Q3 Anti-Amyloid Therapies for Alzheimer Disease

Which *one* of the following statements about anti-amyloid therapies for Alzheimer disease is *false*?

- ❍ 1. They have shown evidence for slowing clinical disease progression.
- ❍ 2. Eligibility criteria would include the confirmation of the presence of amyloid in the brain by either amyloid-PET scan or CSF analysis.
- ❍ 3. Treatment would be reserved for patients with moderate to severe disease.
- ❍ 4. Follow up magnetic resonance imaging of the brain is required to screen for development of amyloid-related imaging abnormalities.

Educational Point: As the Canadian population ages, the prevalence of dementia due to Alzheimer disease (AD) is increasing. Development of novel pharmacologic therapies for AD has been challenging, with no new treatment for AD approved in Canada since 2004. **In a phase 3 study published in 2022, participants receiving lecanemab – an anti-amyloid**

monoclonal antibody – demonstrated a 27% slowing of clinical disease progression over 18 months compared with those receiving placebo. Further, a phase 3 study of the anti-amyloid monoclonal antibody donanemab demonstrated a 38% slowing of clinical disease progression compared with placebo among participants with low to medium levels of tau pathology, representing an earlier stage of AD. While these differences were statistically significant, debate about the clinical significance of these findings has been ongoing. As of July, 2024, neither of these are yet approved for use in Canada.

Patient eligibility for anti-amyloid therapy will be based on numerous factors. Treatment is indicated for individuals with mild cognitive impairment (defined as objective cognitive abnormality on testing with loss of independence for at least 1 instrumental activity of daily living) due to underlying AD.

Biological AD is defined as the presence of pathologic brain accumulation of β-amyloid and phosphorylated tau. **For anti-amyloid antibody therapy to be considered, amyloid presence must be confirmed via biomarker testing such as amyloid-positron emission tomography (amyloid-PET) scans or cerebrospinal fluid (CSF) analysis via lumbar puncture.** Access to amyloid-PET and CSF analysis is currently limited to specialized memory clinics in Canada, so interested patients will need referral to specialist care.

Both lecanemab and donanemab are administered as intravenous infusions given over approximately 1 hour per infusion. Lecanemab requires infusions every 2 weeks, while donanemab is infused once monthly. Duration of therapy is typically 18 months, though long-term extension studies are investigating longer treatment courses.

Anti-amyloid antibody therapy is associated with risks – such as amyloid-related imaging abnormalities (ARIA), which may represent cerebral edema or cerebral hemorrhage – in up to 37% of treated individuals. Most instances of ARIA are asymptomatic, though 3% to 6% may be symptomatic, causing headache, dizziness, confusion, visual disturbance, or focal neurologic manifestations. Symptomatic ARIA usually resolve following cessation of anti-amyloid antibody treatment, though rarely may require intravenous or oral corticosteroid therapy and may not fully resolve. **Baseline and multiple routine follow-up MRI scans of the brain are required to monitor patients for risk and development of ARIA,** directed by specialist care, though this may also engage primary care practitioners.

Early cognitive assessment is warranted, as benefits of anti-amyloid therapy appear greater in earlier stages of AD, and patients and families may raise cognitive concerns with physicians earlier if anti-amyloid treatments are approved.

Box 1. Patient factors contraindicating lecanemab use

- Cognitively intact status, defined as normal performance on full objective cognitive testing
- **Moderate to severe dementia, defined as cognitive impairment sufficient to impair at least 1 basic activity of daily living (eg, dressing, hygiene)**
- Non–Alzheimer disease dementia
- Baseline MRI scan with evidence of substantial cerebral ischemic or hemorrhagic disease, or patient inability or unwillingness to undergo multiple MRI scans
- Anticoagulant use
- Unwillingness to accept multiple intravenous infusions or subcutaneous injections for 18 months or longer
- Substantial frailty or multiple medical comorbidities (eg, stroke, seizure disorder, bleeding disorders, immunologic disorders) that reduce resilience to intensive treatment and potential side effects

MRI—magnetic resonance imaging.

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In the United States, lecanemab costs $26 500 per year of treatment. Canadian pricing has yet to be determined. Other barriers to treatment may include limited access to cognitive specialists, and limited MRI and infusion site capacities.

The correct answer is 3.

Reference: Frank A, Frank C, and Molnar F. Potential of anti-amyloid therapies for patients with Alzheimer disease in Canada. *Can Fam Physician* 2024; 70: 537-8.
Link: https://www.cfp.ca/content/70/9/537.long
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