Consensus Statement Regarding the Application of Biogen to Health Canada for Approval of Aducanumab

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ABSTRACT

Alzheimer's disease is a major cause of morbidity and mortality. Currently, there are no disease-modifying pharmacotherapies for this condition. Aducanumab, an amyloid beta-directed monoclonal antibody that targets aggregated forms of amyloid-beta in the brains of people with Alzheimer's disease, has raised hopes that such a therapy has been discovered, but its approval by the US Food and Drug Administration has engendered a good deal of controversy. A similar application for approval has been submitted to Health Canada. In response to this, a group of Canadian clinical dementia experts representing a number of organizations, including the Canadian Geriatrics Society, was convened by the Canadian Consortium on Neurodegeneration in Aging (CCNA) to discuss the evidence currently available on this agent and seek consensus on what advice they would offer Health Canada on the application. There was wide-spread agreement that it would be premature for aducanumab to receive approval for the treatment of Alzheimer's disease.

It was also noted that the Canadian health-care system is poorly prepared at this time to deal with a disease-modifying therapeutic with targeting, administration, and monitoring characteristics like aducanumab. In this paper, the consensus reached is presented along with its underlying rationale.

Key words: aducanumab, Alzheimer's disease, drug therapy

KEY POINTS

- Aducanumab is an amyloid beta-directed monoclonal antibody targeting aggregated forms of amyloid-beta in the brains of people with Alzheimer's disease.
- This agent was recently approved for the treatment of Alzheimer's disease by the US Food and Drug Administration and an application is being considered by Health Canada.
- The authors of this paper and the organizations they represent feel approval by Health Canada would be premature at this juncture, as there is a need for both wider dissemination of currently available information and additional data on the efficacy and safety of aducanumab.
- The Canadian health-care system is currently poorly prepared to deal with a disease-modifying therapeutic for Alzheimer's disease sharing the characteristics of this agent.

CONSENSUS STATEMENT

In response to Biogen's recent (May 2021) application to Health Canada for approval of aducanumab following its approval by the US Food and Drug Administration (FDA) for the treatment of Alzheimer's disease (AD),* leaders of our organizations and prominent Alzheimer's disease clinical experts in Canada met to discuss the situation.

All of us support the need for the research community and the pharmaceutical industry to remain dedicated to finding effective new treatments for all phases of AD, including the pre-dementia stage of mild cognitive impairment (MCI). We are also sensitive to the lack of an approved disease-modifying therapy for patients with AD, and to the fact that dementia advocacy groups have applauded the accelerated approval of aducanumab by the FDA in the US.

RECOMMENDATION TO HEALTH CANADA

The clinical dementia expert community in Canada has not seen all the evidence being brought forward by Biogen to support their application. Even so, what is available suggests aducanumab does not meet accepted criteria for clinical efficacy, safety, and risk/benefit of an agent for Alzheimer's disease that would justify Health Canada regulatory approval. The uncertainty about the phase 3 trials leaves our clinical and scientific community wanting more proof, as would come from a further phase 3 trial.

While we recognize the urgent need to give hope to patients and not needlessly delay the introduction of an effective therapeutic, introducing a medication that does not meet the threshold for clinically relevant benefit could, in fact, have detrimental effects. There are major questions about costs and benefits, coupled with the likelihood that, if approved, any such drug will be highly sought by those seeking any hope at any cost. Approval by Health Canada will have significant implications for further research into better treatments and will establish a very low benchmark for future approvals. For any such disease-modifying treatment introduced for AD, the risks of a very broad regulatory label based on biomarker outcome leaves the clinical community without guidance on how to use the treatment appropriately, including which patients should be treated, for how long, and with what measures of efficacy. The national academic and clinical dementia expert community commits to voluntarily participate in a broadly-based working group to advise Health Canada from a researcher/clinician perspective on how best to evaluate and introduce, if deemed sufficiently effective, an anti-amyloid disease-modifying therapy for AD in Canada.

COMMENTS ON THE CURRENT SITUATION

We wish to elaborate on a set of eight issues raised by the current situation.

Evidence of Aducanumab Efficacy

We are in a situation where all the relevant data supporting Biogen's application for approval of aducanumab as disease-modifying therapy for Alzheimer's disease, first to the FDA and now Health Canada, have not yet been published or otherwise made available to experts outside the FDA's expert advisory committee. The fact that the FDA's own advisory committee did not support approval of the application by Biogen to the FDA (10 of eleven members voted against approval, while the 11th member was undecided) must therefore stand as a major "red flag" in how Canadian regulatory bodies and health care practitioners assess this medication. A recent independent review from the Institute for Clinical and Economic Review[1] reached much the same conclusions. We urge Biogen to make all relevant data available for scrutiny, including outcomes in the open label long-term extension phase which have never been made public.

Evaluation Criteria

Based on the limited data made available to date, Canadian clinical dementia experts urge caution in the deliberations about approval by Health Canada at this time. Accepted criteria for gauging the clinical meaningfulness of any statistically significant treatment effect of an agent being evaluated for Health Canada for approval include: (a) the treatment should be biologically plausible; (b) there should be a dose response; (c) the effect size should be large enough to be at least clinically detectable; (d) there should be convergence of measures within

a trial; and, (e) there should be reproducibility between trials.[2] Based on the data we have seen thus far, aducanumab only meets the first and weakest of these criteria. Clinical efficacy has not been proven by the widely accepted FDA standard of two successful phase 3 studies. In this case, one study (EMERGE) met endpoints, while another study (ENGAGE) failed to do so. This does not provide sufficient converging evidence, and we feel the futility analysis that led to the early termination of the studies may have been correct. Post-hoc analyses, such as those used by Biogen showing success in subgroups at the highest dosage, are notoriously unreliable. The biomarker support critical for the FDA's approval—evidence of lowering amyloid levels within the brain—would only be sufficient if amyloid was a demonstrated and accepted surrogate measure that indicated dementia progression and/or reversal, which is not the case.[3] We are of the opinion that a further phase 3 high-dose trial is needed to assess whether aducanumab is truly a clinically efficacious agent.[4]

Third Trial Proposal

The alternative proposed by the FDA—that the medication be conditionally approved, but that another trial is undertaken and reported within nine years—is not sufficiently urgent or timely in its proposed time frame. We are convinced that trials of the desired magnitude could be undertaken and completed within a much shorter period when mandated.

Dangers of Premature Approval

While we recognize the urgent need to "give hope" with a "treatment that can be beneficial at the early stages of AD and MCI",[5] we believe introducing a medication with a limited (or perhaps not clinically relevant) benefit and with significant risks, including the high rate of amyloid-related imaging abnormalities with both brain swelling and microbleeds, could in fact have detrimental effects. It would: (a) set a bad precedent by establishing such a low bar for therapeutic success (the approval provided by FDA for aducanumab, based on a surrogate biomarker outcome, will promote others to seek the same indication without proving clinical benefits); (b) possibly impede recruitment into randomized control trials where placebos are compared with other promising agents; (c) lead to disillusionment and loss of confidence in the drug regulatory system if it later proves that the medication is not effective; (d) potentially detract from other elements of clinical care for AD by steering money and resources into setting up the infrastructure required for disease-modifying therapies; and (e) increase the burden on the health-care system and specialist physician resources in return for little gain.

Targeted Use

If the drug is approved in Canada despite the limited evidence, we strongly recommend that its labelling have important constraints that align with the specific population enrolled and safety measures taken in the studies that led to the drug's approval. This would include a labelled stage indication (i.e., "MCI due to Alzheimer's disease" or "Mild AD dementia"), since these were the inclusion criteria for the phase 3 studies. It should only be administered to individuals demonstrating abnormal presence of brain amyloid. Individuals should undergo MRI for pre-existing microhemorrhages (ARIA-H) prior to their receiving aducanumab, and after initiation of therapy, to monitor for the development of this complication. Guidance on what would be unacceptable MRI changes after initiation of therapy will have to be developed. This means the medication should only be used where there is sufficient rapid access to MRI to be able to safely monitor for amyloid-related imaging abnormalities (ARIA).

Lack of Readiness in Canada to Accommodate any Pharmacological Disease-Modifying Therapy for AD

The RAND Corporation, in a preparedness study of the Canadian health-care system,[6] highlighted current deficiencies. These are not insurmountable, but authorities should be well aware of the enormous changes that will be needed. The introduction of an effective anti-amyloid disease-modifying therapeutic agent for MCI or early AD dementia would likely require important changes in the delivery of dementia care in the following four areas.

a) In Canada, most care for dementia is currently provided in the primary care sector, but with disease-modifying therapies like aducanumab, there would be a need for a greater proportion of persons with suspected AD undergoing a specialist-based dementia evaluation as a prelude to the use of an intravenous, disease-modifying therapy for a subgroup of AD patients with specific characteristics. All Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTD)[7,8,9,10,11] have emphasized that most dementia care should and can be provided in the primary care sector. There are currently an insufficient number of specialists and memory clinics to accommodate a dramatic change in care patterns that approval of an expensive, disease-modifying therapy targeted to a particular subgroup of persons living with AD could require. The potential implications of such a shift in the locus of where dementia care is provided will require careful planning and resources require careful consideration by practitioners and policy-makers.

b) The evaluation of amyloid status as part of diagnostic assessment would become necessary, in our opinion. In all provinces and territories, amyloid PET scanning and lumbar puncture capacity (the current approaches to identifying underlying AD pathology) are presently limited, and serum amyloid biomarkers of AD remain unproven for clinical use.

c) Monthly intravenous infusions for thousands of individuals would become necessary for most disease-modifying therapeutics, and capacity for this is currently limited.

d) MRI for therapeutic follow-up would have to be much more accessible than is currently the case across Canada.

Amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhages, occurred in 35% of individuals who were treated with the highest dose of aducanumab in clinical trials.[4,12] Patients in the phase 3 trials of all anti-amyloid drug trials have been monitored with repeated, thin slice MRI scans before and after initiation of therapy, and immediately when any concerning symptoms such as headache, dizziness, or grogginess arose. There needs to be regular, scheduled access to MRI over the course of dose titration, with access to additional MR scanning if ARIA are observed. MRI access to follow therapy must be available for safety reasons if anti-amyloid disease-modifying therapy is introduced in Canada, and the medical community, hospitals, and provincial funding agencies must be mobilized to achieve this. Additionally, MRI protocols would need to be altered and neuroradiologists trained to detect ARIA.

Value for Investment

A cost/benefit analysis of aducanumab in the U.S. from the Institute for Clinical and Economic Review found "that the evidence is insufficient to conclude that the clinical benefits of aducanumab outweigh its harm" and that "the annual proposed cost would not be in alignment with its clinical benefits".[1] Given the single-payer health-care system in Canada, the benefits of an expensive, disease-modifying therapy for MCI or mild dementia due to AD will need to be balanced against other potential uses of limited public financial resources. For instance, potentially preventable dementia risk factors were responsible for up to 40% of dementia cases in evaluations by the Lancet Commission.[13] A companion paper noted that there are effective interventions for hypertension (including stroke prevention strategies), smoking cessation, diabetes prevention, and untreated mid-life hearing loss.[14] Aggressive public treatment interventions for these (or public programs on blood pressure control, prediabetes, or exercise) are feasible, would produce cost savings, and would likely considerably reduce number of individuals with dementia,[15] comparing favourably with the 20% slowing in the progression of cognitive decline which Biogen argues would occur with aducanumab. The national dementia strategy should be debating and comparing these alternatives. Furthermore, if covering the costs of treatment is left to personal financial resources, there will be unequal access to this agent in Canada, and families will be confronted with difficult—at times impossible—financial choices.

Further Work to be Done

Our organizations and the individual researchers and clinicians working in the field of dementia are willing to voluntarily participate in a broadly based working group to advise Health Canada from a researcher/clinician perspective on the complex issues raised by aducanumab and other disease-modifying therapeutics. Such a working group could collaborate with regulators to review the criteria for approval of disease-modifying therapies for neurocognitive disorders. It could also help define the requirements to use an anti-amyloid disease-modifying treatment in Canada. Among other groups, we believe it would be vital to also involve persons at risk for or living with dementia. We are committed to working with Health Canada and other authorities to define and implement solutions now to address Canada's "preparedness gap", and to prepare our health-care system for the introduction of effective disease-modifying therapies for dementia.

This statement was prepared and endorsed by members of the following organizations:

- Canadian Consortium on Neurodegeneration in Aging (CCNA) is a Canadian national umbrella organization for research on dementia funded by CIHR and partners with 350 researchers across Canada.
- Consortium of Canadian Centres for Clinical Cognitive Research (C5R) is a not-for-profit research network of 30 academic memory clinics and research sites across Canada that conduct clinical trials in the desire to research and develop treatments for patients with mild cognitive impairment, Alzheimer's disease, as well as other forms of dementia.
- Canadian Academy of Geriatric Psychiatry (CAGP) is a national organization of psychiatrists and health professionals dedicated to promoting mental health in the Canadian elderly population through the clinical, educational, research and advocacy activities of its membership.
- Canadian Geriatrics Society (CGS) is the professional society for Geriatric Medicine specialists and Care of the Elderly specialists, and has over 500 members representing such specialists, along with medical students and residents, as well as other physicians and members of allied health professions with an interest in the health care of older adults.
- Ontario Neurodegenerative Disease Research Initiative (ONDRI) brings together Ontario's research scientists and clinicians to tackle the complexity of dementia by studying multiple diseases related to neurodegeneration. ONDRI is funded by the Ontario Brain Institute.
- Toronto Dementia Research Alliance (TDRA) is a University of Toronto collaboration of scientists and clinicians which aims to better understand, prevent, and treat dementia, and embed research into care.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Chertkow has participated as an unpaid advisor in 2020 for establishment of an international database by Biogen.

Rockwood is Co-founder of Ardea Outcomes, which (as DGI Clinical) in the last three years has contracts with pharma and device manufacturers (Biogen, Hollister, Novartis, Nutricia, Roche, Takeda) on individualized outcome measurement. In 2019 he accepted an honorarium from Biogen for taking part in an interview.

Dr. Black discloses that in the last 5 years (2016-2021) she has received personal fees for ad hoc consulting from Hoffman LaRoche, Biogen, Pfizer, Eli Lilly, Novartis and Merck. She has also received personal fees for speaking from Biogen, Eli Lilly and Novartis. Dr. Black discloses support to her institution for contract research from Eli Lilly, GE Healthcare, Eisai Biogen, Genentech, Optina, Hoffman LaRoche, NovoNordisk, and UCB.

Dr. Borrie is principal investigator for Biogen and a sub-investigator for Eisai for two clinical trials and does not personally receive any compensation from Biogen.

Dr. Hsiung has received research support as a clinical trials site investigator from Anavax, Biogen, Eli Lilly and Roche.

Dr. Kirk has participated in and been recompensed by advisory boards for Biogen, Genzyme and Roche. He has also received compensation for speaking engagements with Biogen.

Dr. Masellis reports consulting fees from Biogen Canada relevant to the submitted work. Dr. Nygaard is a paid, independent consultant to Biogen Canada National Advisory Board.

Dr. Verret has received funds from Biogen (for the ENGAGE TRIAL). He is a member and has received funds for the advisory boards of Biogen, Roche, Abbvie; and has received funds from Biogen for continuous medical education.

David Hogan, Natalie Phillips, Manuel Montero-Odasso, Shabbir Amanullah, Christian Bocti, Howard Feldman, Morris Freedman, and Tarek Rajji report no conflicts of interest relating to this consensus statement.

*On July 8, 2021, the FDA announced that the indication for aducanumab would be limited to mild cognitive impairment and mild Alzheimer's disease

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