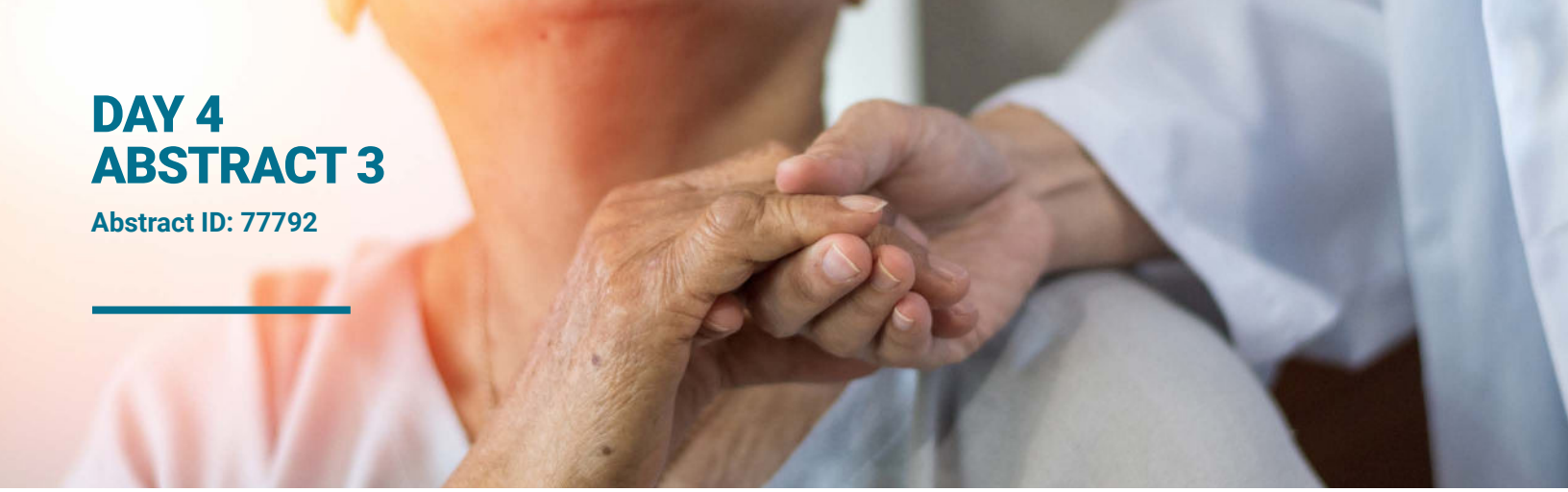

DAY 4
ABSTRACT 3

Abstract ID: 77792

ARIA-E, ARIA-H, and CAA-related inflammation: time of reconsiderations?

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Background: Evidence from published clinical trials suggests that high-dose of monoclonal antibodies (mAbs) are needed to significantly remove parenchymal-deposited Aβ plaques. However, high-dosing mAbs resulted in a 25-35% increased risk of amyloid-related imaging abnormalities-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H) side events. Although most ARIA-E are incidentally recognized as clinically silent during pre-planned safety monitoring MRI scans and suggested to be managed by dose reduction or suspension, it is noticeable that half of ARIA-E progressed to symptomatic at continued dosing and to associate with late occurrence of ARIA-H. Of particular importance, a few of them aggravated to potentially severe brain injury or death due to fatal CAA-related events. Increased evidence from natural history studies suggests that ARIA-E is the iatrogenic manifestation of cerebral amyloid angiopathy-related inflammation (CAA-ri), a rare autoimmune encephalopathy due to raised anti-Aß autoAbs levels in the cerebrospinal fluid (CSF).

Method: Natural history study of CAA-ri demonstrated that immunotherapy-related ARIA-E share several commonalities with the spontaneous occurrence of autoAbs-related ARIA-E, including fluid, MRI, and PET biomarker changes and the potential response to treatment outcomes.

Result: The prospective longitudinal monitoring of patients with CAA-ri provide evidence for a regional and temporal association of ARIA-E on MRI with focal peaks of neuroinflammation on microglial-PET imaging. This association was strong in patients with positive CSF markers of AD (ATN positive) and comorbid CAA pathology on MRI, while it was negligible in patients with CAA disease w/o AD (ATN negative). Raised CSF concentrations of anti-Aß autoAbs were found in all patients at (sub)acute presentation, and reduced within 5 months from the ARIA-E index event, in parallel with evidence of radiographic resolution of ARIA-E. At follow-up MRI scan, the occurrence of new hemorrhagic markers (aka ARIA-H in trials) were found only in patients with coexisting CAA and AD comorbid pathology. The MRI scales for ARIA commonly used in clinical trials only partially paralleled the clinical, biological, and MRI findings.

Conclusion: This suggests that to mitigate and monitor the risk of ARIA, more sensitive, specific, cost-effective and easy to interpret diagnostic tools and biomarkers than MRI alone will be needed for precision drug-dose tailoring.