ADUHELM: RUSH TO JUDGEMENT?

BY THE NTG ADUHELM AND DOWN SYNDROME MEDICAL ADVISORY GROUP

SUMMARY

The authors raise issues related to Down syndrome and the use of Aduhelm, Biogen's new drug for use with early-stage Alzheimer's disease. Issues noted include a lack of data on applicability of drug with adults with Down syndrome, lack of protocols for its use by practitioners, and unknowns as to efficacy of the drug with presence of high amyloid load from early age. Authors recommend (a) including participants with Down syndrome in ongoing and further clinical trials and research, (b) assuring research-informed appropriate oversight over its usage, (c) developing protocols that guide assessment and decision-making for the use of the drug with this group, (d) screening systematically for early symptoms of AD, (e) determining optimal age for prophylactic use of drug, (f) involving families and caregivers in the prescribing and using decision-making process, and (g) providing orientation and education to healthcare providers and ancillary staff involved with use and aftercare.

Globally, people are living longer than ever before, including adults with intellectual disability. Age-associated physical and cognitive decline is commonly a part of the aging process that will eventually have an impact on most people. Some of these changes may be normal but some may herald the onset of dementia stemming from Alzheimer's disease (AD) and other neurodegenerative diseases. As noted by the WHO[1] and in the US National Plan to Address Alzheimer's Disease[2] many adults with an intellectual disability will face the same concerns about cognitive decline when they age and for the most part experience similar prevalence rates of dementia as the general population.[3] However, adults with Down syndrome, one of the most common forms of intellectual disability, have an extremely high risk for AD dementia. Therefore, they face a more substantial concern for developing cognitive decline due to the accumulation of beta amyloid protein, often starting while they are in their teens.[4, 5] As noted by the NIH, DS is a noted risk factor for early-onset AD.[6]

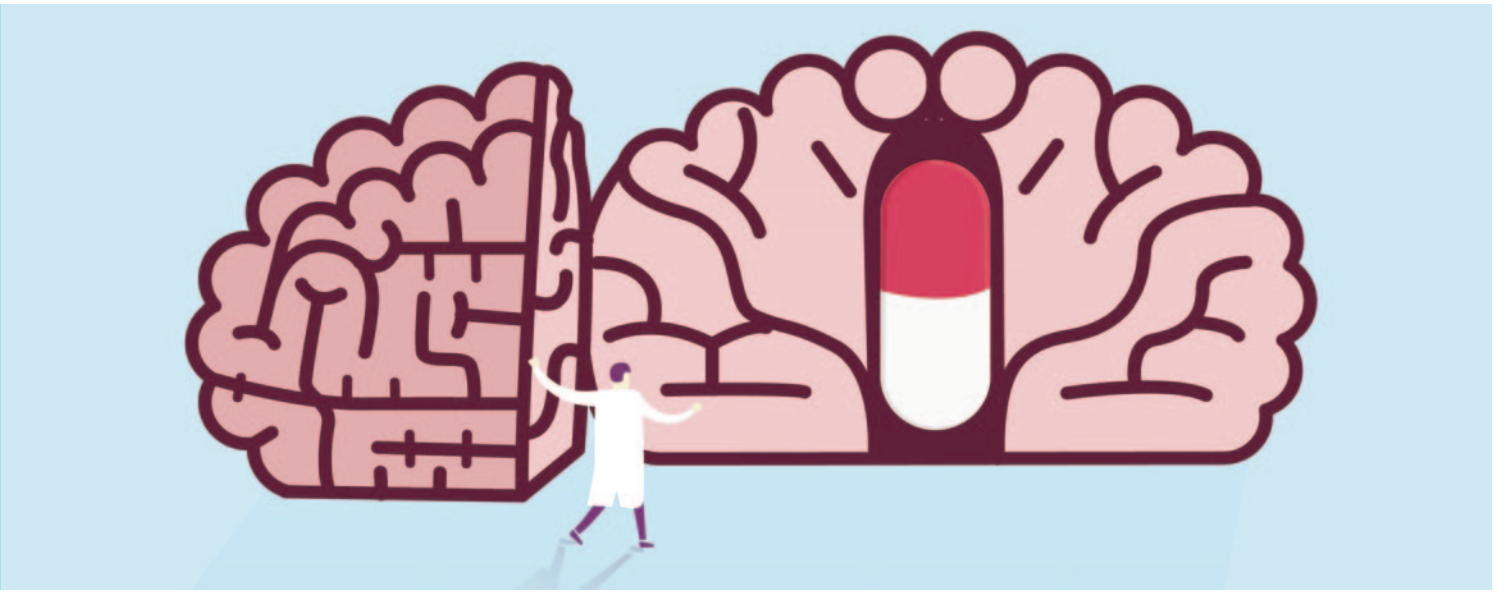
It is estimated that the lifetime risk of AD dementia is >90%[7] and it is the leading cause of death for older adults with Down syndrome.[8] Estimates are that there may be some 57,700 adults age 40 and older with Down syndrome,[9, 10] and that their average age at death is 55.8.[11] Many people with Down syndrome are diagnosed with AD dementia in their 50s but it is not uncommon for symptoms to also occur in their late 40s.[12] Once identified, AD in many people with Down syndrome can be rapid, leading to progressive cognitive decline, and is often associated with significant behavioral distress, seizures, gait dysfunction, markedly increased care needs, and death within five to seven years from diagnosis.[13]

Parents, siblings, and other caregivers embrace, encourage, advocate, and often begin the fight for services and aid for their family members with Down syndrome beginning at birth. This continues throughout childhood, adolescence, and into young adulthood as family members work to ensure their offspring receive access to equitable care and support in all aspects of their lives – including education, healthcare, vocational support, social inclusion, and civil rights. The concern that they will have to deal with and worry about early-onset AD is a hugely emotional and difficult prospect – especially when the previous ensuing years often involved battles to provide a positive and proactive approach to life, the promotion of greater autonomy, and inclusion, and support for the most of what societal integration would offer.

The realization that AD may be on the horizon for many adults with Down syndrome may not have been something that families and other caregivers thought about during earlier years when they were advocating for issues noted above. However, recent research in AD biomarkers and therapeutics for the general population and specifically for adults with Down syndrome has increased attention and dedicated focus to determine whether there might be ameliorative measures forthcoming that might help stave off or mitigate the effects of AD in adults with Down syndrome.[14,15] The recent news of the FDA's accelerated approval of Biogen's Aduhelm (aducanumab)[16] for the treatment of adults with mild cognitive impairment and dementia stemming from AD has created an avalanche of obvious interest about this product's utility and application for adults with Down syndrome.

But is this exciting news justified and does it provide the options and hope that many families have been expecting? The reality is that this new medication's availability is far from a straightforward solution for not only those adults with AD in the general population, but also for adults with Down syndrome and their families.[17]

The conundrum for families, caregivers, and adults with Down syndrome themselves, is this: the clinical trials noting the efficacy of aducanumab were conducted only on neurotypical adults with symptoms of MCI or dementia. Thus, it is unknown to what degree aducanumab may help people with Down syndrome, as they were not included among the trial participants. Questions arise as to



PROCEED WITH CAUTION: As protocols for the use of aducanumab are implemented, adults with Down syndrome must be provided with equitable care and support once diagnosed with AD.

whether aducanumab's impact on brain amyloid, associated vascular complications, doses used and its tritration in neurotypical adults may or may not be similar in adults with Down syndrome. Furthermore, cognitive benefits have yet to be clearly demonstrated with aducanumab as well as whether the MRI-related changes [including amyloid related imaging abnormalities (ARIA)] and other possible side effects (e.g., brain swelling and microhemorrhages) would also would also apply to adults with Down syndrome. To what degree are these factors equally applicable for adults with Down syndrome who are at high risk for early-onset dementia stemming from Alzheimer's disease? Are there additional side effects that we may not be aware of as there are no studies that include people with Down syndrome related to the overexpression of other proteins from chromosome 21?

Research in the last several years is providing new data that are beginning to shed evidence about the pathology and natural history of AD in people with Down syndrome, including biomarker research and potential therapeutics.[18, 19] Research demonstrates that beta amyloid (which is present in excess in people with Down syndrome due to the extra copy of the amyloid precursor protein on chromosome 21) begins to accumulate early in life, and steadily builds up over decades long before cognitive decline is notable. [20] The data also indicate AD biomarkers in people with Down syndrome behave similarly to those with other genetic forms of AD.[21] Further, vascular (blood vessel) complications including microhemorrhages (small bleeds) are not uncommon.[22] Like most people who are diagnosed with AD, there are variabilities as to the age of onset of mild cognitive impairment (MCI) and dementia, as well as the rate of progression and its trajectory in people with Down syndrome.

A key question is whether the much earlier accumulation of amyloid and degree of vascular changes that we typically see in older adults with Down syndrome respond to aducanumab in a predictable and clear fashion. Also, as amyloid accumulation is seen in 100% of adults with Down syndrome over age 40, to what degree will this affect testing and assessment for AD, as it is known that this build-up is prevalent also in asymptomatic adults with Down syndrome. During the treatment phase, will the individual's underlying cognitive and lifelong intellectual disability have an impact upon his or her ability to tolerate post-infusion testing (including MRIs) and being exposed to invasive biomarker measures. Given significant loss of cognition in some people with DS and AD (that is not regained) after the often-required anesthesia for MRI, will potential gains from using aducanumab be lost by post-anesthesia effects? Also, will follow-up assessments of their cognition and behaviors be clear to those who must care and support them as well as to provide feedback to the healthcare provider treating them? In addition, what will be the prescribed optimal timeline for receiving infusions and how will decisions be made relative to termination of treatment?

Most healthcare providers, including neurologists, are not trained to assess and diagnose AD in adults with intellectual disability (including adults with Down syndrome). During the pre-prescription assessment phase, specific challenges may arise in communicating with the patient, parsing memory loss from premorbid intellectual functioning, and mitigating examination intolerance. Most memory centers are bereft of staff skilled in interviewing and assessing persons with pre-existing cognitive limitations and who also may be uninformed as to the best courses of health and social care for adults with Down syndrome.[23, 24]

As protocols for the use of aducanumab are implemented, adults with Down syndrome must be provided with equitable care and support once diagnosed with AD. This includes understanding whether prescribing aducanumab is medically indicated and appropriate, as well as ensuring equitable access to the medication once that determination is made (including medication cost supported by insurers and CMS).[25]

Leaders in the Down syndrome advocacy community are exercising due caution at this point with respect to recommendations given the paucity of empirical support for applicability of aducanumab for persons with Down syndrome and are (a) calling for the inclusion of participants with Down syndrome in ongoing and further clinical trials and research, (b) asking for research-informed appropriate oversight over its usage, as well as safety data on adu-

canumab, and (c) stating that the development of protocols to guide the clinical practice of assessment and decision-making should include provisions for the use of aducanumab with this group. The NIH-funded Alzheimer's Clinical Trials Consortium – Down Syndrome (ACTC-DS) network is poised to address some of these questions in collaboration with Biogen and various regulatory agencies by running safety studies on persons with Down syndrome. However, given the longitudinal nature of such studies, answers to many of these questions may not be available for several years.

Advance protocols for assessment and use should be agreed upon by expert panels to, at minimum, provide cautioned guidance for practitioners considering prescribing aducanumab in adults with Down syndrome (and other intellectual disabilities). Firstly, a well-defined screening process is needed for determining the stage of AD, as well as a well-recognized and approved process for the therapeutic use of aducanumab that all healthcare providers could follow to ensure safety and ability to determine efficacy in adults with Down syndrome specifically, and with adults with intellectual disability generally. Secondly, needed also is a commitment to early detection and screening by the nation's disability services provider network and state regulatory authorities to pick up on early symptoms at a stage when the use of aducanumab may be effective. Thirdly, the involvement of families of the adult with Down syndrome and other caregivers in the decision-making process is imperative and needs to be appreciated while the prescribed medical care is being provided. Lastly, an orientation and education package is necessary to help educate healthcare providers and any ancillary staff involved in the clinical use of this therapeutic.

The strong and cohesive network of Down syndrome advocacy stakeholders and associated professional and healthcare groups are willing and able to work in partnership with governmental agencies and provider associations, as well as with the biopharmaceutical industry to move this forward. We all wish for the new advancements in AD therapeutics to succeed for the millions affected by sporadic AD as well as those thousands who are genetically determined to develop early-onset AD. Dedicated clinical trials for people with Down syndrome or the inclusion of people with Down syndrome in ongoing studies is critical. Building an information base to aid with the assessment of AD dementia in adults with Down syndrome, providing medical management guidelines when therapeutics are prescribed and used, and follow-along guidance not only for recognizing adverse effects, but also for enabling those adults on the medication to function optimally with clinically meaningful benefit.

Thus, we are calling for action. •

This article, the result of a collaborative effort, was coordinated by the National Task Group on Intellectual Disabilities and Dementia Practices (NTG) and led by Seth M. Keller, MD, Co-President of the NTG.

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