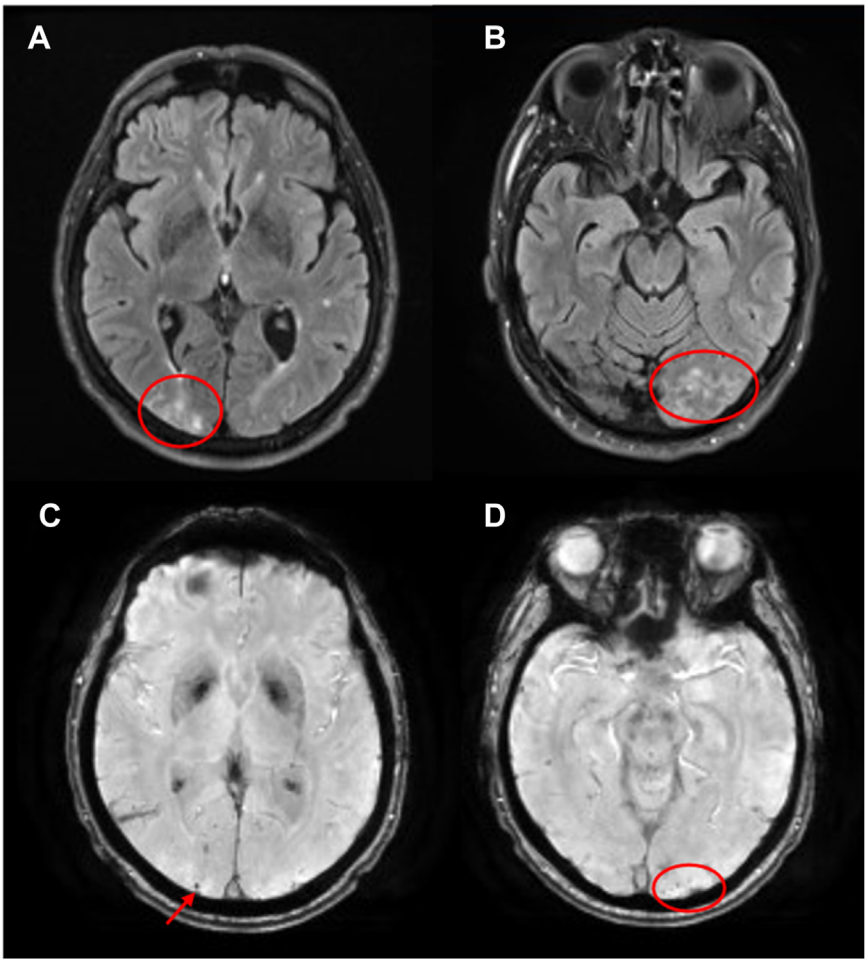

Figure 2. Example of cerebral amyloid angiopathy-RI edema and microhemorrhages, which has a similar radiographic appearance to amyloid-related imaging abnormalities. *A,* Right occipital parenchymal edema and sulcal effusion. *B,* Left occipital parenchymal edema and sulcal effusion. *C, D* Microhemorrhages in the regions of edema, single right occipital, and several clustered left occipital microhemorrhages. The authors acknowledge Dr. Petrice Cogswell and Dr. Jonathan Graff-Radford at Mayo Clinic-Rochester for providing these MRI images.

software added to radiologist review increases the diagnostic accuracy of both amyloid-related imaging abnormalities-E and amyloid-related imaging abnormalities-H.[37]

Amyloid-related imaging abnormalities may also lead to other downstream adverse effects. A case report from the CLARITY-Alzheimer's disease study describes fatal cerebral arteritis in an apolipoprotein gene-e4 homozygous 79-year-old after the third infusion of lecanemab.[38] The patient experienced seizures precipitated by multifocal swelling and a marked increase in the number of cerebral microhemorrhage. She progressively worsened despite high-dose corticosteroids and antiseizure medication and died 5 days later. Autopsy showed moderate severity Alzheimer's disease and severe cerebral amyloid angiopathy with perivascular lymphocytic infiltrates, reactive macrophages, and fibrinoid degeneration of vessel walls, suggestive of cerebral arteritis.[38] Another case report of an apolipoprotein gene-e4 homozygous 65-year-old with mild Alzheimer's disease on lecanemab (in the follow-up, open-label phase of the CLARITY-Alzheimer's disease study) described catastrophic hemorrhagic conversion following alteplase administration for acute ischemic stroke.[39] He presented with aphasia and left gaze preference due to acute ischemic stroke. The patient decompensated after most of the alteplase dose was administered. The computed tomography (CT) at that time showed extensive multifocal intraparenchymal hemorrhages. The alteplase was stopped, and hemostatic agents were administered. The patient died after family withdrew care.[39] This case suggests that thrombolytics for acute ischemic stroke should be avoided in patients taking anti-amyloid therapies for Alzheimer's disease, although more research in this area is needed.

Infusion Reactions. The most common adverse effect of anti-amyloid therapies is infusion reaction, which occurs in up to a third of patients.[12,20] In the lecanemab CLARITY-Alzheimer's disease study, most infusion reactions were mild or moderate (96%) and occurred with the first infusion (75%).[20,40] Infusion reactions appear to be less common with donanemab (8.7% of the TRAILBLAZER-ALZ 2 participants) but were nonetheless the primary reason for trial discontinuation in 3.6% of donanemab patients.[12] Infusion-related reactions including fever and flu-like symptoms (eg, chills, achiness, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.[40] These reactions typically occur within 30 minutes of the end of the infusion and can be treated with corticosteroids and antihistamines (eg, diphenhydramine). Anaphylaxis was rare in clinical trials.[11,12,20]

Risk of Bleeding on Concomitant Anticoagulants. As anti-amyloid therapies may cause amyloid-related imaging abnormalities-H, which can include ICH, anticoagulants should be prescribed very cautiously with anti-amyloid therapies. In both the lecanemab and donanemab studies, patients taking anticoagulants were not excluded from enrollment into clinical trials but comprised a minority of patients.[9,14] A patient from the CLARITY-Alzheimer's disease extension trial taking lecanemab and apixaban for atrial fibrillation experienced an ICH, calling to question if the benefit of concomitant anti-amyloid therapy and anticoagulant therapy exceeds the risk of bleeding.[41] Until more information is available, coadministration of anti-amyloid therapies and anticoagulants should be on a case-by-case basis with careful monitoring for amyloid-related imaging abnormalities-H and other life-threatening bleeding events.

In order to characterize the safety of anti-amyloid therapies, a Registry for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's disease was created by the Center for Medicare and Medicaid Services.[42] It collects information from clinicians to facilitate and ensure appropriate patient selection in the use and follow-up of anti-amyloid therapies. Although the availability of data and knowledge of these therapies remains limited, and the number of patients who are eligible and meeting criteria to receive therapies still early, the public health relevance and effect of these treatments for an aging population are significant. As more therapies are developed (including easier to administer therapies such as oral treatment rather than infusions) and become more cost effective, it will be critical for ED clinicians and patients to be prepared and aware of anti-amyloid therapy adverse effects and how to manage these.[43]

Approach to Identification of Anti-Amyloid Therapies and Treatment of Amyloid-related Imaging Abnormalities

There are several reasons why emergency medicine clinicians should be familiar with anti-amyloid therapies. First, patients may present to the ED with vague or nonspecific symptoms such as headache, dizziness, confusion, gait disturbance, and seizures that clinicians may not associate with anti-amyloid therapy, leading to premature closure in the diagnostic evaluation.[11,12,20] When combined with a history of Alzheimer's disease, these symptoms should trigger the emergency medicine clinician to look for anti-amyloid therapies in medication histories. Failing to connect these conditions could be potentially deleterious (eg, as in the case above where thrombolytics were administered for acute ischemic stroke symptoms, resulting in subsequent hemorrhagic conversion), especially if amyloid-related imaging abnormalities are missed or misinterpreted as acute ischemic stroke in the ED.[39] Second, a pragmatically challenging aspect of detecting amyloid-related imaging

abnormalities in the ED is the need for MRI, which is not routinely performed or available in many EDs.[26,44] Even if MRI is available, the reading radiologist may be unfamiliar with anti-amyloid therapies in order to diagnose amyloid-related imaging abnormalities. Depending on the size of the bleed and location, amyloid-related imaging abnormalities-H may be detected by CT, although it is best observed on MRI. It is characterized by the presence of hemosiderin, which manifests as parenchymal microhemorrhages or as leptomeningeal superficial siderosis. Amyloid-related imaging abnormalities-E is more problematic to detect in the absence of MRI. With an ever-aging population and different formulations of anti-amyloid therapies in development, including through subcutaneous administration, which may increase the future uptake, it is critical for health care systems to develop feasible diagnostic protocols by which to inform management decisions for the expected increase in patients on anti-amyloid therapies who will be presenting to EDs of all sizes.[16] As such, emergency physicians can expect to encounter patients taking anti-amyloid therapies more often, and devising strategies to identify a patient on anti-amyloid therapies and recognize their associated adverse effects is important. Even if the intervention is communication with the prescribing neurologist or geriatrician, which may help to prevent adverse effects in this delicate patient population.

As such, we propose a framework that emergency physicians can readily adopt in their workflow and environment to assist in evaluating and treating these patients (Table 2). First, we recommend assembling a trained multiprofessional team, including emergency physicians, neurology, radiology, pharmacists, informatics, geriatrics, and emergency medicine management, based on institutional resources, to develop a strategy to identify patients on anti-amyloid therapy and, particularly, those who may be presenting with adverse effects from anti-amyloid therapies, and also serve as a communication pathway to disseminate timely information on this rapidly evolving subject. This strategy may vary by institution, but an example could entail an automated best practice alert

Table 2. Key considerations for recognizing and treating ED patients presenting on anti-amyloid therapies.

Assemble a multidisciplinary team to establish communication pathways, identify ED patients on anti-amyloid therapies, and develop treatment protocols • Pathways should include a plan for patients presenting to the ED, hospitalized patients, and those visiting outpatient clinicians • If a multidisciplinary team is not feasible at a given site, at a minimum emergency physicians, neurologists, and radiologists should be able to recognize these patients and be aware of anti-amyloid therapy's adverse effects
Establish communication pathway with Alzheimer's disease expert or anti-amyloid therapy prescriber
Identify patients with Alzheimer's disease presenting to the ED on active anti-amyloid therapy • Consider incorporating electronic medical record alerts • Development a plan to discuss with a neurologist with expertise in Alzheimer's disease and radiologist training in detecting amyloid-related imaging abnormalities o May require transfer to higher level of care • Corroborate history with patient and/or caregiver • Determine if presentation is related to anti-amyloid therapy adverse effect (eg, ARIA-E or ARIA-H)
Determine if MRI evaluation is feasible for any patient population • If unable to be obtained locally, a pathway for transfer to a higher level of care should be established • We strongly recommend MRI prior to administration of thrombolytic in AIS or avoidance of thrombolytics • We recommend obtaining an MRI as soon as feasible for patients presenting with severe symptoms of amyloid-related imaging abnormalities (eg, seizures or status epilepticus, encephalopathy, altered mental status or stupor, focal neurologic deficits, visual changes or gait disturbances) • For minor symptoms (eg, headache, dizziness, and nausea), the decision to MRI can be deferred at the discretion of neurology consultation
Consider other common adverse effects: • Headache, dizziness, seizures: rule out amyloid-related imaging abnormalities; treatment per standard protocols • Infusion reactions: typically mild-moderate; treat with supportive care, intravenous fluids, analgesics, antiemetics as needed • Anaphylaxis: treatment does not change from standard management (eg, epinephrine, corticosteroids, and antihistamines)
Establish treatment contraindications: • Add to stroke protocols as relative contraindication (a relative contraindication is not an absolute contraindication and can be overridden if the benefits are deemed to outweigh the risks)
Considerations for non-anti-amyloid therapy-related ED complaints: • Need for acute anticoagulation requires careful consideration of risks vs benefits with Alzheimer's disease expert
Disseminate and update staff with education regularly

ED, emergency department; ARIA-H, amyloid-related imaging abnormality (hemosiderosis); ARIA-E, amyloid-related imaging abnormality (edema); AIS, acute ischemic stroke; MRI, magnetic resonance imaging.

when a patient presents with an active anti-amyloid therapy on their medication list. Medication reconciliation is challenging in the ED, with limited time and resources to track down medication lists, especially outside of the presenting institution.[45] Although technology can break down some barriers by allowing sharing of patient information across electronic medical records, these data are inconsistent. Additionally, patients with Alzheimer's disease may not be able to report that they are on an anti-amyloid therapy, so interviewing family or caregivers is imperative. Anti-amyloid therapies are biweekly or monthly infusions; as such, they are administered at infusion centers

Table 3. Clinical questions, uncertainties, and areas for future research focus.

Area of Focus	Questions
Optimal duration of MRI monitoring for amyloid-related imaging abnormalities detection	• What is the optimal timeline for MRI monitoring of patients on anti-amyloid therapies to detect amyloid-related imaging abnormalities early, especially regarding long-term monitoring?
Risk factors for amyloid-related imaging abnormalities	• What are the most predictive genetic, clinical, and imaging risk factors for amyloid-related imaging abnormalities, including the role of apolipoprotein gene-e4 and baseline cerebral amyloid angiopathy?
Diagnostic accuracy of amyloid-related imaging abnormalities in the ED	• Which patients benefit most from access to MRI? • How can amyloid-related imaging abnormalities be reliably diagnosed in the ED, particularly in centers with limited MRI access? • Can amyloid-related imaging abnormalities symptoms and presentations be identified without MRI?
AIS and thrombolytics	• Does thrombolysis for AIS worsen amyloid-related imaging abnormalities-H in patients on anti-amyloid therapies? • How should amyloid-related imaging abnormalities be managed in patients presenting with stroke-like symptoms?
Concomitant use of anticoagulants and anti-amyloid therapies	• Which patient-specific factors and disease states warrant anticoagulation initiation in patients on anti-amyloid therapies? • What is the bleeding risk associated with the combination of anti-amyloid therapies and anticoagulants in patients with Alzheimer's disease? How should anticoagulation be managed? • When should anti-amyloid therapies be discontinued when anticoagulation is needed?
Concomitant use of antiplatelet therapy and anti-amyloid therapies	• Can antiplatelet therapy be safely used in patients on anti-amyloid therapies? • Does antiplatelet therapy affect the risk of amyloid-related imaging abnormalities or other adverse effects?
Real-world data	• How do real-world clinical outcomes of anti-amyloid therapy treatment compare to trial results, particularly in terms of adverse effects, efficacy, and quality of life? • How often do patients present to the ED on anti-amyloid therapies? What are common ED presentations? • How often are anti-amyloid therapies the cause of ED visits? What frequency of anti-amyloid therapy-related conditions are undetected/unrecognized in the ED? During hospitalization?
Effect of anti-amyloid therapy discontinuation on disease progression	• What are the effects of stopping or interrupting anti-amyloid therapy on disease progression in patients with Alzheimer's disease? • Should anti-amyloid therapies be discontinued following an ED visit? If so, under what circumstances?
Education on anti-amyloid therapies	• What educational interventions are most effective in improving patient and caregiver knowledge about anti-amyloid therapies, amyloid-related imaging abnormalities, and the risks associated with treatment? • What educational interventions are most effective in improving emergency medicine clinician knowledge about anti-amyloid therapies, amyloid-related imaging abnormalities, and the risks associated with treatment?

MRI, magnetic resonance imaging; *ED*, emergency department; *AIS*, acute ischemic stroke.

and may not be on traditional medication lists. Therefore, it is important to specifically ask if the patient receives regular infusions for Alzheimer's disease. If anti-amyloid therapy is corroborated with the patient or family, then the multidisciplinary team of a neurologist and radiologist should be alerted if the patient's complaint is likely due to the anti-amyloid therapy (eg, amyloid-related imaging abnormalities-related symptoms) or the presenting complaint could affect anti-amyloid therapy (eg, a complaint necessitating anticoagulation therapy). This process could be similar to a stroke "code" notification.

If the presenting complaint is likely due to amyloid-related imaging abnormalities, an MRI should be obtained if the symptoms are moderate or severe (eg, seizures, altered mental status) or if acute ischemic stroke is suspected. The challenges of obtaining an MRI in the ED are well documented, and even the most well-resourced institution may not have 24/7 access.[44] This may require transfer to an outside institution (eg, similar to how patients with acute ischemic stroke may be transferred to a comprehensive stroke center). For patients presenting with stroke-like symptoms on anti-amyloid therapy, we recommend strongly weighing the risk of hemorrhage against the benefit offered by thrombolytics. Whether thrombolytics exacerbate amyloid-related imaging abnormalities-H has not been explicitly studied.[35] Although not an absolute contraindication to thrombolysis, we recommend obtaining an MRI prior to administration of thrombolysis. Endovascular thrombectomy is reasonable in patients on anti-amyloid therapies with an accessible occlusion.

In patients on anti-amyloid therapies presenting to the ED with indications for new initiation of anticoagulant therapy (eg, venous thromboembolism, atrial fibrillation, or acute myocardial infarction), the decision to initiate an anticoagulant should be weighed very cautiously given the increased risk of bleeding posed by anti-amyloid therapy. For short-term anticoagulation for acute thrombosis, an interruption of anti-amyloid therapy for a short time may be warranted. Particularly for long-term anticoagulant use for atrial fibrillation, ED clinicians should rely on cardiology and the anti-amyloid therapy prescriber to determine an appropriate course of action.

Antiplatelet therapy may be associated with less risk of ICH relative to that of anticoagulants.[35] The CLARITY-Alzheimer's disease trial showed that patients demonstrated lower rates of amyloid-related imaging abnormalities-E, microhemorrhages, and cortical superficial siderosis in patients receiving antiplatelet therapy and lecanemab rather than lecanemab alone, suggesting that antiplatelet therapy is safe.[20] Furthermore, the Restart or STop Antithrombotics Randomized Trial included 537 patients with a recent ICH who were previously on antiplatelet therapy for secondary prevention, randomized to either restart or discontinue aspirin, and found no difference in ICH recurrence between the 2 groups.[46] Accordingly, it is reasonable to initiate or continue antiplatelet therapy in patients receiving anti-amyloid therapies, although the risks and benefits should be carefully considered. Dual antiplatelet therapy remains an area of clinical uncertainty in patients receiving anti-amyloid therapies.

Overall, communication between the ED clinician, neurologist, radiologist, anti-amyloid therapy-prescribing physician, and the patient and family or caregiver is important to ensure that patients are appropriately treated to mitigate the risks and maximize the benefits of anti-amyloid therapies.[7] Currently, there are several areas of uncertainty in the emergency medicine clinical practice that present many opportunities for future research in this area (Table 3).

Anti-amyloid therapies are novel disease-modifying therapies for Alzheimer's disease associated with serious adverse effects, including amyloid-related imaging abnormalities-E and amyloid-related imaging abnormalities-H. Emergency medicine clinicians should be aware of the risks of anti-amyloid therapies, especially in patients presenting to the ED with neurologic symptoms, including acute ischemic stroke. Special consideration should be given to the initiation of thrombolytic and anticoagulant therapy in patients on anti-amyloid therapies to minimize risk of amyloid-related imaging abnormalities.

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