Potential of anti-amyloid therapies for patients with Alzheimer disease in Canada

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As the Canadian population ages, the prevalence of dementia due to Alzheimer disease is increasing,[1] placing substantial stress on affected individuals, their loved ones, and society as a whole. Development of novel pharmacologic therapies for Alzheimer disease has been challenging, with no new treatment for Alzheimer disease approved in Canada since 2004.[2] 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 (based on cognitive and functional measures).[3] This represents approximately 4 to 5 months of delay in disease-related clinical progression over 1.5 years.[4] Further, a phase 3 study of the anti-amyloid monoclonal antibody donanemab demonstrated a 35% slowing of clinical disease progression compared with placebo among participants with low to medium levels of tau pathology, representing an earlier stage of Alzheimer disease.[5] While these differences were statistically significant, debate about the clinical significance of these findings has been ongoing. Lecanemab and donanemab were under review by Health Canada as of July 2024 and are not yet approved for use in Canada.

In 2022 an application to Health Canada for approval of aducanumab, an earlier anti-amyloid agent, was withdrawn.[6] A commentary published in *Canadian Family Physician* discussed this process.[7] If Health Canada approves lecanemab or donanemab, family physicians will likely encounter many patients with questions about these treatments.

Eligibility for anti-amyloid therapy

Patient eligibility for anti-amyloid therapy will be based on numerous factors, as outlined in appropriate use recommendations for lecanemab in the United States by Cummings et al.[8] Treatment is indicated for individuals with mild cognitive impairment (defined as objective cognitive abnormality on testing with preserved independence for daily functioning) or mild dementia (defined as objective cognitive abnormality on testing with loss of independence for at least 1 instrumental activity of daily living) due to underlying Alzheimer disease.

Biological Alzheimer disease is defined as the presence of pathologic brain accumulation of β-amyloid and phosphorylated tau.[9] 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. Substantial progress has been made in the development of blood tests for amyloid, tau, and phosphorylated tau biomarkers, which may one day replace the use of amyloid-PET scans or CSF analysis for patients needing to qualify for anti-amyloid therapies.[10]

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.[11,12] Lecanemab is also being developed as a weekly subcutaneous injection that could be administered at home. Duration of therapy is typically 18 months, though long-term extension studies are investigating longer treatment courses. Long-term effects of anti-amyloid therapies are not yet known.

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.[3,5] 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.[8] Baseline and multiple routine follow-up magnetic resonance imaging (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. Urgent unplanned MRI scans will be needed for patients with symptomatic ARIA. Genotyping for apolipoprotein E, also directed by specialist care, can help stratify patients for risk of ARIA, with the *e4/e4* genotype associated with greatest risks.[3,5]

Drawing on the appropriate use recommendations for lecanemab,[8] we have summarized key criteria that would exclude patients from treatment in **Box 1**; Cummings et al provide an extensive list of inclusion and exclusion criteria.[8] Family physicians who identify exclusion criteria can direct patients and families to more traditional approaches to dementia care. Patients should be told that anti-amyloid therapy can slow disease progression but is not a cure. Early cognitive assessment is warranted, as benefits of anti-amyloid

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.

therapy appear greater in earlier stages of Alzheimer disease,[5] and patients and families may raise cognitive concerns with physicians earlier if anti-amyloid treatments are approved. Motivated patients (ie, those willing to undergo extensive investigations and treatment) who do not have exclusionary factors can be referred to a specialized memory clinic for further evaluation and potential anti-amyloid treatment, where available.

Clinical trials testing lecanemab and donanemab did not include adequate numbers of people from diverse populations in their samples.[3,5] Future clinical trials must achieve more representative inclusivity during recruitment to ensure safety and efficacy are proven in the general population.

Potential barriers to access

If Health Canada approves anti-amyloid antibody therapies for treatment of patients with Alzheimer disease, additional issues will arise regarding reimbursement for treatment costs. In the United States, lecanemab costs $26,500 (US) per year of treatment.[13] Canadian pricing has not yet been determined. A full pharmacoeconomic assessment of anti-amyloid therapy in the Canadian context will be necessary. Over time it is hoped that privately funded employer-based insurance plans will provide reimbursement for these treatments, but provincial and territorial drug coverage will likely be limited to focused populations based on cost-benefit analyses. Less expensive blood tests for biomarkers would improve equitable access to treatment, though other access barriers remain, such as limited understanding of dementia among the public, limited supplies of family physicians and cognitive specialists, and limited MRI and infusion site capacities. A multidisciplinary group of dementia experts has been convened to explore ways the Canadian health care system may evolve to accommodate the use of anti-amyloid therapies.[14]

Conclusion

As real-world evidence for use of anti-amyloid antibody therapies accumulates, and as we learn more about their efficacy and safety in various target populations, appropriate use recommendations for these treatments will be adjusted. It is hoped that anti-amyloid therapies will be the first of many advancements in this field that improve quality of life of individuals and families suffering from the effects of dementia and Alzheimer disease.

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Competing interests
None declared

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