Accelerating the Journey from Idea to Utilization

Leqembi: A New Therapy for Alzheimer's Disease

About I2U

Idea to Utilization (I2U) is an initiative committed to identifying and addressing the barriers impeding the uptake of breakthrough medicines across Canada. With foundational funding from Novartis, this collaborative mechanism is being led by Santis Health and guided by an independent panel of advisory board experts. **To learn more, visit www.i2u.ca**

ABSTRACT

Current treatments for Alzheimer's Disease (AD) only treat symptoms and do not slow its progression, posing a significant burden on the Canadian economy and health care system for both patients and their care partners - costing approximately $10.4 billion. Leqembi is a new FDA-approved drug that helps slow the progression of the Alzheimer's when taken in the early stages of the disease. This case study focuses on potential future implementation challenges associated with delivering Leqembi that will need to be considered if market approval Is granted by Health Canada. These challenges include: 1) the lack of screening protocols to diagnose Alzheimer's disease at its early stages; and 2) limited diagnostic testing capacity needed to monitor patients, especially PET and MRI. Leqembi provides patients with MCI/ mild Alzheimer's disease and their families new hope and an option to delay the progression of this devastating disease. However, its implementation and impact are dependent on two key factors: 1) developing/adapting a screening protocol for early diagnosis of Alzheimer's and 2) enhancing health system infrastructure in the area of diagnostic imaging.

Leqembi: Slowing the Progression of Alzheimer's Disease

Alzheimer's disease is an illness that causes physiological changes to the brain, i.e., an accumulation of amyloid plaques and neurofibrillary, or tau tangles, that affect one's memory, thinking, and communication abilities. [i,ii] It is the most common cause of dementia and occurs most often in those ages 65 years or older, but can also present itself in patients as young as the age of thirty. Dementia is now the seventh leading cause of mortality globally.[iii] In 2020, about 600,000 Canadians were living with dementia – a number that is expected to almost triple to 1.7 million by 2050. Dementia also poses a significant burden on the economy and health care system, costing Canadians $10.4

billion in publicly-funded and out-of-pocket health care expenses and Organization for Economic Co-operation and Development (OECD) countries 1.3 trillion per year.[iv,v]

The only treatment options currently available target the symptoms of the Alzheimer's disease, at later stages of the disease, and these include cholinesterase inhibitors and glutamate antagonists. Leqembi (*lecanemab*) is a humanized IgG1 monoclonal antibody (beta-amyloid-directed monoclonal antibodies) for treatment of Alzheimer's disease.[vi] Leqembi is classified as a disease modifying therapy that slows the progression of the disease only when taken in the early stages of Alzheimer's (mild cognitive impairment and mild AD.) Therefore, timely diagnosis with biological confirmation of Alzheimer's disease pathophysiology – i.e., amyloid beta accumulation – is critical for Leqembi to be effective.

Mechanism and Delivery

Monoclonal antibodies target germs in our immune system including proteins.[vii] Leqembi specifically targets the amyloid beta protein and is effective in patients with mild cognitive impairment (MCI) or mild dementia stage of disease related to Alzheimer's only.[viii] Patients should be diagnosed clinically with MCI and confirmed biological pathology with an abnormal positron emission tomography (PET) scan, or the presence of amyloid beta protein measured in cerebral spinal fluid.[ix]

Overall, the treatment protocol of Leqembi can be broken down into four steps:

1. **Diagnosis of early onset of Alzheimer's disease**: Patients that present with typical signs and symptoms of affected memory and thinking skills undergo a PET scan or cerebral fluid analysis to determine the presence of amyloid-beta accumulation and determine clinical diagnosis of MCI due to Alzheimer's disease.[x]

2. **Leqembi administration**: Leqembi is administered intravenously once every two weeks with no dose titration required.

3. **Observation & follow-up**: Patients are treated based on a baseline MRI and monitored for potential side effects, particularly amyloid-related imaging abnormalities (ARIA), by conducting multiple MRI scans. It is recommended that monitoring with MRI occurs prior to the 5th, 7^{th,} and 14th infusions[xi], and thus the drug will need longer-term follow-up.

4. **Treatment duration:** Treatment is sustained until either all amyloid plaque is removed, or the patient progresses to later stages of disease.

Access in Canada and US

Currently, Leqembi has not yet received regulatory approval from Health Canada and is only available to Canadians who are participating in experimental drug trials.[xii] Earlier this year, Leqembi received FDA approval through an accelerated approval pathway based on "unmet medical need".[xiii] Given this FDA approval and the small number of available therapies for people with Alzheimer's disease, it is believed that Health Canada may also follow the US lead. As such, it is imperative to understand potential implementation challenges if it becomes available to fully capture the full system value of this drug. Leqembi costs about $26,500 US per year.[xiv]

Potential Future Implementation Challenges

Although Leqembi has not yet been approved in Canada, there are two main health system challenges that must be addressed for its effective implementation:

1. **There is no formal screening protocol to diagnose early stages of Alzheimer's disease**

   Given that Leqembi is only effective in those who are diagnosed with the preliminary stages of Alzheimer's disease, catching the early signs and symptoms of patients with MCI is essential for the administration of this drug. Unfortunately, there are no screening protocols in Canada for early diagnosis, and as a result, diagnosis of Alzheimer's typically occurs at advanced stages of the disease. To ensure early diagnosis, screening protocols need to include identifying the signs and symptoms of MCI, and confirmation using biologic tests.

   To provide Canadian physicians with screening protocols, there are American clinical practice guidelines for diagnosing and treating MCI available that guideline developers can either adopt or adapt to the Canadian context.[xv,xvi] Once a guideline is developed and its awareness is spread via hospitals and physician organizations, family doctors, geriatricians, and other clinicians in each of the provinces and territories can incorporate these protocols in their practice.

2. **Reimbursement and prescriptions will require access to biologic tests and side-effect monitoring with MRIs**

   For Leqembi to be reimbursed and prescribed by clinicians, a biologic diagnosis of MCI and capacity for physicians to monitor and manage potential side effects (i.e., ARIA) with multiple MRIs is required. Canada is currently lacking infrastructure

to biologically diagnose MCI with a limited number of PET scan machines, technology for cerebral spinal fluid analysis (lumbar puncture and sample analysis), and MRI machines across the country. Between 2019 and 2020, there were only 57 PET scans and 378 MRI units across Canada, representing a capacity per capita that is significantly lower than in most OECD countries.[xvii,xviii,xix] Furthermore, the pandemic has resulted in backlogs in diagnostic testing and procedures, which exacerbates delays, reduces screening capabilities, and prioritizes their use for acute patients.

More broadly, addressing these cultural and infrastructure issues in our health care delivery in Canada will also positively impact other diseases, and help prime the system for other breakthrough therapies. This includes shifting the health care system to be a more proactive and focused on preventing and / or delaying diseases, like Alzheimer's.

Conclusion

Leqembi provides patients with mild Alzheimer's disease and their families new hope and an option to delay the progression of this devastating disease. However, its implementation and impact are dependent on two key factors: 1) developing/adapting a screening protocol for early diagnosis of Alzheimer's and 2) enhancing health system infrastructure in the area of diagnostic imaging.

Ensuring equitable access to diagnostic tools – PET scans and cerebral fluid analysis – and MRIs to monitor patient's safety from potential side-effects should be strongly considered as Canada continues its clinical trials and as Leqembi undergoes Health Canada review. Additionally, prioritizing treating patients with acute care given all the health care backlogs and staffing / family doctor shortages is challenging not only for Leqembi but also during the roll-out of other breakthrough therapies.

Overall, this case study provides an excellent example of the importance of long-term cultural and infrastructure investments to achieve readiness for medical innovations. These changes aren't up to any one stakeholder to achieve – this must be a collaborative effort between government, academia, and industry.

References

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