Clinical Implementation of Lecanemab: Challenges, Questions and Solutions

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The U.S. Food and Drug Administration (FDA) has approved lecanemab (Leqembi™), a humanized anti-amyloid β (Aβ) monoclonal antibody, for the treatment of early Alzheimer's disease (AD), based on the phase 2 clinical trial data using the accelerated pathway on January 6, 2023, and Leqembi is already commercially available in the U.S. since January 18. Lecanemab has already completed a confirmatory phase 3 trial (CLARITY-AD) of 1795 early AD participants which met the primary endpoint, showing a ~27% reduction of clinical decline measured by Clinical Dementia Rating-Sum of Boxes (CDR-SB) (1). The supplemental Biologics License Application (sBLA) for the traditional approval of Leqembi has just been granted Priority Review, with a Prescription Drug User Fee Act (PDUFA) action date of July 6, 2023. These urgent circumstances prompted the AD and Related Disorders Therapeutics Work Group, comprised by the U.S. experts in AD clinical research, to develop the Appropriate Use Recommendation (AUR) for Leqembi (2).

The AUR aims at helping the clinicians to use Leqembi for the treatment of AD in real-world settings, and covers important points including appropriate patient selection by clinical, imaging and biomarker evaluations, administration and safety monitoring of Leqembi, with special emphasis on the diagnosis and management of amyloid-related imaging abnormality (ARIA), complying to the FDA-approved prescribing information (PI).

ARIA-E (with edema) and ARIA-H (with hemorrhage) are one of the most common side effects of amyloid-removing antibody medications, and the incidence rates of ARIA with lecanemab were relatively lower compared to those with other antibodies (i.e., aducanumab, donanemab, gantenerumab), allowing the concomitant use of oral anticoagulants during the clinical trials. The AUR recommends excluding patients using warfarin, vitamin K antagonists, direct oral anticoagulants (dabigatran, rivaroxaban, edoxaban, apixaban, betrixaban) or heparin until more evidence is accumulated regarding the safety of lecanemab in patients on anticoagulant. This may be a reasonable and deliberate recommendation. Also, considering the report of a case that developed severe multifocal cerebral hemorrhages by the use of tissue plasminogen activator for a concomitant acute embolic stroke (3, 4),

the AUR recommends that patients on lecanemab not be treated with acute thrombolytics until safety evidence of their combined use becomes available. Autopsy of this present case showed diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within the blood-vessel walls. Although histopathological changes of ARIA in the brains of patients who have participated in the clinical trials of anti-Aβ antibodies have not been reported (except for the present case (3)), the AUR suggest that another fatal case presenting with severe ARIA-E and ARIA-H exhibited a clinical syndrome resembling cerebral amyloid angiopathy-related inflammation (CAA-ri) (5) or Aβ related angitis (ABRA) (6). If CAA-ri/ABRA frequently predisposes to such unusually severe cases of ARIA-E combined ARIA-H, quantitation of anti-Aβ autoantibodies in cerebrospinal fluids prior to antibody treatment might work as a prediction biomarker for severe ARIA (7). APOEε4 genotype increases the risk of ARIA-E and ARIA-H by treatment with lecanemab (1, 8). The FDA-approved PI recommends to inform patients that, although ARIA can occur in any patient treated with LEQEMBI, there is an increased risk in patients who are ApoEε4 homozygotes, and that there is a test available to determine ApoEε4 genotype. The AUR also recommends APOE genotyping to inform discussions of lecanemab therapy, and refers to the importance of genetic counseling to enable appropriate treatment discussions, considering the heritability of APOEε4 genotype to increase the risk for developing AD.

The clinical trial data of CLARITY-AD, on which the AUR is based, poses us with further interesting questions about the efficacy of lecamenab in different subpopulations, although with limitations in statistical power (1). There is a compelling need for treatment of early-onset AD (EOAD) with symptom onset at age <65 years, although the 166 lecanemab treated patients in CLARITY-AD between the age of 50 to 64 years showed only 6% slowing of decline in CDR-SB, in contrast to the 40% slowing in patients older than 75 years. The reason for this low efficacy in young early AD patients remains unclear, but it may be reasonable to speculate that EOAD patients had more severe neuropathology at baseline and progressed faster compared with the older patients, which may be confirmed by the tau PET substudy data etc. This urges us to explore better

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methods to diagnose EOAD patients at earlier stages, e.g., early MCI or preclinical AD, so that we can intervene into the AD pathophysiology earlier to help delay the progression of the EOAD patients. Another interesting subpopulation difference is found in the APOE genotype: ApoEε4 noncarriers showed the highest % slowing of decline (41%), whereas ApoEε4 homozygotes paradoxically showed a 22% worsening. Although the results might have been biased, for example, by the non-normality in the inclusion of slow progressors in the placebo group of ApoEε4 homozygotes (9), it is possible that lecanemab was more effective in ApoEε4 noncarriers than in carriers, in contrast to the higher efficacy reported in ApoEε4 carriers in aducanumab (8) and donanemab (10). It is tempting to speculate that different antibodies might have different mode of engagements with distinct target Aβ populations, e.g., lecanemab might have higher affinities to Aβ species that are preferentially deposited in the brains of ApoEε4 noncarriers, and possibly related to neurotoxicity but lesser to ARIA, whereas other antibodies were prone to bind more abundant and insoluble species increased by ApoEε4, leading to higher amyloid removal, and incidence of ARIA. Careful pathological and biochemical examinations of autopsied brains of patients with different ApoE genotypes treated by lecanemab, as well as the quantitative comparison of the centiloid levels of amyloid removal by PET, may provide us with clues to these questions.

The lecanemab AUR leaves the problems as to how to monitor the effectiveness of treatment and when to stop the therapy an open question, stating that "once treatment is initiated, supportive evidence of effectiveness may include less-than-expected decline on standard rating instruments performed by clinicians or change of trajectory of cognitive decline observed by family members.", acknowledging that "Confirmation of efficacy of lecanemab in the clinical setting is not feasible since the change in the rate of decline is relatively subtle, a change in rate of decline cannot be detected without multiple comprehensive trial-like assessments collected longitudinally, trajectories vary among and within patients, and comparison with a placebo group is not available." This is quite a persuasive and reasonable statement, although clinicians who treat the early AD patients with lecanemab may wish to have some hints for the criteria for stopping lecanemab therapy. In the AUR for aducanumab, the workgroup recommended that "progression into the more advanced phases of AD will prompt reassessment of treatment continuation. Progression into moderate dementia is signaled by progression to CDR global score of 2.0, decline of MMSE scores below 20, and loss of autonomy on key ADLs.", and the Expert Panel recommended the clinicians to carefully review the evidence of benefit and the potential risk in patients who progress to moderate dementia after appropriate use of aducanumab in early AD (11). The clinical implementation of Leqembi in the real-world

will facilitate our understanding of the natural course of lecanemab-treated early AD patients, which will guide us to better decide whether to continue or stop the antibody medication.

The AUR emphasizes that communication with patients and their families regarding potential benefits and potential harms of treatment with lecanemab is essential for those administering this agent. This may be vital to the safe and successful use of an innovative new drug like lecanemab.

If the effects of DMTs to slow the cognitive decline remain constant, the numeric benefit would be expected to accrue over time (12), and the delay in the progression of symptoms would be magnified: the CDR-SB data from the Clarity-AD show that lecanemab delayed the progression of clinical decline by 5.3 months at the end of the 18-months trial, and if the effect persists toward the subsequent 6 months, the delay effect is augmented to 7.5 months (9). To ascertain whether the effects of lecanemab is sustained over several years and achieve clinical meaningfulness, and for the surveillance of putative side effects, post-marketing, open-label extension of clinical trials, and the use of registries for patients receiving lecanemab or other monoclonal antibodies, represented by Alzheimer's Network for Treatment registries, may be crucial to facilitate data collection and guide any necessary use adjustments.

Lastly, the AUR for lecanemab may provide the non-US countries where lecanemab has been filed for approval with important information. An application for manufacturing and marketing approval for lecanemab in Japan has recently been designated for Priority Review by the Japanese Ministry of Health, Labour and Welfare, which is granted to new medicines recognized as having high medical utility for serious diseases and is expected to shorten the target total review period. The guideline for promoting the optimal use will simultaneously be issued by the Ministry upon approval.

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